Synthesis of Heterocyclics via Enamines. II* Reactions of Cyclohex-1-enyl -aniline, -morpholine and -piperidine with 1,1-Dimethyl-3-oxobutyl Isothiocyanate

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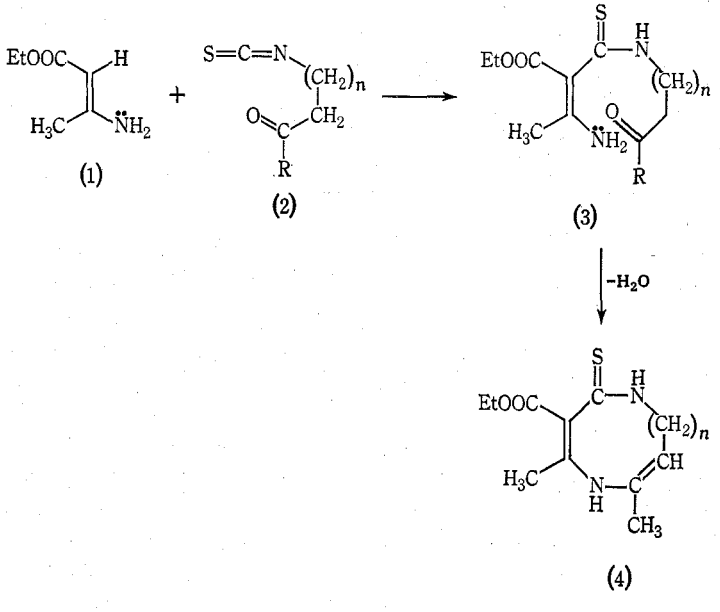
Abstract

The condensation of cyclohex-1-enylaniline (8) with 1,1-dimethyl-3-oxobutyl isothiocyanate (5) gave 1,4,5,6,7,8,9,10-octahydro-2,4,4-trimethyl-1-phenyl-1,5-benzodiazocine-6(1*H*)-thione (9) as the major product and 3-phenyl-4,6,6-trimethyl-1,2,3,6-tetrahydropyrimidine-2-thione (7; R = Ph) as the minor product. The similar condensations of (5) with cyclohex-1-enylmorpholine and cyclohex-1-enylpiperidine formed the 1-thiocarbamoyl derivatives through β-elimination of the intermediate (15).

Introduction

Currently there is a considerable interest in the synthesis of medium sized heterocyclic ring compounds because of their CNS depressant[1–3] and systemic fungicidal



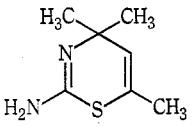
Scheme 1

* Part I, *Aust. J. Chem.*, 1973, **26**, 2453.

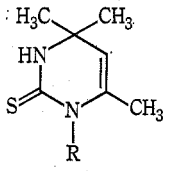
[1] Sternbach, L. H., *Chem. Ind.* (London), 1970, 599.
[2] Stevens, G. de, in 'Topics in Heterocyclic Chemistry' (Ed. R. N. Castle) p. 154 (Wiley–Interscience: New York 1969).
[3] Popp, F. D., and Noble, A. C., in 'Advances in Heterocyclic Chemistry' (Ed. A. R. Katritzky) p. 21 (Academic Press: New York 1967).

potentialities.[4] 4-Mercaptopyrimidines have been obtained by the reaction of the isothiocyanato carbon of acyl isothiocyanates (RCONCS) with the enamine β-carbon of ethyl β-aminocrotonate (1)[5] followed by cyclodehydration. If we replace RCONCS by α- or β-isothiocyanato ketones (e.g. $RCOCH_2(CH_2)_nNCS$; $n = 0, 1$) (2), this approach would provide a facile synthesis of 1,4-diazepines (4; $n = 0$) and 1,5-diazocines (4; $n = 1$) (Scheme 1).

