Tetrahedron. Vol 32, pp. 1911 to 1916 Pergamon Press 1976. Printed in Great Britain

KETENE-S,S-ACETALS—VI†

SYNTHESIS OF 3,3-BIS-(METHYLTHIO)-2-PROPENE-2-ALKYL-1-ARYL-1-ONES AND THEIR REACTION WITH GUANIDINE: A NOVEL ROUTE FOR PYRIMIDINE SYNTHESIS

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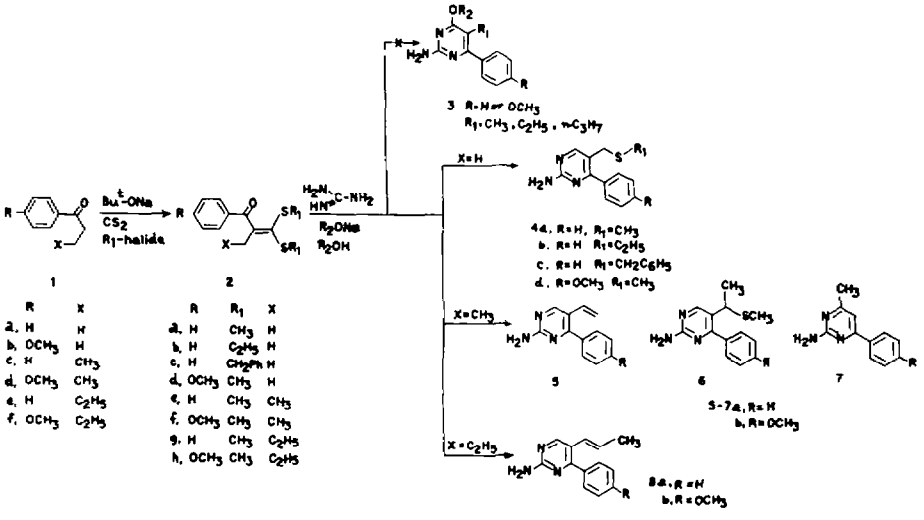
(*Received in the UK 7 January 1976; Accepted for publication 13 February 1976*)

Abstract—The α-ketoketene-S,S-acetals **2a–h** have been synthesized from the appropriate ketones **1a–f** in good yields by extending the established method. The acetals **2a–d** react with guanidine in the presence of sodium ethoxide to give pyrimidines **4a–d** in 35–59% overall yields (Scheme 1). Treatment of **2e** with guanidine similarly gave **5a** in 23% yield. However, the reaction of **2e** with guanidine in the presence of sodium n-propoxide gave a mixture of three products from which **5a** was isolated as major product (20%) with **6a** (7%) and **7a** (5%). Under similar reaction conditions, **2f** gave **5b**, **6b** and **7b** in identical yields. Treatment of **2g–h** with guanidine in the presence of sodium n-propoxide gave only **8a** (28%) and **8b** (23%) respectively. The formation of these pyrimidines involves base induced 1,3-proton migration in **2a–h** to give intermediate olefins **10a–h**.

In the preceding paper[1] we have described a general method for the synthesis of various alkoxypyrimidines by reacting the corresponding α-keto and α-cyanoketene-S,S-acetals[1] with guanidine and thiourea in the presence of sodium alkoxides. A large number of pyrimidine derivatives was required containing an alkyl chain in the 5 position, as potential dihydrofolate enzyme inhibitors.[2] The ketoketene - S,S - acetals **2a–h** which carry alkyl groups at the α-position were considered logical precursors for the synthesis of these pyrimidines **3** (Scheme 1). However, when **2a–h** were reacted with guanidine, either in the presence of sodium ethoxide or n-propoxide, the desired pyrimidines **3** ($R_1 = CH_3$, C_2H_5 or n-C_3H_7) (Scheme 1) were not obtained, although the products thus obtained were identified as pyrimidines with different structural features.

The previously unknown ketoketene - S,S - acetals **2a–h** required in the present investigation were conveniently prepared from ketones **1a–f** (Scheme 1) and carbon disulphide in the presence of sodium t-butoxide followed by alkylation with alkyl halides in one step in 40–70% yields.[3] For 10–14 h under reflux **2a–d** reacted with guanidine in the presence of sodium ethoxide solution, to give pyrimidines **4a–d** in 35–55% overall yields (Scheme 1). None of the acetals **2a–d** gave the expected pyrimidines **3** (R = H or OCH_3, $R_1 = CH_3$, $R_2 = C_2H_5$) (Scheme 1). The structures of **4a–d** were established from their analytical and spectral data. The mass spectrum of **4a** showed the molecular ion peak at M^+ 231 ($C_{12}H_{13}N_3S$). Its IR spectrum showed three peaks in the NH_2 stretching region, 3460 (ν_{as} NH_2 unassoc), 3236 (ν_{as} NH_2 assoc) and 3115 cm^{-1} (ν_s NH_2 assoc). In $CHCl_3$, however, four well resolved peaks were observed. The absorption peak at 3530 and 3410 cm^{-1} could be assigned to the NH_2 unassociated asymmetrical and symmetrical vibrational modes respectively, while the bands at 3305 and 3180 cm^{-1} (weak band) were assigned for associated, but the same vibrational modes. The strong band at 1649 cm^{-1} (KBr)



Scheme 1.

