CONVENIENT PREPARATIONS OF 1,8-DIOXO-6-THIOXOPIPERAZINO[1,2-c] - PERHYDROPYRIMIDINES

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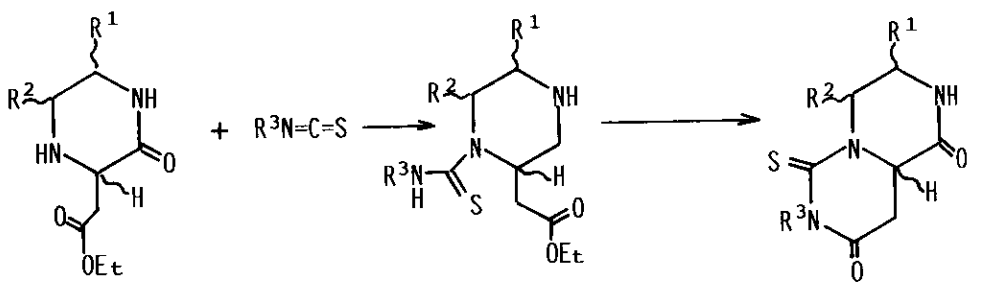
Abstract——— Hydrolysis of 4-thiocarbamoyl-3-ethoxycarbonylmethylpiperazin-2-ones **3** in alkaline solution followed by acidification afforded 1,8-dioxo-6-thioxopiperazino[1,2-c]perhydropyrimidines **4** in 65-85% yields.

3-Ethoxycarbonylmethylpiperazin-2-one **1** which was prepared from ethylenediamine and diethyl fumarate has been utilized to synthesize piperadinopyrimidines.[1-3]

In our study on the synthesis of fused saturated heterocyclic compounds aimed at the biological activity, we examined the reaction of **1** with isothiocyanates **2** followed by cyclization to thioxopiperidino[1,2-c]perhydropyrimidines **4**.



1a: $R^1=R^2=H$
b: $R^1-R^2=(CH_2)_4$

2a: $R^3=Ph$
b: $R^3=Naph$
c: $R^3=p\text{-}ClPh$
d: $R^3=PhCO$
e: $R^3=cyclohexyl$
f: $R^3=Me$

3a: $R^1=R^2=H, R^3=Ph$
b: $R^1=R^2=H, R^3=Naph$
c: $R^1=R^2=H, R^3=p\text{-}ClPh$
d: $R^1=R^2=H, R^3=PhCO$
e: $R^1=R^2=H, R^3=cyclohexyl$
f: $R^1-R^2=(CH_2)_4, R^3=Ph$
g: $R^1-R^2=(CH_2)_4, R^3=Me$

4a-g

The reaction of **1** with **2** was carried out in benzene at room temperature to afford 4-thiocarbamoyl-3-ethoxycarbonylmethylpiperazin-2-ones **3** in 80-90% yields. The structure of **3** was determined on the basis of ir and ^{1}H-nmr spectral data and elemental analyses. The results are summarized in Table 1.

Table 1 5,6-Disubstituted 3-Ethoxycarbonylmethyl-4-thiocarbamoylpiperazin-2-ones **3**