Earlier, we reported that the electrophilic isothiocyanato carbon of 1,1-dimethyl-3-oxobutyl isothiocyanate (5) failed to react with the enamine carbon of (1) and gave 2-amino-4,4,6-trimethyl-1,4-dihydro-1,3-thiazine (6) and/or 4,6,6-trimethyl-1,2,3,6-tetrahydropyrimidine-2-thione (7; R = H) through its interaction with the enamine



(6)



(7)

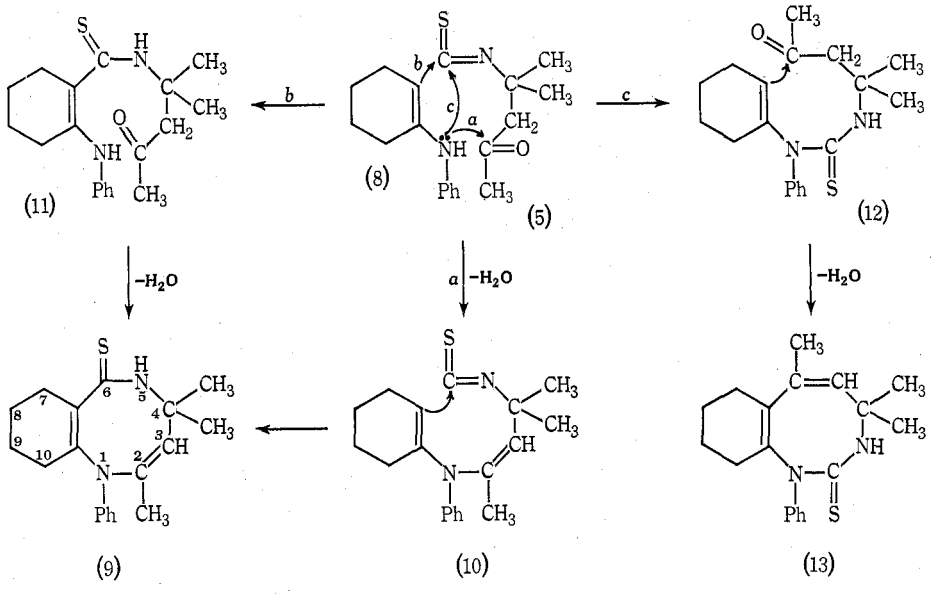
nitrogen.[6] This was attributed to both the reduced nucleophilicity of the enamine β-carbon due to the presence of the ethoxycarbonyl group and the reduced electrophilicity of the isothiocyanato carbon atom due to its insulation from the activating conjugative influence of the carbonyl group.[7] Here we report the reactions of the pentanone (5) with cyclohex-1-enyl-aniline, -morpholine and -piperidine which possess relatively enhanced nucleophilicity at the β-carbon.

Results and Discussion

The product obtained from the condensation of the enamine (8) and the pentanone (5) gave on chromatography a faster moving component, A, m.p. 211–212°, $M^{+\cdot}$ *m/e* 312. The intensities of the isotopic peaks in the parent ion cluster in the mass spectrum are consistent with the molecular formula $C_{19}H_{24}N_2S$ [*m/e* 312 (100%), 313 (23·230), 314 (7·016), 315 (1·177), 316 (0·115)]. Its solubility in aqueous sodium hydroxide and reprecipitation after acidification indicated the presence of a thiol function. In its i.r. spectrum, the absorption for C=O and N=C=S groups were absent but bands at 3170 and 1590 cm^{-1} for NH and conjugated enamine[8] vibrations were present. From these data the structure 1,4,5,6,7,8,9,10-octahydro-2,4,4-trimethyl-1-phenyl-1,5-benzodiazocine-6(1*H*)-thione (9) was assigned. N.m.r. values further corroborated the structure: δ 1·32 (3H, s, CH_3), 1·37 (3H, s, CH_3), 1·5–2·3 (11H, m, CH_3C=CH and $(CH_2)_4$), 5·45 (1H, m, CH=C), 6·8–7·5 (5H, m, aromatic H), 9·6 (1H, m, NH). The minor component B, m.p. 192–193°, was found to be identical with

[4] Woodcock, D., *Chem. Brit.*, 1970, **6**, 220.
[5] Stevens, G. de, Smolinsky, B., and Dorfman, L. *J. Org. Chem.*, 1964, **29**, 1115.
[6] Singh, H., and Singh, S., *Aust. J. Chem.*, 1973, **26**, 2453.
[7] Singh, H., Singh, S., and Jain, S. L., *Chem. Ind.* (London), 1971, 729.
[8] Taylor, E. C., and McKillop, A., in 'Advances in Organic Chemistry' (Ed. E. C. Taylor) p. 4 (Interscience: New York 1970).

an authentic sample of the pyrimidine (7; R = Ph).[6,9]* A third slow moving minor component could not be isolated in amounts sufficient for characterization.