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†CDRI communication No. 2140.

was assigned to NH_2 internal deformation which moves to a value of 1600 cm^{-1} in $CHCl_3$. Further evidence for the structure of **4a** was derived from its NMR spectrum. The singlets at δ 1.97 (3H) was due to $-SCH_3$ group and the other singlet at δ 3.55 (2H) was assigned to the methylene protons. The presence of a broad multiplet at δ 5.75 (2H, NH_2, exchangeable with D_2O), another multiplet at δ 7.43 (5H, arom) and a singlet at δ 8.27 (H-6) are all in agreement with the assigned structure. The formation of **4b** and **4c** carrying S-ethyl and S-benzyl groups from **2b** and **2c** respectively further confirms the structure of **4a**. In addition, the compounds **4a–c** yielded a single product **13a** (Scheme 2) on Raney nickel desulphurisation, while **4d** gave **13b** as expected. **4a** and **4d** were subjected to hydrogen peroxide oxidation, when the corresponding sulphones **14a** and **14b** were obtained.

The formation of **4a–d** can be rationalized in terms of a base-induced 1,3-proton transfer to give the intermediate olefins **10a–d** (Scheme 2). The 1,3-proton transfer in these systems is not very unusual, since the 3d orbital participation of the two adjascent sulphur atoms greatly stabilize the negative charge on the carbon atom next to them.[4] The olefins **10a–d** then undergo nucleophilic allylic displacement with guanidine with explusion of methyl mercaptan to give **11** which after intramolecular cyclization **12** followed by proton shift gives the pyrimidines **4a–d** (Scheme 2).

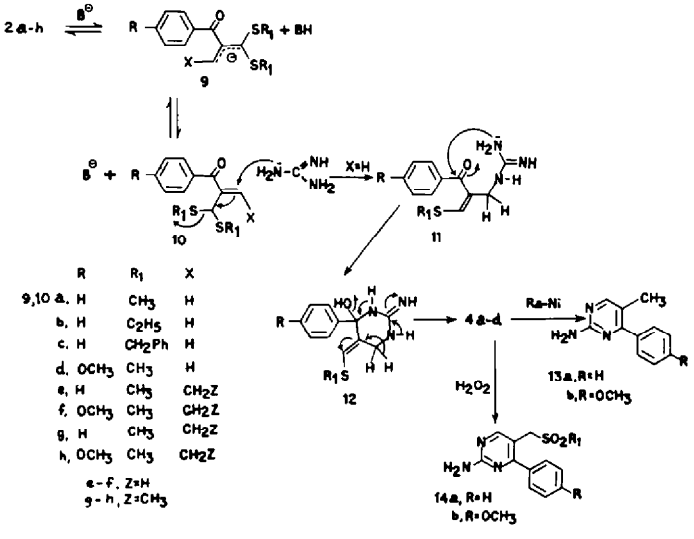
The reactions of **2e–f** were next examined. When **2e** was treated with guanidine in refluxing sodium ethoxide solution for 12 h, the product isolated after chromatographic separation was identified as 2 - amino - 4 - phenyl - 5 - vinylpyrimidine **5a** (22%) (Scheme 1). However, with a view to increasing the yield of **5a**, the above reaction was carried out in boiling sodium n-propoxide solution, when a mixture of three products was obtained (TLC), isolated in pure form by column chromatography and fractional crystallization. The first two compounds were identified as 2 - amino - 4 - phenyl - 5 - α - (methylthio)ethyl-pyrimidine **6a** (7%) and 2 - amino - 4 - phenyl - 6 - methylpyrimidine **7a** (6%) respectively, while the third compound was identified as **5a** (20%). The pyrimidine **7a** was reported earlier by a different method[5] and our compound was found to be identical with the reported one (m.m.p., IR and NMR). The ketene - S,S - acetal **2f** similarly gave a mixture of three products **5b**, **6b** and **7b** in identical yields, in the presence of sodium n-propoxide and guanidine.

The structural evidence for **5a** was derived from its elemental analysis mass, IR and NMR spectral data. Its mass spectrum showed a molecular ion peak at M^+ 197 ($C_{12}H_{11}N_3$). The IR spectrum showed the absorption bands at 3334 (ν_{as} NH_2, 1H unassoc), 3236 (ν_{as} NH_2 assoc) and 3090 cm^{-1} (ν_s NH_2 assoc). In $CHCl_3$, four well resolved peaks at 3530 (ν_{as} NH_2 unassoc), 3424 (ν_s NH_2 unassoc), 3305 (ν_{as} NH_2 assoc) and 3180 (ν_s NH_2 assoc) were observed. The deformation band at 1639 cm^{-1} (KBr) was found to be shifted to a value of 1600 cm^{-1} in $CHCl_3$.

The structure of **5a** was best confirmed by its NMR spectrum (Fig. 1). The characteristic ABC spectrum spreaded in the 5–7 ppm region resembling either to that of 4-vinylpyridine[6] or 5-vinyl pyrimidine[7] is evident from its splitting pattern as well as the coupling constants. The broad signal masked in the BC part of the spectrum at δ 5.58 (2H, NH_2, exchangeable with D_2O), a multiplet at δ 7.53 (5H, arom) and a characteristic low field singlet due to H-6 at δ 8.55 fully confirm the structure assigned to **5a**.

The structure of **6a** was similarly confirmed by its analytical and spectral data. The mass spectrum showed a molecular ion peak at M^+ 245 and was analysed for $C_{13}H_{15}N_3S$. Its IR spectrum displayed absorption bands, almost similar to **4a** and **5a**. Thus the three bands (KBr) characteristic of NH_2 group were observed at 3375 (ν_{as} NH_2 1H unassoc), 3289 (ν_{as} NH_2 assoc) and 3145 (ν_s NH_2 assoc) in addition to the NH_2 deformation band at 1642 cm^{-1}. Further evidence for the structure of **6a** was obtained from its NMR spectrum. A doublet at δ 1.40 (3H, CH_3–CH, J = 6.5 Hz), a singlet at δ 2.00 (3H, $-SCH_3$) and a quartet at δ 3.93 (1H, $-CH-CH_3$, J = 6.5 Hz) are characteristic of the side chain at the 5-position. In addition, the multiplet at δ 5.60 (2H, NH_2, exchangeable with D_2O), another multiplet at δ 7.43 (5H, arom) and a singlet at δ 8.52 (1H, H-6) further confirm the structure **6a**. Further support for the structures **5a** and **6a** was derived from their conversion to a single identical compound **17a**. Thus **5a** on hydrogenation and **6a** on Raney nickel desulphurization also yielded **17a** (m.p., m.m.p., IR and NMR) (Scheme 3).