	mp(°C)	Yield(%)	IR ν_{max}^{KBr} cm^{-1}	^{1}H-NMR(DMSO-d_6) δ	Analysis(%) Calcd. (Found) C	H	N
3a	136-137	92	3250(NH) 3150(NH) 1723(C=O) 1680(C=O)	1.33(3H,t,CH_3,J=7.2Hz), 2.86-3.40(4H,m,CH_2x2), 3.70(1H,m,CH),4.30(2H,q, CH_2,J=7.2Hz),5.15(2H,m, CH_2),6.94(1H,s,NH),7.04-7.57(5H,m,Ph),9.89(1H,s,NH)	56.06 (56.37)	5.96 (5.99)	13.07 (13.00)
3b	150	97	3320(NH) 3180(NH) 1720(C=O) 1670(C=O)	1.33(3H,t,CH_3,J=7.2Hz), 3.09-3.32(4H,m,CH_2x2), 3.75(1H,m,CH),4.29(2H, q,CH_2,J=7.2Hz),5.47(2H, m,CH_2),6.96(1H,s,NH),7.37-7.57 and 7.75-7.98(7H,m, Napth),9.77(1H,s,NH)	61.44 (61.19)	5.70 (5.55)	11.31 (11.57)
3c	159-160	90	3250(NH) 3060(NH) 1700(C=O) 1680(C=O)	1.20(3H,t,CH_3,J=7.2Hz), 2.93(2H,d,CH_2,J=6.0Hz), 3.35(2H,s,CH_2),4.08(2H, q,CH_2,J=7.2Hz),4.51-4.91 (2H,m,CH_2),5.63(1H,t,CH,J= 6.0Hz),7.35(4H,s,Ph),8.23 (1H,s,Ph),9.57(1H,s,NH)	50.63 (50.52)	5.10 (5.23)	11.81 (12.15)
3d	94-95	98	3350(NH) 3325(NH) 1720(C=O) 1690(C=O) 1640(C=O)	1.12(3H,t,CH_3,J=7.2Hz), 2.74-3.05(4H,m,CH_2),3.34 (2H,q,CH_2,J=7.2Hz),5.40 (1H,m,CH),7.24-7.61 and 7.88-8.20(5H,m,Ph),8.22 (1H,s,NH),10.84(1H,s,NH)	55.00 (54.84)	5.48 (5.27)	12.03 (11.78)
3e	129	80	3310(NH) 3210(NH) 1728(C=O) 1667(C=O)	1.15(3H,t,CH_3,J=7.2Hz), 1.30-2.00(11H,m,CH_2x5 and CH),2.78-3.27(4H,m, CH_2x2),4.03(2H,q,CH_2,J= 7.2Hz),4.56(2H,m,CH_2), 5.40(1H,t,CH,J=6.0Hz), 7.41(1H,d,NH,J=6.0Hz), 8.08(1H,br,NH)	55.02 (54.76)	7.70 (7.48)	12.83 (13.12)
3f	89	70	3276(NH) 3170(NH) 1710(C=O) 1684(C=O)	1.36(3H,t,CH_3,J=7.2Hz), 1.44-1.90(8H,m,CH_2x4), 2.70-3.16(4H,m,CH_2 and CHx2),7.28-7.66(5H,m,Ph and NH),10.20(1H,s,NH)	60.78 (60.54)	6.71 (6.73)	10.93 (10.93)
3g	125	84	3330(NH) 3150(NH) 1720(C=O) 1670(C=O)	1.30(3H,t,CH_3,J=7.2Hz), 1.50-2.20(8H,m,CH_2x4), 2.79-3.27(7H,m,N-CH_3,CH_2, and CHx2),7.73(1H,s,NH), 8.20(1H,s,NH)	53.65 (53.87)	7.40 (7.11)	13.40 (13.17)

Direct cyclization of **3** to **4** failed in treating with sodium ethoxide in ethanol, but the ring closure of **3** was achieved by hydrolysis in CH_2Cl_2-KOH in the presence of triethylbenzylammonium chloride as a phase transfer catalyst followed by acidification with 6N HCl to give **4** in 55-85% yields. The results are shown in Table 2.

The structure of **4** was assigned on the basis of the spectral data. The high resolution mass spectra indicated the parent ion corresponding to the assigned structure. The ir spectra showed two carbonyl absorptions of the amides at 1700-1650 cm^{-1} and the NH absorptions at 3300-3150 cm^{-1}, respectively. The ^{13}C-nmr spectra of **4a** revealed three carbon atoms of the thione and the two carbonyl groups at 167.7, 172.8, and 182.7 ppm, respectively.

The reaction is assumed to proceed by alkaline hydrolysis of the carboxylates **3** followed by cyclization with dehydration between the resulting carboxylic acid and the thioureido NH group upon acidification.

The pharmacological activities of these new compounds are currently being investigated.

Table 2 3,4,7-Trisubstituted 1,8-Dioxo-6-thioxopiperazino[1,2-c]perhydropyrimidines **4**

	mp(°C)	Yield(%)	IRν_{max}^{KBr} cm^{-1}	^{1}H-NMR(DMSO-d_6) δ	HR-MS(M^+) (Calcd.)
4a	196	65	3150(NH) 1700(C=O) 1660(C=O)	2.40-3.20(2H,m,CH_2),3.55 (4H,m,CH_2x2),5.58(1H,t,CH, J=7.2Hz),7.17-7.70(5H,m,Ph) 9.86(1H,s,NH)	275.0718 (275.0728)
4b[1]	135	85	3300(NH) 1670(C=O) 1640(C=O)	2.94(2H,d,CH_2,J=7.2Hz),4.05 (4H,m,CH_2x2),5.48(1H,t,CH, J=7.2Hz),7.20-8.20(7H,m, Naph),8.24(1H,s,NH)	325.0870 (325.0885)
4c	162	75	3220(NH) 1700(C=O) 1640(C=O)	2.88(2H,d,CH_2,J=7.2Hz),3.28 (2H,m,CH_2),4.15-4.89(2H,m, CH_2),5.36(1H,t,CH,J=7.2Hz), 7.31(4H,m,Ph),9.78(1H,br,NH)	309.0337 (309.0339)
4d	172	75	3300(NH) 1680(C=O) 1630(C=O)	2.74-4.03(6H,m,CH_2x3),5.51 (1H,t,CH,J=7.2Hz),7.39-7.91 (5H,m,Ph),10.90(1H,br,NH)	311.0308 (311.0311)
4e	202	72	3300(NH) 1730(C=O) 1670(C=O)	1.00-1.97(11H,m,CH_2x5 and CH),2.28(2H,d,CH_2,J=7.2Hz), 3.23(2H,m,CH_2),3.93-4.82(2H, m,CH_2),5.09(1H,t,CH,J=7.2Hz), 8.16(1H,br,NH)	281.1230 (281.1198)