Scheme 2

The possible pathways for this reaction are postulated in Scheme 2. The possibility of the cyclodehydration of (12) to give (13) and thereby the structure (13) for component A would be remote but an unambiguous synthesis of the diazocine (9) was warranted. We reasoned that an intermediate of type (11), precursor of (9), could exclusively be formed by using an enamine possessing a tertiary nitrogen, which would not react[10] with carbonyl and isothiocyanato carbons (Scheme 2; routes *a* and *c*). Consequently a synthesis of (9) was undertaken involving the formation of (15) from (5) and (14; X = O, CH_2) followed by hydrolysis to give diketone (16) which on condensation with aniline would form (9) (Scheme 3). At ambient temperature, the condensation of (14; X = O) and (5) showed little progress but on heating at 100–110°, it was almost complete in approximately 20 h and the product was subjected to chromatography. The fast moving component, C (10%), m.p. 69–71°, ν_{max} 3375 (NH), 1680 (C=O),[11a] 1525 cm^{-1} (N–C=S),[11b,12] was assigned structure (17; X = O)* by comparison with an authentic sample of (17; X = O) obtained from morpholine and (5). The second and major component, D (70%), m.p. 255–256°, ν_{max} 3320 (NH), 1570 (C=C–N),[8] 1510 cm^{-1} (N–C=S),[11b,12] $M^{+\cdot}$ *m/e* 226, was assigned the structure 2-morpholinocyclohex-1-enecarbothioamide (18; X = O). The intensities

* Compounds (7; R = Ph) and (17; X = O, CH_2) may have been formed from aniline and morpholine originating from the enamine or from starting material impurities.

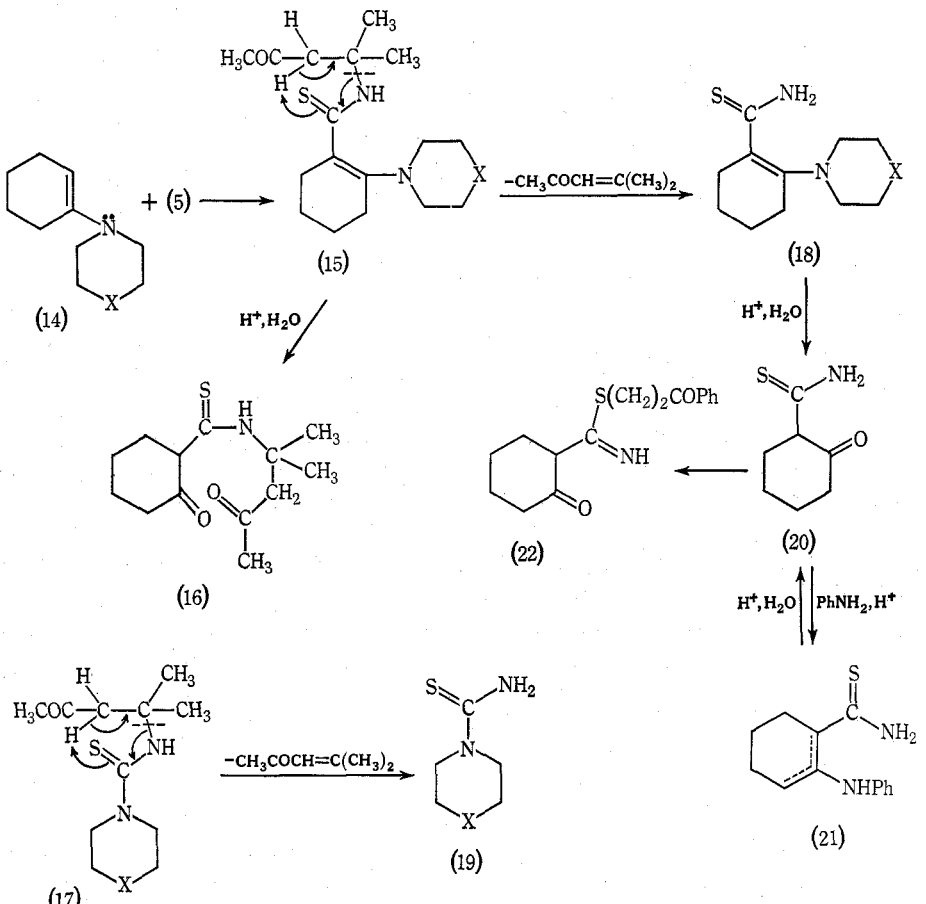
[9] Mathes, R. A., Stewart, F. D., and Swedish, F., Jr, *J. Amer. Chem. Soc.*, 1948, **70**, 1952.