The analogous reaction of **2g–h** with guanidine in the



Scheme 2.

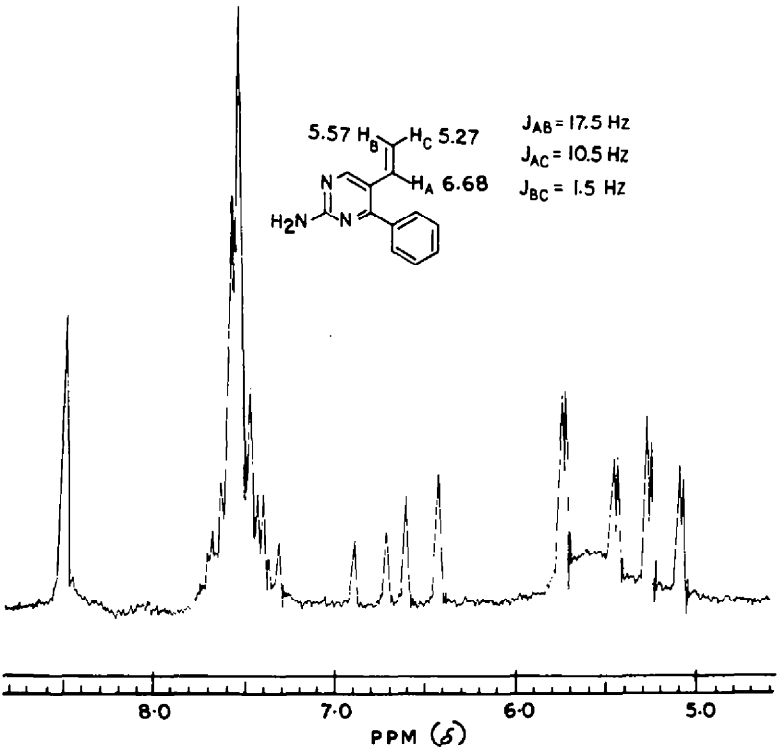
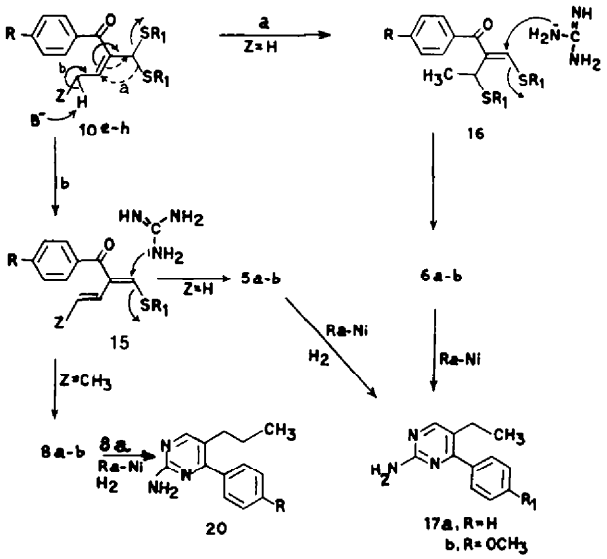


Fig. 1.



Scheme 3.

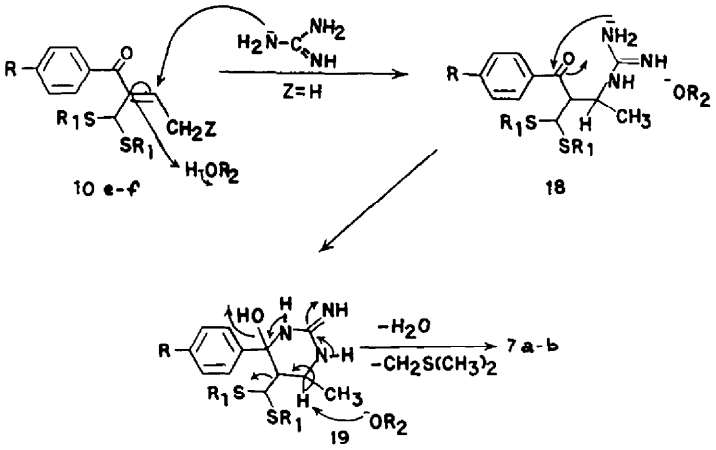
presence of sodium n-propoxide solution yielded only **8a** and **8b** respectively. One of these compounds **8a** was hydrogenated to give **20** (Scheme 3).

The mechanism for the formation of **5a–b**, **6a–b** and **8a–b** is shown in the Scheme 3. The olefins **10e–h** (Scheme 2) assumed to be the general intermediates through 1,3-proton migration, presumably undergo further base catalyzed allylic elimination to give the diene **15**, which on subsequent displacement by guanidine followed by cyclization give either **5a–b** (Z = H) or **8a–b** (Z = CH_3). On the other hand, the olefins **10e–f** (Z = H) may undergo 1,3-shift (broken arrow path a) to give **16**, which then undergo usual sequence of reactions with guanidine to give the pyrimidines **6a–b**.

The formation of **7a–b** is depicted in the Scheme 4. It is probable that the initial Michael type attack of guanidine is followed by proton abstraction from alcohol to give the intermediate **18**, which on further cyclization followed by elimination of formaldehyde - S,S - acetal yield **7a–b**.

