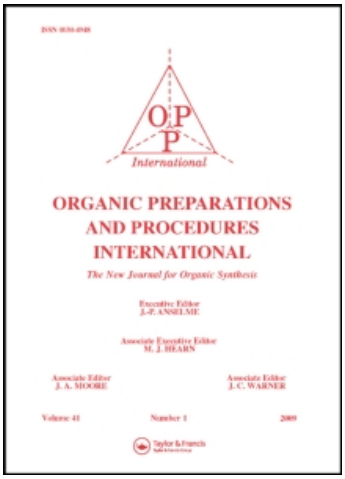

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SYNTHESIS OF *N*-(5-AMINO-2-PYRIMIDn)-*N'*-[4-(*p*-FLUOROPHENYL)-4-OXOBUTYL]PIPERAZINE, A USEFUL INTERMEDIATE TO ANTIPSYCHOTIC AGENTS

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OPPI BRIEFS

SYNTHESIS OF *N*-(5-AMINO-2-PYRIMIDYL)-*N'*-[4-(*p*-FLUOROPHENYL)-4-OXOBUTYL]PIPERAZINE, A USEFUL INTERMEDIATE TO ANTIPSYCHOTIC AGENTS

Submitted by (09/28/99) Gianluigi Broggini* and Gaetano Zecchi

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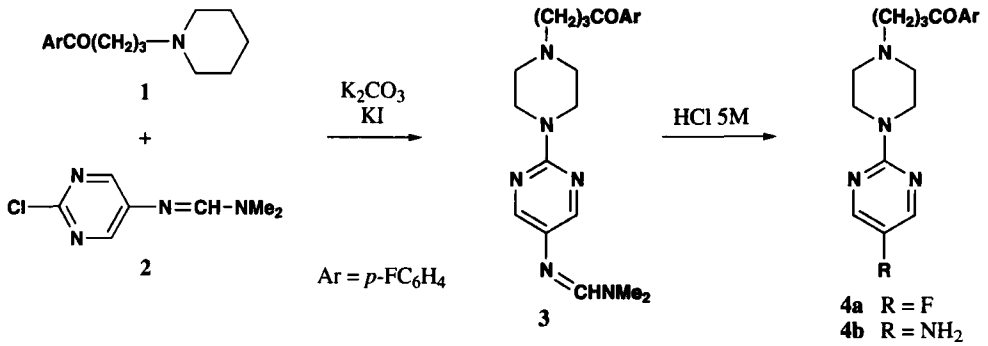
N-(5-Fluoro-2-pyrimidyl)-*N'*-[4-(*p*-fluorophenyl)-4-oxobutyl]piperazine (**4a**) and the corresponding secondary alcohol have been reported to possess antipsychotic properties.[1,2] Owing to our interest in this area of application, we felt desirable to have in hand a series of structurally related substrates bearing a wide variety of substituents on the pyrimidine ring. As a versatile and useful intermediate for this purpose, we devised a synthesis of the hitherto unknown amino derivative **4b**, described here.

Our synthetic sequence exploits the reaction of the two species **1** and **2** already reported in the literature. Satisfactory yields on preparative scale were obtained.



EXPERIMENTAL SECTION

Melting points were determined on a Büchi apparatus and are uncorrected. IR spectra were taken on a Perkin-Elmer 1725X FT spectrophotometer. NMR spectra were recorded on a Bruker 300 MHz instrument; chemical shifts are given in ppm from TMS. Mass spectra were measured on a WG-70EQ apparatus.

2-Chloro-5-(dimethylaminomethyleneamino)pyrimidine (2).- A solution of 5M LiCl in 4M HCl (210 mL) and 2-amino-5-(dimethylaminomethyleneamino)pyrimidine[3] (6.8 g, 41.5 mmol) was cooled at -10° and treated portionwise with $NaNO_2$ (5.7 g, 83 mmol). The mixture was stirred at 0° for 1 h, diluted with dichloromethane (100 mL) and basified to pH 9 with a satured solution of K_2CO_3. The organic layer was dried (Na_2SO_4) and evaporated under reduced pression to give **2** (1.5 g, 62%), mp. 103-104° (hexane-benzene) (lit.[4] 102-103°).

^1H NMR ($CDCl_3$): δ 3.15 (s, 3H), 3.19 (s, 3H), 7.52 (s, 1H), 8.21 (s, 2H); MS *m/z* 184 (M^+).

Anal. Calcd. for $C_7H_9ClN_4$: C, 45.64; H, 4.93; N, 30.43. Found: C, 45.59; H, 4.84; N, 30.55

***N*-(5-Dimethylaminomethyleneamino-2-pyrimidyl)-*N'*-[4-(*p*-fluorophenyl)-4-oxobutyl]-piperazine (3).**- A mixture of **1**[5] (1.1 g, 6 mmol), **2** (1.6 g, 6 mmol), K_2CO_3 (2.5 g, 18 mmol) and KI (0.050 g, 0.3 mmol) in acetonitrile (15 mL) was refluxed under stirring for 27 h. After dilution with dichloromethane (15 mL) and filtration, the solvent was removed under reduced pressure. The residue was chromatographed on a silica gel column with dichloromethane-methanol 12:1 as eluent to give **3** (1.1 g, 46%), mp. 147-149° (hexane-benzene).