[10] Alt, G. H., in 'Enamines: Synthesis, Structure and Reactions' (Ed. A. G. Cook) p. 115–64 (Marcel Dekker: New York 1969).

[11] Nakanishi, K., 'Infrared Absorption Spectroscopy' (*a*) p. 167, (*b*) p. 54 (Holden-Day: San Francisco 1964).

[12] Bellamy, L. J., 'The Infrared Spectra of Complex Molecules' p. 357 (John Wiley: New York 1958).

of the isotopic peaks in the parent ion cluster in its mass spectrum which are listed below were in agreement with those calculated for the molecular formula $C_{11}H_{18}NOS$ [*m/e* 226 (100%), 227 (14·197), 228 (5·580), 229 (0·662), 230 (0·049)]. N.m.r. values further corroborated the structure: δ 1·35 (6H, s), 2·34 (2H, s), 5·66 (2H, s, exchanged with D_2O), 3·20–3·74 (8H, m, morpholine hydrogens). The thioamide (18; X = O) could be formed from the intermediate (15; X = O) by β-elimination[13] of mesityl oxide (Scheme 3). The last component, E, (20%), m.p. 175–176°, ν_{max} 3430–3350 (NH), 1320 cm^{-1} (N–C=S),[11b,12] M^+ *m/e* 146, was assigned the structure (19; X = O). This was further supported by its formation from compound (17; X = O) by heating. So in the reaction of (5) and (14; X = O), (19; X = O) was formed from (17; X = O) through pyrolytic β-elimination of mesityl oxide.



Scheme 3

Likewise, cyclohex-1-enylpiperidine (14; X = CH_2) gave the three products F (17; X = CH_2), G (18; X = CH_2) and H (19; X = CH_2).

On acidic hydrolysis both (18; X = CH_2) and (18; X = O) formed the same product, 2-oxocyclohexanecarbothioamide (20), $M^{+\cdot}$ *m/e* 157, ν_{max} 3225 (NH), 1600 (C=O),[11a] 1315 cm^{-1} (N=C=S),[11b,12] which formed a 2,4-dinitrophenylhydrazine

[13] March, J., 'Advanced Organic Chemistry' p. 747 (McGraw-Hill: New York 1968).

derivative. The presence of a thioamido group in (20) was supported by its condensation with β-chloropropiophenone in the presence of aqueous sodium hydroxide to give the derivative (22).[14] The presence of a C=O group in (20) was further evidenced by its condensation with aniline in the presence of *p*-toluenesulphonic acid to furnish 2-anilinocyclohex-1(or 2)-enecarbothioamide (21), $M^{+\bullet}$ *m/e* 232. The intensities of the isotopic peaks in the parent ion cluster were in agreement with their intensities calculated for the molecular formula $C_{13}H_{16}N_2S$ [*m/e* 232 (100%), 233 (16·375), 234 (5·696), 235 (0·751)]. On acid hydrolysis (21) gave (20). These chemical transformations further indicated the presence of thiocarbamoyl and carbonyl groups in (20) and provided added support for structure (18) assigned to the major product obtained in the condensation of (14) and (5).

The approach to the synthesis of (9) (Scheme 2) was unsuccessful, but the above results showed that in the condensation of (5) with (14), the increase in nucleophilicity of the enamine β-carbon and the lack of reaction of C=O and N=C=S at tertiary nitrogen has resulted in the exclusive attack of the enamine carbon on the isothiocyanato carbon. This gave the intermediate (15) which underwent β-elimination* incorporating a thiocarbomoyl group at the enamine β-carbon (18). These observations indirectly support the pathways *b* and/or *c* in Scheme 2.

Experimental

Melting points were determined in capillaries. Infrared spectra were run in KBr discs on a Perkin–Elmer 337 spectrometer. N.m.r. spectra were recorded on Varian A-60 and HA-100 instruments in $CDCl_3$ with tetramethylsilane as internal standard. Analyses were performed at the Central Drug Research Institute, Lucknow. T.l.c. plates were coated with silica gel G and were run in $CHCl_3$–EtOH (95 : 5 v/v) and spots were developed in an iodine chamber. For column chromatography neutral alumina (BDH) was used.