EXPERIMENTAL

M.ps (capillary method) are uncorrected. The IR spectra were recorded on Perkin–Elmer 137, 177 and 337 spectrophotometers. The NMR spectra were recorded on a Varian A-60D spectrometer



Scheme 4.

using TMS as internal standard and the values are expressed in (ppm). The mass spectra were recorded on a Hitachi RMU-6E mass spectrometer fitted with direct inlet system.

Starting materials. The ketones **1a–f**, propiophenone **10**, b.p. 125–30° (21 mm);[8] butyrophenone **1c**, b.p. 125–30° (21 mm);[9] valerophenone **1e**, b.p. 135–140° (25 mm);[9] p-methoxybutyrophenone **1d**, b.p. 160° (20 mm), m.p. 21°[11] and p-methoxyvalarophenone **1f**, b.p. 165–7° (14 mm), m.p. 26°[12] were prepared by reported methods.

Ketene-S,S-acetals **2a–h**

General procedures. A mixture of ketones **1a–f** (0.5 mol) and CS_2 (0.5 mol) was added dropwise to a suspension of t-But–ONa (1.00 mol) in benzene (500 ml) and was stirred until (2–3 h) it turned into an orange red colour. Alkyl iodide (1.1 mol) was then added with stirring and cooling and the clear suspension was allowed to stand for 1 h. It was then refluxed on a water bath for 5 h and a cooled mixture was quenched on ice water. The benzene layer was separated and the aqueous phase was extracted with benzene (200 ml). The combined extract, was washed (H_2O), dried (Na_2SO_4) and concentrated to give the crude acetals **2a–h** which are described below.

3,3 - *Bis(methylthio)* - 2 - *methyl* - 1 - *phenyl* - 2 - *propene* - 1 - *one* **2a** was purified by chromatography on silica gel using benzene–hexane (1:5) mixture to give pure **2a**, b.p. 168–70°/13 mm Hg; yield 25 g (66%); IR (film) 1667 cm^{-1} (C=O); NMR ($CDCl_3$) 2.02 (s, 3H, $-SCH_3$); 2.20 (s, 3H, $-COCH_3$); 2.33 (s, 3H, $-SCH_3$); 7.50–5.87 (m, 5H arom). (Found: C, 60.60; H, 5.48. Calc. for $C_{12}H_{14}OS_2$ (238.3): C, 60.50; H, 5.92%).

3,3 - *Bis(ethylthio)* - 2 - *methyl* - 1 - *phenyl* - 2 - *propene* - 1 - *one* **2b** was purified by chromatography on silica gel using benzene-hexane (1:5) mixture to give pure **2b**; b.p. 182°/13 mm Hg; yield 69.8 g (60%); IR (film) 1667 cm^{-1} (C=O); NMR ($CDCl_3$) 1.02 (t, 3H, $-SCH_2-CH_3$); 1.30 (t, 3H, $-SCH_2-CH_3$); 2.18 (s, 3H, $-COCH_3$); 2.58 (q, 2H, $-SCH_2-CH_3$); 2.73 (q, 2H, $-SCH_2-CH_3$); 7.47–7.83 (m, 5H arom). (Found: C, 63.10; H, 7.13. Calc. for $C_{14}H_{18}OS_2$ (266.3): C, 63.15; H, 6.81%).

3,3 - *Bis(benzylthio)* - 2 - *methyl* - 1 - *phenyl* - 2 - *propene* - 1 - *one* **2c** was purified by crystallization from benzene–hexane (1:1) mixture as colourless needles, m.p. 66°; yield 78 g (40%). IR(KBr) 1670 cm^{-1} (C=O). NMR ($CDCl_3$), 1.97 (s, 3H, $-COCH_3$); 3.94 (s, 2H, $-SCH_2-C_6H_5$); 4.08 (s, 2H, $-SCH_2-C_6H_5$); 7.20–7.38 (m, 5H arom). (Found: C, 73.49; H, 5.36. Calc. for $C_{24}H_{22}OS_2$ (390.4): C, 73.83; H, 5.68%).

3,3 - *Bis(methylthio)* - 2 - *ethyl* - 1 - (p - *methoxyphenyl*) - 2 - *propene* - 1 - *one* **2d** was purified by chromatography on silica gel using benzene–hexane (1:5) mixture to give **2d**; b.p. 182–84°/13 mm Hg; yield 64.5 g (73%). IR (film) 1667 cm^{-1} (C=O). NMR ($CDCl_3$) 2.03 (s, 3H, $-SCH_3$); 2.12 (s, 3H, $-CO-CH_3$); 2.37 (s, 3H, $-SCH_3$); 3.85 (s, 3H, p-$H_3CO-C_6H_4$); 6.90–7.75 (dd, 4H arom A_2B_2). (Found: C, 58.45; H, 5.77. Calc. for $C_{13}H_{16}O_2S_2$ (268.3): C, 58.20; H, 6.01%).

3,3 - *Bis(methylthio)* - 2 - *ethyl* - 1 - *phenyl* - 2 - *propene* - 1 - *one* **2e** was purified by chromatography on silica gel using benzene–hexane (1:5) mixture to give **2e**; b.p. 192°/16 mm Hg; yield 79.5 g (71%). IR (film) 1667 cm^{-1} (C=O). NMR ($CDCl_3$) 1.02 (t, 3H, $-CH_2-CH_3$); 2.00 (s, 3H, $-SCH_3$); 2.32 (s, 3H, $-SCH_3$); 2.65 (q, 2H, $-CH_2-CH_3$); 7.40–7.80 (m, 5H arom). (Found: C, 61.55; H, 6.21. Calc. for $C_{13}H_{16}OS_2$ (252.3): C, 61.40; H, 6.39%).