IR (Nujol): 1690 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.97 (dt, *J* = 7.0, 7.1, 2H), 2.44 (t, *J* = 7.0, 2H), 2.48 (t, *J* = 5.0, 4H), 2.98-3.02 (overlapping, 8H), 3.69 (t, *J* = 5.0, 4H), 7.11 (dd, *J* = 8.6, 8.8, 2H), 7.42 (s, 1H), 8.00 (dd, *J* = 8.8, 5.5, 2H), 8.04 (s, 2H); MS *m/z* 398 (M^+).

Anal. Calcd. for $C_{21}H_{27}FN_6O$: C, 63.28; H, 6.83; N, 21.10. Found: C, 63.19; H, 6.94; N, 21.18

***N*-(5-Amino-2-pyrimidyl)-*N'*-[4-(*p*-fluorophenyl)-4-oxobutyl]piperazine (4b).**- A solution of **3** (0.825 g, 2.1 mmol) in 5M HCl (8 mL) and dioxane (4 mL) was refluxed for 22 h. The mixture was concentrated under reduced pressure, treated with aqueous 0.1N NaOH and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and evaporated; the residue was chromatographed on a silica gel column with dichloromethane-methanol 8:1 as eluent to give **4b** (0.53 g, 75%), mp. 144-145° (hexane-benzene).

IR (Nujol): 1675, 3420 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.98 (dt, *J* = 7.0, 7.1, 2H), 2.42-2.52 (overlapping, 6H), 3.00 (t, *J* = 7.1, 2H), 3.66 (t, *J* = 5.0, 4H), 7.12 (dd, *J* = 8.6, 8.8, 2H), 7.99 (dd, *J* = 8.8, 5.5, 2H), 8.05 (s, 2H); MS *m/z* 343 (M^+).

Anal. Calcd. for $C_{18}H_{22}FN_5O$: C, 62.94; H, 6.46; N, 20.40. Found: C, 62.88; H, 6.34; N, 20.52

Acknowledgements.- We are grateful to CNR for financial support.

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SYNTHESIS OF *N*-(3-MERCAPTOPROPANOYL)-AZA-18-CROWN-6, *N*-(4-MERCAPTOBUTANOYL)-AZA-18-CROWN-6 AND THEIR DIMERS

Sumitted by (01/04/99

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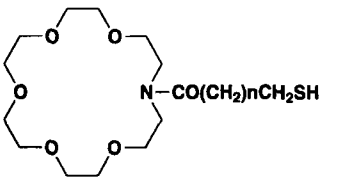
The characterisation of self-assembled monolayers (SAMs) and their application in electro-analytical chemistry such as inorganic sensors, organic and bioorganic sensors, has attracted a great deal of attention recently[1-3]. Thiol-based SAMs, derived from adsorption of functionalized alkane disulfides, sulfides or thiols on gold surfaces, are one of the most important and frequently used monolayers in electroanalytical applications[4,5]. We required **1** and **2** as a starting material for the preparation of SAMs for metal ion sensing applications.



1 n = 1

2 n = 2

Despite their simple structures, no syntheses of **1** and **2** have been described. It was envisaged that these compounds could be derived from the condensation of monoaza-18-crown-6 (**3**) with readily available 3-mercaptopropanoic acid and γ-thiobutyrolactone (**5**). Although synthesis of *N*-pyrrol-3-ylacetyl monoaza 18-crown-6 via *N,N'*-dicyclohexylcarbodiimide (DCC) mediated coupling of pyrrole-3-acetic acid and azacrown ether has been reported[6], this method could not be applied to synthesis of *N*-(meracptoalkanoyl) azacrown ethers **1** and **2**. Attempts to couple 3-mercaptopropanoic acid with monoaza-18-crown-6 in the presence of DCC led to a very messy reaction, while reaction of *S*-carbobenzyloxy-3-mercaptopropanoic acid (**4**)[7] gave very low yields of the desired product **1a** which could not be separated from the reaction mixture. Thus, the reaction of *S*-benzyloxycarbonyl-3-mercaptopropanoyl chloride with monoaza 18-crown-6 (**3**) followed by deprotection was investigated.

Monoaza-18-crown-6 (**3**) reacted smoothly with *S*-benzyloxycarbonyl-3-mercaptopropanoyl chloride, prepared from 3-mercaptopropanoic acid (**4**) and thionyl chloride, to give a good yield of *N*-(*S*-benzyloxycarbonyl-3-mercaptopropanoyl)-aza-18-crown-6 (**1a**). The best results were obtained when dry acetone in the presence of anhydrous sodium hydrogen carbonate was used as a solvent.

The ^{1}H NMR spectrum of **1a** showed the presence of two triplets at δ 2.74 and 3.10 corresponding to H2' and H1' respectively and infrared absorption at 1707 and 1637 cm^{-1} corresponding to the thioester and amide groups. Removal of the benzyloxycarbonyl group using sodium methoxide