Reaction of Cyclohex-1-enylaniline (8) with 1,1-Dimethyl-4-oxobutyl Isothiocyanate (5)

A mixture of equimolar amounts of (8) and (5) was heated under anhydrous conditions in an oil bath at 110–112° and the reaction was complete after *c.* 10 h. The dark brown reaction mixture comprised two main components A (R_F 0·94) and B (R_F 0·85) which were isolated after repeated chromatography. Component A (9) (80%)† was eluted with benzene, m.p. 211–212° (benzene) (Found: C, 73·4; H, 7·8; N, 8·6. $C_{19}H_{24}N_2S$ requires C, 73·1; H, 7·7; N, 9·0%). $M^{+\bullet}$ *m/e* 312; for i.r., n.m.r. and mass spectra see Discussion. The component B (7; R = Ph) was washed with $CHCl_3$–benzene (9 : 1), m.p. 192–193° (EtOH). It was identical (R_F, m.p., m.m.p.) with an authentic sample of (7; R = Ph).

N-(*1,1-Dimethyl-3-oxobutyl*)*morpholinocarbothioamide* (*17*; *X* = *O*)

Equimolar amounts of morpholine and (5) were mixed. The temperature of the reaction mixture rose to 50°. On keeping overnight, the product which separated as shining white *crystals* was collected and was crystallized from ethanol, m.p. 69–71° (yield 92%) (Found: C, 53·9; H, 8·3; N, 11·6. $C_{11}H_{20}N_2O_2S$ requires C, 54·1; H, 8·2; N, 11·5%). ν_{max} (KBr) 3375 (NH), 1680 (C=O), 1525 cm^{-1} (N–C=S).

N-(*1,1-Dimethyl-3-oxobutyl*)*piperidinocarbothioamide* (*17*; *X* = CH_2)

On mixing equimolar quantities of piperidine and (5), the temperature rose to 60°. The reaction mixture was kept overnight and the shining *crystals* that separated were collected, m.p. 71–72°

* For intermediates (10) or (11), further condensation reactions were preferred over β-elimination.
† These are approximate compositions only, determined visually by comparison of t.l.c. spots.

[14] Singh, H., and Lal, K. B., *J. Chem. Soc., Perkin Trans. 1*, 1972, 1799.

(benzene) (yield 80%) (Found: C, 59·3; H, 9·1; N, 11·4. $C_{12}H_{22}N_2OS$ requires C, 59·5; H, 9·1; N, 11·6%). ν_{max} (KBr) 3350 (NH), 1680 (CO) 1520 cm^{-1} (N–C=S).

Morpholinocarbothioamide (19; X = O)

Compound (17; X = O) was heated in an oil bath at 100–110° for 2 h. The *product* obtained was purified by chromatography, m.p. 175–176° (ethanol) (Found: C, 40·9; H, 6·9; N, 18·9. $C_5H_{10}N_2OS$ requires C, 41·1; H, 6·9; N, 19·2%). ν_{max} (KBr) 3330 (NH), 1625, 1320 cm^{-1} (thiourea).

Piperidinocarbothioamide (19; X = CH_2)

This *compound*, m.p. 98–99° (benzene), was similarly obtained from (17; X = CH_2) (Found: C, 50·3; H, 8·6; N, 19·3. $C_6H_{12}N_2S$ requires C, 50·0; H, 8·3; N, 19·4%). ν_{max} (KBr) 3400–3250 (NH), 1585, 1320 cm^{-1} ($(NH)_2CS$).

Reaction of Cyclohex-1-enylmorpholine (14; X = O) with (5)

A mixture of equivalent amounts of freshly distilled (14; X = O) and (5) were kept at room temperature for a number of days. Samples on t.l.c. did not show any progress in reaction. The mixture was heated at 115–120° under anhydrous conditions and it took *c.* 70 h for completion of the reaction. The reaction mixture comprised three components: C, R_F 0·6, D, R_F 0·5, and E, R_F 0·18, which were isolated by repeated chromatography. The compound C (10%) was eluted with benzene, m.p. 69–70° (EtOH), and was found to be identical (R_F, m.m.p.) with an authentic sample of (17; X = O). The major component D (70%) was washed from the column with benzene–chloroform (9 : 1), m.p. 255–256° (EtOH). It was identified as *2-morpholinocyclohex-1-enecarbothioamide* (18; X = O), $M^{+\bullet}$ *m/e* 226 (Found: 58·8; H, 8·1; N, 12·4. $C_{11}H_{18}N_2OS$ requires C, 58·4; H, 8·0; N, 12·4%). The n.m.r. and i.r. spectra are given in the Discussion. The component E (20%) was washed from the column with chloroform, m.p. 175–176° (ethanol). It was identical (R_F, m.m.p.) with an authentic sample of morpholinocarbothioamide (19; X = O). $M^{+\bullet}$ *m/e* 146.