3,3 - *Bis(methylthio)* - 2 - *ethyl* - 1 - (p - *methoxyphenyl*) - 2 - *propene* - 1 - *one* **2f** was purified by chromatography on silica gel using benzene–hexane (1:5) mixtue to give **2f**; b.p. 178°/12 mm Hg; yield 70 g (50%). IR (film) 1667 cm^{-1} (C=O). NMR ($CDCl_3$) 1.00 (t, 3H, $-CH_2-CH_3$); 2.08 (s, 3H, $-SCH_3$); 2.33 (s, 3H, $-SCH_3$); 2.70 (q, 2H, $-CH_2-CH_3$); 3.87 (s, 3H, p-$H_3CO-C_6H_4$); 6.97–7.90 (dd, 4H arom, A_2B_2). (Found: C, 59.33; H, 6.22. Calc. for $C_{14}H_{18}O_2S_2$ (282.3): C, 59.57; H, 6.43%).

3,3 - *Bis(methylthio)* - 2 - *n* - *propyl* - 1 - *phenyl* - 2 - *propene* - 1 - *one* **2g** was purified by chromatography on silica gel using benzene–hexane (1:5) mixture to give **2g**; b.p. 184°/10 mm Hg; yield 69.8 g (60%). IR (film) 1667 cm^{-1} (C=O). NMR ($CDCl_3$) 0.93 (t, 3H, $-CH_2-CH_2-CH_3$); 1.45 (sext, 2H, $-CH_2-CH_2-CH_3$); 2.03 (s, 3H, $-SCH_3$); 2.35 (s, 3H, $-SCH_3$); 2.66 (t, 2H, $-CH_2-CH_2-CH_3$); 7.50–7.85 (m, 5H arom). (Found: C, 63.34; H, 6.29. Calc. for $C_{14}H_{18}OS_2$ (266.3): C, 63.15; H, 6.81%).

3,3 - *Bis(methylthio)* - 2 - *n* - *propyl* - 1 - (p - *methoxyphenyl*) - 2 - *propene* - 1 - *one* **2h** was purified by chromatography on silica gel using benzene–hexane (1:5) mixture to give **2h**; b.p. 210–12°/10 mm Hg; yield 91 g (62%). IR (film) 1664 cm^{-1} (C=O). NMR ($CDCl_3$) 0.93 (t, 3H, $-CH_2-CH_2-CH_3$); 1.45 (sext, 2H, $-CH_2-CH_2-CH_3$); 2.10 (s, 3H, $-SCH_3$); 2.35 (s, 3H, $-SCH_3$); 2.73 (t, 2H, $-CH_2-CH_2-CH_3$); 3.88 (s, 3H, p-$H_3CO-C_6H_4$); 6.98–7.88 (dd, 4H arom A_2B_2). (Found: C, 60.45; H, 6.49. Calc. for $C_{15}H_{20}O_2S_2$ (296.3): C, 60.80; H, 6.80%).

Reaction of ketene - S,S - acetals **2a–d** *with guanidine*

General procedure. A mixture of **2a–d** (0.02 mol) and guanidine nitrate (0.02 mol) was refluxed for 10–14 h in the presence of sodium alkoxide (0.04 mol) in the corresponding alcohols (75 ml). The solvent was distilled off under reduced pressure and the residue was extracted with chloroform, washed (H_2O), dried (Na_2SO_4) and concentrated to give crude pyrimidines **4a–d**, which are described below.

2 - *Amino* - 4 - *phenyl* - 5 - (*methylthio*) - *methylpyrimidine* **4a** *from* **2a** was purified by chromatography on silica gel using chloroform and crystallized (EtOH) as colourless needles; m.p. 124°; 2.5 g (55%). (Found: C, 62.23; H, 6.02; N, 17.99. Calc. for $C_{13}H_{13}N_3S$ (231.3): C, 62.33; H, 5.67; N, 18.17%).

2 - *Amino* - 4 - *phenyl* - 5 - (*ethylthio*) - *methylpyrimidine* **4b** *from* **2b** purified by chromatography on silica gel using chloroform and crystallised (EtOH) as colourless needles, m.p. 86°; 2.5 g (50%). IR (KBr) 3336, 3236, 3195 (ν_{NH_2}) and 1639 (δ_{NH_2}); $CHCl_3$: 3530, 3420, 3305, 3180 (ν_{NH_2}) and 1605 (δ_{NH_2}) cm^{-1}. NMR ($CDCl_3$) 1.15 (t, 3H, $-CH_2-S-CH_2-CH_3$); 2.47 (q, 2H, $CH_2-S-CH_2-CH_3$); 3.62 (s, 2H, $-CH_2-S-CH_2-CH_3$); 5.77 (bm, 2H, NH_2); 7.50 (m, 5H

arom); 8.35 (s, 1H, H-6). (Found: C, 63.22; H, 5.96; N, 16.86. Calc. for $C_{13}H_{15}N_3S$ (245.3): C, 63.66; H, 6.16; N, 17.13%).

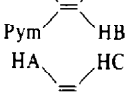
2 - *Amino* - 4 - *phenyl* - 5 - (*benzylthio*) - *methylpyrimidine* **4c** *from* **2c** was purified by chromatography on silica gel using chloroform and crystallized (EtOH) as colourless needles, m.p. 142°; 2.5 g (31%). IR (KBr) 3397, 3268, 3135 (ν_{NH_2}) and 1644 (δ_{NH_2}); ($CHCl_3$): 3530, 3420, 3310, 3190 (ν_{NH_2}) and 1600 (δ_{NH_2}) cm^{-1}. NMR ($CDCl_3$) 3.50 (s, 2H, CH_2–S–CH_2–C_6H_5); 3.60 (s, 2H, –CH_2–S–CH_2–C_6H_5); 5.60 (bm, 2H, NH_2); 7.22–7.45 (m, 10H arom); 8.32 (s, 1H, H-6). (Found: C, 70.06; H, 5.36; N, 13.52. Calc. for $C_{18}H_{17}N_3S$ (307.4): C, 70.34; H, 5.58; N, 13.67%).