4f	300	85	3150(NH) 1730(C=O) 1620(C=O)	0.92-2.10(10H,m,CH_2x4 and CHx2),2.57(2H,d,CH_2,J=7.2Hz),3.80(1H,t,CH,J=7.2Hz),7.09--7.59(5H,m,Ph),7.94(1H,br,NH)	329.1180 (329.1198)
4g[2]	262-263	69	3200(NH) 1680(C=O) 1670(C=O)	1.10-1.92(10H,m,CH_2x4 and CHx2),3.06(2H,d,CH_2,J=7.2Hz),3.28(3H,s,CH_3),4.70(1H,t,CH,J=7.2Hz),8.33(1H,br,NH)	267.1047 (267.1042)

1) ^{13}C-Nmr(DMSO-d_6)δ:36.3,39.7,42.4(CH_2),57.7(CH),123.7,125.6,125.8,126.0,126.6,128.0(aromatic CH),130.5,133.8,137.0(aromatic -$\dot{C}$-),167.7(C=S),172.8,182.7(C=O)

2) ^{13}C-Nmr(DMSO-d_6)δ:24.0,27.4,27.7,29.6(CH_2),33.3(N-CH_3),52.2,53.1,70.2(CH),164.1(C=S),169.9,180.1(C=O)

EXPERIMENTAL

All the melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Ir spectra were recorded as KBr pellet on a Jasco IRA-1 grating infrared spectrophotometer. ^{1}H-Nmr spectra were determined with a Hitachi R-600 spectrometer using tetramethylsilane as an internal standard. ^{13}C-Nmr spectra were recorded with a JEOL JNM-GX400 (100MHz). Mass spectra were measured with a JEOL JMX-DX 303 HF mass spectrophotometer.

3-Ethoxycarbonylmethylpiperazin-2-ones 1

The compound **1a** was prepared from ethylenediamine 6.0g (100 mmol) and diethyl fumarate 17.2g(0.1 mol) by Philip's method.[4] yield 18.2g (92%). mp 101.5-102.5°C (lit.[4] 109-110 C).

The compound **1b** was obtained by refluxing a solution of 1,2-diaminocyclohexane (mixture of cis and trans) 11.4g (0.1 mol) and diethyl fumarate 17.2g (0.1 mol) in EtOH (80 ml). yield 21.8g (91%). mp 123-124°C. $IR\nu_{max}^{KBr}$ cm^{-1}:3290(NH), 3180(NH), 1730(C=O). ^{1}H-Nmr(DMSO-d_6)δ:1.27(3H,t,CH_3,J=7.2 Hz),1.40-1.86(9H,m,CH_2x4 and NH),2.52-3.40(4H,m,CH_2 and CHx2),3.92(3H,m,CH_2 and CH),6.78(1H,s,NH). Hhms(EI):240.1474(M^+,calcd 240.1492).

The ^{1}H-nmr spectrum (400MHz) of **1b** showed the mixtures of diastereomers, but each isomers could not be assigned.

3-Ethoxycarbonylmethyl-4-thiocarbamoylpiperazin-2-ones 3

To a stirred suspension of 1 (1.86g,10 mmol) in benzene (30 ml) was added isothiocyanate 2 (10 mmol) at room temperature. After stirring was continued for 2 h, the precipitates were filtered. The filtrate was

evaporated to one-third volume in vacuo. Ether was added to the residue to separate the precipitates. The combined precipitates were recrystallized from $CHCl_3$-hexane. The results are summarized in Table 1.

7-Substituted 1,8-Dioxo-6-thioxopiperazino[1,2-c]perhydropyrimidines 4

To a solution of 3 (10 mmol) in CH_2Cl_2 (30 ml) was added aqueous 10% KOH (18 mmol, 10ml) and a saml1 amount of benzyltriethylammonium chloride as a phase-transfer catalyst. The reaction mixture was vigorously stirred for 4-5 h at room temperature. The aqueous layer was separated and acidified with 6N HCl. The separated crystals were collected and recrystallized from dioxane or ethyl acetate. In the case of **3f-g**, powdered KOH 0.56g (10 mmol) was used instead of 10% KOH.

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