Reaction of 1-Cyclohex-1-enylpiperidine with (5)

A mixture of equimolar amounts of freshly distilled 1-cyclohex-1-enylpiperidine and (5) was heated at 125–130° under anhydrous conditions. The reaction was complete in *c.* 6 h. The product comprised three components: F, R_F 0·70, G, R_F 0·64, and H, R_F 0·06, which were isolated by chromatography. The component F (10%), m.p. 71–72° (EtOH), was identical (R_F, m.m.p.) with an authentic sample of (17; X = CH_2). The component G (50%), m.p. 220–222° (benzene), was identified as *2-piperidinocyclohex-1-enecarbothioamide* (Found: C, 64·2; H, 9·0; N, 12·9. $C_{12}H_{20}N_2S$ requires C, 64·3; H, 8·9; N, 12·5%). ν_{max} (KBr) 3755 (NH), 1545 cm^{-1} (C=C–N). The component H (40%), m.p. 98–99° (benzene), was identical (R_F, m.m.p.) with an authentic sample of (19; X = CH_2).

2-Oxocyclohexanecarbothioamide (20): Hydrolysis of (18; X = O, CH_2)

A solution of (18; X = O) (2·25 g) in 2N hydrochloric acid (10 ml) was heated in a water bath for 1 h. On cooling a crystalline *product* separated which was collected and crystallized from ethanol (1·1 g), m.p. 138–139° (Found: C, 53·5; H, 7·4; N, 8·8. $C_7H_{11}NOS$ requires C, 53·5; H, 7·0; N, 8·9%). R_F 0·34; $M^{+\bullet}$ *m/e* 157; n.m.r.: δ 1·22 (s, 6H), 2·58 (s, 3H), 3·74 (s, 2H, exchanged with D_2O). Similarly (18; X = CH_2) was hydrolysed in 2 h to give (20), identical with the above product. The 2,4-dinitrophenylhydrazine derivative of (20) had m.p. 210–211° (EtOH) (Found: N, 21·0. $C_{13}H_{14}N_5O_4S$ requires N, 20·8%).

2-Anilinocyclohex-1-(or 2)-enecarbothioamide (21)

This was obtained by refluxing equimolar amounts of (20) and aniline in anhydrous benzene in the presence of *p*-toluenesulphonic acid for 1 h. The product obtained after distilling off the solvent was crystallized from ethanol, m.p. 233–234°, R_F 0·42, $M^{+\bullet}$ *m/e* 232.

Hydrolysis of (21) into (20)

Compound (21) was hydrolysed by heating in 2N hydrochloric acid for 3 h. The product that separated had identical R_F with (20) obtained earlier.

S-(2-Benzoylethyl)-2-oxocyclohexanecarboximidothioate (22) from (20) and β-Chloropropiophenone

Compound (20) (1·57 g 0·01 mol) was dissolved in 0·5N aqueous sodium hydroxide solution (40 ml, 0·01 mol) and a solution of β-chloropropiophenone (1·68 g, 0·01 mol) in ethanol (5 ml) was added. The mixture was shaken vigorously for about 5 min and the *product* that separated was collected, washed with water, dried and crystallized from ethanol (1·45 g), m.p. 205–206° (Found: C, 66·8; H, 6·8; N, 5·0. $C_{16}H_{19}NO_2S$ requires C, 66·4; H, 6·6; N, 4·8%). R_F 0·80; ν_{max} (KBr) 3150 (NH), 1675 (CO), 1550 cm^{-1} (N–C=S).

Acknowledgments

The authors thank Mr J. Singh, Chemistry Department, Brock University, St Catharines, Ontario, for help in obtaining the mass spectral data, Professor I. S. Bhatia for his interest and the Council of Scientific and Industrial Research for a Senior Research Fellowship (to S.S.).

Manuscript received 10 June 1974