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# Hindered Rotations in Carbamoylethyl-thiocarbamate Derivatives

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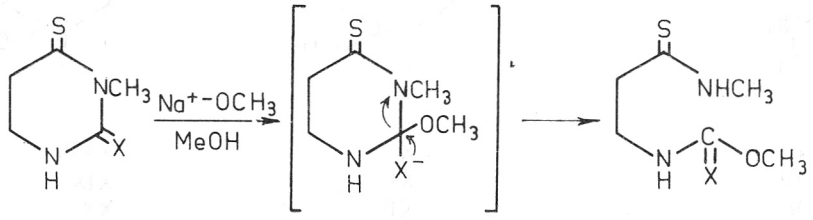
The synthesis of methyl N-[2-(carbamoyl)-ethyl]carbamates and their thio-analogues is described. The NMR spectra of thio--carbamates indicated hindered rotation around C—N bonds and separation of two geometrical isomers.

The characteristic reactivity of 5,6-dihydro-3-methyl-4-thiouracil (I, X=O) and 5,6-dihydro-3-methyl-2,4-dithiouracil (I, X=S) towards nucleophiles[1] affected the pyrimidine ring cleavage to methyl N-[2-(methylthiocarbamoyl) ethyl]carbamate (XVI) and methyl N-[2-(methylthiocarbamoyl)ethyl]thiocarbamate (XXI). Thus, during the course of our studies on unusual nucleosides[2] and fragmentations of their pyrimidine moiety[1], the systematic preparation of hitherto unknown carbamoylethyl-carbamates and their thio-analogues appeared to be of interest. Carbamates and thiocarbamates[3,4] are particularly interesting because of their chemical structure and properties as well as their pharmaceutical, pesticidal[5], insecticidal, fungicidal and medical[6] uses.




I
X=O or S

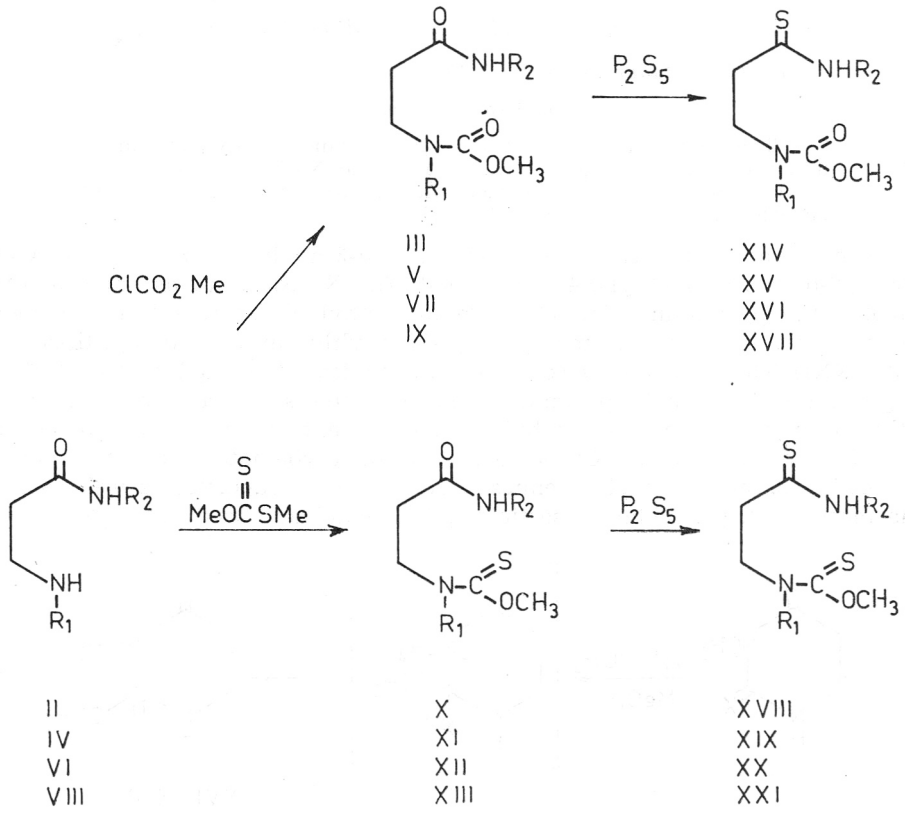
XVI X=O
XXI X=S

In considering the methods for the preparation of methyl N-[2-(carbamoyl) ethyl]carbamate (III), methyl N-methyl, N-[2-(carbamoyl)ethyl]carbamate (V), methyl N-[2-(methylcarbamoyl)ethyl]carbamate[1] (VII) and methyl N-methyl, N-[2-(methylcarbamoyl)ethyl]carbamate (IX), the reaction of methyl chloroformate[7,8] with 3-aminopropionamide (II), 3-methylaminopropionamide (IV), 3-amino N-methylpropionamide (VI) and 3-methylamino N-methylpropionamide (VIII) has been investigated.