2 - *Amino* - 4 - (*p* - *methoxyphenyl*) - 5 - (*methylthio*) - *methylpyrimidine* **4d** *from* **2d** was purified by chromatography on silica gel using chloroform and crystallized (EtOH) as a colourless needles, m.p. 98–9°; 1.89 g (35%). IR (KBr): 3386, 3236, 3145 (ν_{NH_2}) and 1656 (δ_{NH_2}); ($CHCl_3$): 3535, 3425, 3320, 3195 (ν_{NH_2}) and 1605 (δ_{NH_2}) cm^{-1}. NMR ($CDCl_3$): 2.18 (s, 3H, –CH_2S–CH_3); 3.65 (s, 2H, –CH_2–SCH_3); 3.85 (s, 3H, *p*-H_3CO–C_6H_4); 5.75 (bm, 2H, NH_2); 7.02–7.77 (dd, 4H, arom, A_2B_2); 8.33 (s, 1H, H-6). (Found: C, 59.47; H, 5.46; N, 15.86. Calc. for $C_{13}H_{15}N_3OS$ (261.3): C, 59.76; H, 5.79; N, 16.08%).

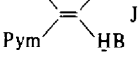
Reactions of **2e** *with guanidine in the presence of sodium ethoxide: formation of* 2 - *amino* - 4 - *phenyl* - 5 - *vinylpyrimidine* **5a**. A mixture of **2e** (10.8 g, 0.04 mol) and guanidine nitrate (4.9 g, 0.04 mol) was refluxed in the presence of sodium ethoxide (0.08 mol) in EtOH (125 ml) for 18 h and work up as usual followed by chromatography on silica gel using chloroform gave **5a** 1.7 g (23%) as a colourless needles; m.p. 144° (EtOH). (Found: C, 72.89; H, 5.43; N, 21.08. Calc. for $C_{12}H_{11}N_3$ (197.3): C, 73.07; H, 5.62; N, 21.30%).

Reaction of **2e** *with guanidine in the presence of sodium n-propoxide: formation of* 2 - *amino* - 4 - *phenyl* - 6 - *methylpyrimidine* **7a**, 2 - *amino* - 4 - *phenyl* - 5 - (α - *methylthio*) - *ethylpyrimidine* **6a** *and* **5a**. A mixture of **2e** (25.2 g, 0.1 mol) and guanidine nitrate (12.2 g, 0.1 mol) was refluxed for 18 h in the presence of n-C_3H_7ONa in n-C_3H_7OH (200 ml) and work up as usual followed by chromatography on silica gel using chloroform gave 0.9 g (5%) of **7a**, m.p. 170° (lit. m.p. 172–3°). IR (KBr): 3375, 3185 (br, ν_{NH_2}) and 1641 cm^{-1} (δ_{NH_2}). NMR ($CDCl_3$) 2.38 (s, 3H, 6-CH_3); 5.33 (bm, 2H, NH_2); 6.90 (s, 1H, H-5); 7.43–7.95 (m, 5H arom). The second eluate ($CHCl_3$) gave 1.7 g (7%) of **6a** as a colourless needles (EtOH), m.p. 121°. (Found: C, 63.80; H, 6.20; N, 17.18. Calc. for $C_{13}H_{15}N_3S$ (245.3): C, 63.66; H, 6.16; N, 17.13%). The eluate ($CHCl_3$) gave **5a** 3.95 g (20%).

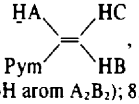
Reaction of **2f** *with guanidine in the presence of sodium ethoxide: formation of* 2 - *amino* - 4 - (p - *methoxyphenyl*) - 5 - *vinylpyrimidine* **5b**. The condensation of **2f** (5.64 g, 0.02 mol) and guanidine nitrate (0.02 mol) in the presence of NaOEt (0.02 mol) in EtOH (150 ml) as described for **5a** gave 1.5 g 33% of **5b** as light yellow needles, m.p. 124°. IR (KBr): 3395, 3256, 3185 (ν_{NH_2}) and 1657 (δ_{NH_2}); ($CHCl_3$): 3535, 3410, 3315, 3180 (ν_{NH_2}) and 1605 (δ_{NH_2}) cm^{-1}. NMR ($CDCl_3$) 3.85 (s, 3H, *p*-H_3CO–C_6H_4); 5.27 (dd, 1H



$J_{C'A}$ = 10.50 Hz; J_{CH} = 1.45 Hz); 5.57 (dd, 1H,

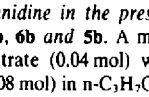


J_{BA} = 17.5 Hz; $J_{BC'}$ = 1.45 Hz); 5.83 (bm, 2H, NH_2);

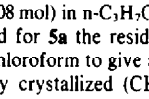
6.68 (dd, 1H,  , J_{AB} = 17.50 Hz; J_{AC} = 10.50 Hz);

6.97–7.60 (dd, 4H arom A_2B_2); 8.52 (s, 1H, H-6). (Found: C, 68.25; H, 5.63; N, 18.33. Calc. for $C_{13}H_{13}N_3O$ (227.3): C, 68.71; H, 5.77; N, 18.47%).

Reaction of **2f** *with guanidine in the presence of sodium n-propoxide: formation of* **7b**, **6b** *and* **5b**. A mixture of **2f** (11.2 g, 0.04 mol) and guanidine nitrate (0.04 mol) was refluxed in the presence of n-C_3H_7ONa (0.08 mol) in n-C_3H_7OH (75 ml) and after usual work up as described for **5a** the residue was chromatographed on silica gel using chloroform to give a mixture of **6b** and **7b**, which were fractionally crystallized ($CHCl_3$) to give more insoluble **7b** as the first crop in almost pure form 0.68 g (8%), m.p. 204°. IR (KBr): 3335, 3235, 3185 (ν_{NH_2}) and 1635 (δ_{NH_2}) cm^{-1}; NMR (TFA) 2.25 (s, 3H, –CH_3); 3.80 (s, 3H, H_3CO–C_6H_4); 6.75–7.64 (dd, 4H arom A_2B_2) 6.85 (S, 1H, H-5). (Found: C, 67.25; H, 6.45; N, 19.25. Calc. for $C_{12}H_{13}N_3O$ (215.3): C, 66.96; H, 6.09; N, 19.52%). The chloroform soluble fraction **6b** obtained after concentration was crystallized (EtOH) as colourless needles, m.p. 143–6°, 0.76 g (7%). IR (KBr) 3356 (ν_s, NH_2 unassoc); 3257 (ν_s NH_2 assoc); 3185 (ν_s NH_2 assoc); 1635 cm^{-1} (δNH_2). NMR



(CDCl₃) 1.52 (d, 3H, –C–CH_3 J = 6.5 Hz); 1.88 (s, 3H, –CH–CH_3);



3.85 (s, 3H, *p*-H_3CO–C_6H_5); 4.02 (q, 1H, –CH–CH_3 J = 6.5 Hz); 4.88 (bm, 2H, NH_2); 6.95–7.45 (dd, 4H arom A_2B_2); 8.50 (s, 1H, H-6). (Found: C, 60.88; H, 6.02; N, 15.18. Calc. for $C_{14}H_{17}N_3OS$ (275.3): C, 61.08; H, 6.22; N, 15.26%). The second eluate ($CHCl_3$) gave 1.35 g (15%) of **5b**.

2 - *Amino* - 4 - *phenyl* - 5 - (2' - *propeneyl*) - *pyrimidine* **8a** *from* **2g** was obtained in 28% yield by reacting **2g**, with guanidine in the presence of n-C_3H_7ONa as described earlier colourless needles, m.p. 202° (EtOH). IR (KBr): 3335, 3245, 3185 (ν_{NH_2}) and 1647 (δ_{NH_2}) cm^{-1}. NMR (TFA) 1.47 (d, 3H, –CH=CH–CH_3, J = 5.00 Hz); 5.90 (m, 1H, –CH=CH–CH_3, J = 5.00 Hz); 6.13 (m, 1H, –CH=CH–CH_3, J = 17.0 Hz); 7.23 (m, 5H arom); 8.33 (s, 1H, H-6). (Found: C, 73.56; H, 6.63; N, 19.69. Calc. for $C_{13}H_{13}N_3$ (213.3): C, 73.21; H, 7.09; N, 19.70%).

2 - *Amino* - 4 - (p - *methoxyphenyl*) - 5 - (2' - *propeneyl*)*pyrimidine* **8b** was obtained in 23% yield from **2h** and guanidine nitrate in the presence of n-C_3H_7ONa and crystallized (EtOH) as colourless needles, m.p. 129–30°. IR (KBr): 3357, 3245, 3189 (ν_{NH_2}) and 1642 (δNH_2) cm^{-1}. NMR ($CDCl_3$) 1.82 (d, 3H, –CH=CH–CH_3, J = 5.5 Hz); 3.85 (s, 3H, *p*-H_3CO–C_6H_4); 5.61 (bm, 2H, NH_2); 6.12 (m, 1H, –CH=CH–CH_3, J = 5.50 Hz); 6.20 (m, 1H, –CH=CH–CH_3, J = 17.50 Hz); 6.95–7.60 (dd, 4H arom A_2B_2); 8.40 (s, 1H, H-6). (Found: C, 69.46; H, 6.40; N, 17.34. Calc. for $C_{14}H_{15}N_3O$ (241.3): C, 69.69; H, 6.27; N, 17.41%).

Desulphurization of **4a–d** *and* **6a–b**. A suspension of Raney nickel (10 g) and **4a–d** and **6a–b** (0.005 mol) in EtOH (50 ml) was refluxed on water bath for 5 h. After usual work up the sulphur free pyrimidines, obtained, are described below.

2 - *Amino* - 4 - *phenyl* - 5 - *methylpyrimidine* **13a** *from* **4a**. Crystallized (EtOH) as colourless needles, 0.76 g (83%), m.p. 154°. IR (KBr): 3334, 3195 (br, ν_{NH_2}) and 1639 (δ_{NH_2}) cm^{-1}. NMR (TFA) 1.95 (s, 3H, 5-CH_3); 7.22 (m, 5H arom); 8.12 (s, 1H, H-6). (Found: C, 70.89; H, 5.68; N, 22.52. Calc. for $C_{11}H_{11}N_3$ (185.2): C, 71.33; H, 5.99; N, 22.69%). Similarly, **4b** and **4c** gave **13a** with identical yields (m.p., m.m.p., superimposable IR).

2 - *Amino* - 4 - (p - *methoxyphenyl*) - 5 - *methylpyrimidine* **13b** *from* **4d**. Crystallized (EtOH) as a colourless needles, 0.9 g (82%), m.p. 148–49°. IR (KBr): 3334, 3205 (b, ν_{NH_2}) and 1639 (δ_{NH_2}) cm^{-1}. NMR ($CDCl_3$) 2.20 (s, 3H, C_5–CH_3); 3.83 (s, 3H, *p*-H_3CO–C_6H_4); 5.57 (bm, 2H, NH_2); 6.97–7.55 (dd, 4H arom A_2B_2); 8.23 (S, 1H, H-6). (Found: C, 66.84; H, 5.93; N, 19.39. Calc. for $C_{12}H_{13}N_3O$ (215.3): C, 66.96; H, 6.09; N, 19.52%).