Treatment of the aminopropionamides[9,10] (II), (IV), (VI) and (VIII) with dimethyl xanthate[11] in anhydrous methanol resulted in the formation of methyl N-[2-(carbamoyl)ethyl]thiocarbamate (X), methyl N-methyl, N-[2-

-carbamoyl)ethyl]carbamate (XI), methyl N-[2-(methylcarbamoyl)ethyl)thiocarbamate[1] (XII) and methyl N-methyl, N-[2-(methylcarbamoyl)ethyl]thiocarbamate (XIII) respectively.

The NMR spectrum of (XII) (see Table), with an unexpected upfield signal $\tau = 7.60$ (S—$CH_3$) indicated methyl thiolcarbamate rather than methyl thiocarbamate[1]. This thiolic structure as one of possible isomers was isolated when propionamide (VI) was treated with dimethyl xanthate.

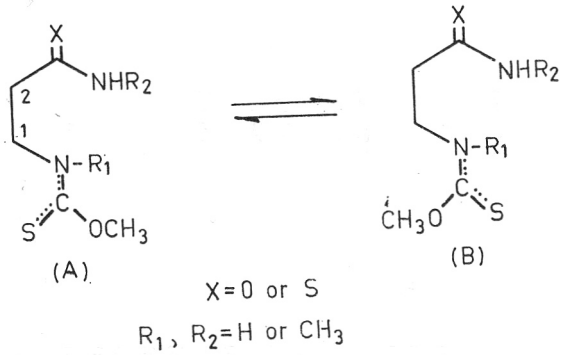



| | |
|---|---|
| $R_1=R_2=H$: | II[9], III, X, XIV, XVIII |
| $R_1=CH_3$, $R_2=H$: | IV[9], V, XI, XV, XIX |
| $R_1=H$, $R_2=CH_3$: | VI[9], VII[1], XII[1], XVI[1], XX[1] |
| $R_1=R_2=CH_3$: | VIII[10], IX, XIII, XVII, XXI |

Thiation of the above mentioned carbamoyl-carbamates (III), (V), (VII), (IX) and carbamoyl-thiocarbamates (X), (XI), (XII), (XIII) with phosphorus

pentasulfide yielded methyl N-[2-(thiocarbamoyl)ethyl)carbamate (XIV), methyl N-methyl, N-[2-(thiocarbamoyl)ethyl]carbamate (XV), methyl N-[2-(methylcarbamoyl)ethyl]carbamate[1] (XVI), methyl N-methyl, N-[2-(methylthiocarbamoyl)ethyl]carbamate (XVII), methyl N-[2-(thiocarbamoyl)ethyl]thiocarbamate (XVIII), methyl *N*-methyl, *N*-[2-(thiocarbamoyl)ethyl] thiocarbamate (XIX), methyl N-[2-(thiocarbamoyl)ethyl]thiocarbamate[1] (XX), and methyl N-methyl, N-[2-(methylthiocarbamoyl)ethyl]thiocarbamate (XXI) respectively.

The NMR spectroscopic investigations of thiocarbamates[4,5,12] unequivocally indicate the co-existence of both *trans* (A) and *cis* (B) isomers*. At ambient temperature the restriction of rotation[13,14] around $>$N—CS of the compounds




(X), (XI), (XIII), (XVIII), and (XX) can be evidenced by the definite doubling of the $H_2$-1 triplets and $R_1$ methyl singlets ($\Delta\tau$ = 0.20—0.25 ppm) (see Table) also affecting the separation of $H_2$-2 triplets ($\Delta\tau$ = 0.11 ppm). These resonance lines coalesce to single broad lines and one singlet for $R_1$ methyl singlets at higher temperature.