2 - *Amino* - 4 - *phenyl* - 5 - *ethylpyrimidine* **17a** *from* **6a**. Crystallized (EtOH) as a colourless needles 0.75 g (75%), m.p. 68°. IR (KBr): 3325, 3135 (b, ν_{NH_2}) and 1639 (δ_{NH_2}) cm^{-1}. NMR ($CDCl_3$) 1.02 (t, 3H, –CH_2–CH_3); 2.53 (q, 2H, –CH_2–CH_3); 5.33 (bm, 2H, NH_2); 7.40 (m, 5H arom); 8.33 (s, 1H, H-6). (Found: C, 72.12; H, 6.41; N, 20.95. Calc. for $C_{12}H_{13}N_3$ (199.3): C, 72.23; H, 6.58; N, 21.09%). This compound was identical with the compound obtained from **5a** on hydrogenation (m.p., m.m.p., superimposable IR).

2 - *Amino* - 4 - (p - *methoxyphenyl*) - 5 - *ethylpyrimidine from* **6b**. Crystallized (EtOH) as a colourless needles 0.69 g (85%), m.p. 87–8°. IR (KBr): 3335, 3195 (b, ν_{NH_2}) and 1653 (δ_{NH_2}) cm^{-1}. NMR ($CDCl_3$) 1.07 (t, 3H, –CH_2–CH_3); 2.48 (q, 2H, –CH_2–CH_3); 3.83 (s, 3H, *p*-H_3CO–C_6H_4); 5.12 (bm, 2H, NH_2); 6.95–7.36 (dd, 4H arom A_2B_2); 8.33 (s, 1H, H-6). (Found: 67.86; H, 6.43; N, 18.18. Calc. for $C_{13}H_{15}N_3O$ (229.3): C, 68.10; H, 6.59; N, 18.33%).

2 - *Amino* - 4 - *phenyl* - 5 - n - *propylpyrimidine* **20** *by hydrogenation of* **8a**. The suspension of Raney nickel (0.25 g) and **8a** (1.05 g, 0.005 mol) in EtOH (30 ml) was hydrogenated in a Paar low pressure hydrogenator (8 h at room temp.). After work up **20** was obtained as colourless needles (EtOH) 0.94 g (88%); m.p.

95–7°. IR (KBr): 3395, 3285, 3185 (ν_{NH_2}) and 1653 (δ_{NH_2}) cm^{-1}. NMR ($CDCl_3$) 0.80 (t, 3H, $-CH_2-CH_2-CH_3$); 1.63 (sext, 2H, $-CH_2-CH_2-CH_3$); 2.50 (t, 2H, $-CH_2-CH_2-CH_3$); 5.33 (bm, 2H, NH_2); 7.27–7.47 (m, 5H arom). (Found: C, 72.72; H, 6.84; N, 19.54. Calc. for $C_{13}H_{15}N_3$ (213.3): C, 73.21; H, 7.09; N, 19.70%). **5a** was similarly hydrogenated to give **17a**.

2 - *Amino* - 4 - *phenyl* - 5 - (*methylsulphonyl*) - *methylpyrimidine* **14a** *from* **4a**. A mixture of **4a** (2.3 g, 0.01 mol) in HOAc (25 ml) and excess of H_2O_2 (30%, 25 ml) was refluxed on a water bath for 3 h. The solvent was distilled off, and poured on crushed ice. It was extracted with EtOAc, washed (H_2O), dried (Na_2SO_4) and the solvent was removed to get crude **14a** which was crystallized (HOAc + H_2O) as a colourless needles, 1.70 g (65%) m.p. 185–6°. IR (KBr): 3425, 3296, 3195 (ν_{NH_2}) and 1642 (δ_{NH_2}) cm^{-1}; 1295 and 1131 cm^{-1} ($-SO_2-$). NMR (TFA) 2.67 (s, 3H, $-CH_2-SO_2-CH_3$); 4.25 (s, 2H, $CH_2-SO_2-CH_3$); 7.27 (m, 5H arom); 8.41 (s, 1H, H-6). (Found: C, 54.51; H, 4.83; N, 15.76. Calc. for $C_{12}H_{13}N_3O_2S$ (263.3): C, 54.75; H, 4.98; N, 15.96%).

2 - *Amino* - 4 - (p - *methoxyphenyl*) - 5 - (*methylsulphonyl*)*methylpyrimidine* **14b** *from* **4b** was prepared as described above in 55% yield as colourless needles (HOAc + H_2O), m.p. 154°. IR (KBr): 3440, 3310, 3195 (ν_{NH_2}) and 1639 (δ_{NH_2}) cm^{-1}; 1300 and 1136 cm^{-1} ($-SO_2-$). NMR (TFA) 2.72 (s, 3H, $-CH_2-SO_2-CH_3$); 3.93 (s, 3H, $H_3CO-C_6H_4$); 4.23 (S, 2H, $-CH_2-SO_2-CH_3$); 6.88–7.30 (dd, 4H arom A_2B_2). (Found: C, 53.34; 5.51; N, 14.09. Calc. for $C_{13}H_{15}N_3O_3S$ (293.3): C, 53.24; H, 5.16; N, 14.33%).

Acknowledgements—We express our thanks to the Director, Dr. Nitya Anand for his helpful discussion and facilities, and Drs. R. Gopalchari and M. M. Dhar for their interest and encouragement. One of us (S.M.S.C.) thanks the C.S.I.R. New Delhi, for a Junior Research Fellowship. We also thank the staff members of our microanalytical as well as spectroscopic laboratories for their excellent technical assistance.

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