The marked influence of the thione group of thiocarbamoyl-carbamates (XIV—XVII) upon the position of $H_2$-2 reveals a downfield shift for 0.36—0.46 ppm when compared with carbamoyl compounds (III), (V), (VII) and (IX). Besides this magnetic anisotropy effect of the thione group[15] the larger size of the sulfur atom in thiocarbamates, compared with oxygen in carbamates, generates intramolecular steric repulsion to a larger extent[16], and consequently causes an increased proportion of the *cis* isomer. The more intense downfield triplets of the C-1 protons of the thiocarbamates (X) and (XVIII) indicate the preferences for *trans* isomer (A) when $R_1$ = H.

However, the N-methyl-thiocarbamates (XI) and (XIII) with the upfield $H_2$-1 triplets and downfield $CH_3$ singlets as slightly more intense resonance lines, indicate a larger proportion of *cis* isomers (B), $R_1$ = $CH_3$.

To explain the magnetically nonequivalent O—$CH_3$ groups in thiocarbamates (X), (XVIII), and (XX) the resonance of the ester oxygen with the thione group[17] can be taken into consideration.


* The *trans* and *cis* isomers are specified according to the relative positions of thiocarbonyl and $R_1$ (H or $CH_3$) on the partial C—N double bond as the reference plane.

TABLE I

*NMR Spectra*[a,b] *(τ values)*

| Compound | $H_2$ — 2 | $H_2$ — 1 | O—$CH_3$ | $R_1$ | $R_2$ | $J_{2,3}$/Hz |
|---|---|---|---|---|---|---|
| III | 7.43 (t) | 6.49 (t) | 6.23 (s) | | | 6.5 |
| V | 7.52 (t) | 6.44 (t) | 6.33 (s) | 7.11 (s) | | 6.7 |
| VII[1] | 7.51 (t) | 6.53 (t) | 6.26 (s) | | 7.20 (s) | 6.5 |
| IX | 7.50 (t) | 6.38 (t) | 6.25 (s) | 7.05 (s) | 7.22 (s) | 6.6 |
| X | 7.53 (t)<br>7.42 (t)[c] (4) | 6.46 (t)<br>6.26 (t)[c] (5) | 6.07 (s)[c] (2)<br>5.99 (s) | | | 6.7<br>6.7 |
| XI | 7.50 (t)[c]<br>7.39 (t) (4)[d] | 6.18 (t)[c]<br>5.96 (t) (5)[d] | 6.04 (s) | 6.72 (s)[c]<br>6.91 (s) (2)[d] | | 6.8<br>6.8 |
| XII | 7.48 (t) | 6.40 (t) | 7.60 (s)* | | 7.19 (s) | 6.7 |
| XIII | 7.53 (t)[c]<br>7.42 (t) (4)[d] | 6.18 (t)[c]<br>5.96 (t) (5)[d] | 6.03 (s) | 6.72 (s)[c]<br>6.92 (s) (2)[d] | 7.31 (s) | *ca.* 6.6<br>6.6 |
| XIV | 7.07 (t)[e] | 6.36 (t)[e] | 6.24 (s) | | | 6.5 |
| XV | 7.12 (t)[e] | 6.34 (t)[e] | 6.33 (s) | 7.09 (s) | | 6.8 |
| XVI[1] | 7.11 (t) | 6.41 (t) | 6.27 (s) | | 6.85 (s) | 6.5 |
| XVII | 7.04 (t) | 6.27 (t) | 6.24 (s) | 7.02 (s) | 6.85 (s) | 6.6 |
| XVIII[f] | *ca.* 7.16 (t)<br>7.05 (t)[e] (4) | *ca.* 6.23 (t)<br>5.98 (t)[e] (5) | *ca.* 6.01 (s)[c]<br>5.95 (s) | | | *ca.* 6.5<br>6.5 |
| XIX[f,d] | *ca.* 6.90 | *ca.* 5.84 | 5.97 (s) | *ca.* 6.84 | | |
| XX[1,f] | 7.15 (t)<br>7.04 (t) (4) | *ca.* 6.18 (t)<br>5.96 (t) (5) | *ca.* 6.03<br>5.96 (s)[c] | | 6.88 (s)<br>6.89 (s) | *ca.* 6.2<br>6.2 |
| XXI[f] | *ca.* 6.90 (t)[d] | *ca.* 5.87 (t)[d] | 5.97 (s) | 6.81 (s) | 6.89 (s) | |

[a] See introduction to Experimental section. [b] Values for triplet (t) refer to multiplet centres. [c] More intense signals. (2), (4) and (5) denote the number of lines in multiplets formed from two triplets. [d] Heated; resonance lines coalesce to a single broad line. [e] Splitting of two outer triplet lines (about 1.0 Hz.). [f] Solution in deuteriochloroform. *ca.* refers to estimated τ and *J* values when resonance is obscured by those of other protons or by low solubility of compound. * Signal for S—$CH_3$.

The methyl signal of the thiocarbamoyl compound (XX) is doubled also revealing the restricted rotation of the methylcarbamoyl moiety around its CS—N < bond.

## EXPERIMENTAL

Melting points, uncorrected, were taken on a Kofler hot stage. UV spectra were measured in 95% ethanol with a Beckmann model DU-2 ultraviolet spectrophotometer. The IR spectra were recorded in potassium bromide pellets using a Perkin-Elmer Infracord model 137. NMR spectra were recorded on a Varian A-60 spectrometer with sodium 3-(trimethylsilyl)propanesulfonate in aqueous solutions as internal standard and tetramethylsilane in organic solutions.

### *Preparation of Carbamoylethyl-carbamates from 3-Aminopropionamide and its N-Methyl Derivatives with Chloroformate[7,8] — General Procedure*

To freshly distilled 3-aminopropionamides[9,10] (II), (IV), and (VIII) (25 mmol) in hot anhydrous dioxan (25 ml), crumbled potassium carbonate (30 mmol) was added. The mixture was chilled by ice, treated portionwise with freshly distilled methyl chloroformate (27 mmol) in dioxan (5 ml), and then stirred for 1 h at room temperature. The precipitate was removed and washed with hot dioxan (30 ml). The filtrate and washing were evaporated to dryness and corresponding carbamoylethyl-carbamates were isolated.

### *Methyl-N-[2-(carbamoyl)ethyl]carbamate (III)*

From 3-aminopropionamide[9] (II) the crystalline product (73%) was isolated (from acetone) and then sublimed at 130° C ($2 \cdot 10^{-2}$ mmHg) as colourless primsm, m. p. 143—144 °C. IR spectrum: 3344, 3155, 2899, 1673, 1639, and 1536 $cm^{-1}$.

*Anal.* $C_5H_{10}N_2O_3$ (146.15) calc'd.: C 41.09; H 6.90; N 19.17%
found: C 41.43; H 7.28; N 19.26%

### *Methyl N-Methyl, N-[2-(carbamoyl)ethyl]carbamate (V)*

3-Methylaminopropionamide[9] (IV) afforded a crystalline product (68%). This gave colourless plates, m. p. 59—60 °C (from methylene chloride—ether). IR spectrum: 3333, 3165, 2924, 1667 (broad), 1613, 1490, and 1439 $cm^{-1}$.

*Anal.* $C_6H_{12}N_2O_3$ (160.17) calc'd.: C 44.99; H 7.55; N 17.49%
found: C 45.02; H 7.87; N 17.11%

### *Methyl N-Methyl, N-[2-(methylcarbamoyl)ethyl]carbamate (IX)*

3-Methylamino N-methylpropionamide[10] (VIII) yielded an oil (53%), distilled, b. p. 130 °C ($10^{-2}$ mmHg), IR spectrum: 3270, 3040, 2907, 1695, 1546, and 1477 $cm^{-1}$.

*Anal.* $C_7H_{14}N_2O_3$ (174.20) calc'd.: C 48.26; H 8.10; N 16.08%
found: C 48.19; H 8.40; N 16.35%

### *Preparation of Carbamoylethyl-thiocarbamates from 3-Aminopropionamide and its N-Methyl Derivatives with Dimethyl Xanthate[11] — General Procedure*

To freshly distilled 3-aminopropionamides[9] (II, IV and VIII [10]) (1 mmol) dissolved in anhydrous methanol, freshly distilled dimethyl xanthate (1.1 mmol) was added. The mixture was kept for 24 h at ambient temperature, evaporated to a residue and chromatographed in methylene chloride on a short silica gel column (1 g, Camag). Methylene chloride—ether (15 ml, 5:1) then eluted corresponding thiocarbamates.

### *Methyl N-[2-(carbamoyl)ethyl]thiocarbamate (X)*

3-Aminopropionamide[9] (II) and dimethyl xanthate yielded a crystalline product (73%), crystallized as colourless needles, m. p. 75—76 °C (from methylene chloride —ether). UV spectrum: $\lambda_{max}$ 242.5 nm, log ε 4.14 and $\lambda_{min}$ 218 nm, log ε 3.17. IR spectrum: 3401, 3205, 2941, 1672, 1647, 1613, and 1522 $cm^{-1}$.

*Anal.* $C_5H_{10}N_2O_2S$ (162. 20) calc'd.: C 37.03; H 6.21; N 17.21; S 19.77%
found: C 36.73; H 6.64; N 17.65; S 19.52%

*Methyl N-Methyl, N-[2-(carbamoyl)ethyl]thiocarbamate (XI)*

3-Methylaminopropionamide[9] (IV) in reaction with dimethyl xanthate yielded a product (57%) which crystallized as colourless needles, m. p. 87—88 °C (from methylene chloride). UV spectrum: $\lambda_{max}$ 247 nm, log ε 4.25 and $\lambda_{min}$ 221 nm, log ε 3.22. IR spectrum: 3448, 3322, 3205, 3125, 1661, 1587, and 1504 $cm^{-1}$.

*Anal.* $C_6H_{12}N_2O_2S$ (176.24) calc'd.: C 40.89; H 6.86; N 15.90; S 18.20%
found: C 40.80; H 7.03; N 15.83; S 18.16%

*Methyl N-Methyl, N-[2-(methylcarbamoyl)ethyl]thiocarbamate (XIII)*

3-Methylamino N-methylpropionamide[10] (VIII) in reaction with dimethyl xanthate yielded an oily product (80%), distilled as colourless oil, b. p. 150 °C ($10^{-2}$ mmHg) UV spectrum: $\lambda_{max}$ 247 nm, log ε 4. 29 and $\lambda_{min}$ 221.5 nm, log ε 3.37. IR spectrum: 3460, 3300, 3058, 2924, 1631, 1555, and 1502 $cm^{-1}$.

*Anal.* $C_7H_{14}N_2O_2S$ (190.26) calc'd.: C 44.20; H 7.42; N 14.73; S 16.82%
found: C 44.21; H 7.69; N 14.78; S 17.05%

*Thiation of Carbamoylethyl-carbamates, Carbamoylethyl-thiocarbamates and their N-Methyl Derivatives — General Procedure*

To carbamoylethyl-carbamates (III, V, IX) and carbamoylethyl-thiocarbamates (X, XI, XIII) (10 mmol) dissolved in anhydrous dioxan (100 ml), phosphorus pentasulfide (12 mmol) was added. The suspension was refluxed for 2 h (unless otherwise stated) and evaporated to dryness. The residue was dissolved in water (30 ml) and extracted with ethyl acetate (30 ml), the extract was evaporated to dryness and dissolved in methylene chloride to be chromatographed on silica gel (25 g, Camag). Methylene chloride (50 ml) eluted impurities and ether pure fraction.

*Methyl N-[2-(thiocarbamoyl)ethyl]carbamate (XIV)*

Methyl N-[2-(carbamoyl)ethyl]carbamate (III) was thiated to a crystalline product (60%). A sample was dissolved in methylene chloride and applied to a silica gel plate (15 g, Merck $HF_{254-366}$). The plate was developed with ether. The fraction detectable under UV lamp was eluted with acetone, evaporated and crystallized, m. p. 83—84 °C (methylene chloride—hexane). UV spectrum: $\lambda_{max}$ 215 and 276.2 nm, log ε 3.51 and 4.10 and $\lambda_{min}$ 232 nm, log ε 2.82. IR spectrum: 3333, 3145, 1695, 1637, and 1515 $cm^{-1}$.

*Anal.* $C_5H_{10}N_2O_2S$ (162.20) calc'd.: C 37.03; H 6.21; N 17.21; S 19.77%
found: C 36.92; H 6.44; N 16.92; S 19.52%

*Methyl N-Methyl, N-[2-(thiocarbamoyl)ethyl]carbamate (XV)*

Thiation of methyl N-methyl, N-[2-(carbamoyl)ehyl]carbamate (V) gave a crystalline product (48%), m. p. 126—127 °C (methanol—ether) as colourless prisms For analysis it was sublimed at 130 °C ($10^{-3}$ mmHg). UV spectrum: $\lambda_{max}$ 206.5 and 269 nm, log ε 3.77 and 3.96 and $\lambda_{min}$ 235 nm, log ε 2.93. IR spectrum 3269, 3086, 2907, 1667, and 1486 $cm^{-1}$.

*Anal.* $C_6H_{12}N_2O_2S$ (176.24) calc'd.: C 40.89; H 6.86; N 15.90; S 18.20%
found: C 40.58; H 7.20; N 15.85; S 17.84%

*Methyl N-Methyl, N-[2-(methylthiocarbamoyl)ethyl]carbamate (XVII)*

Methyl N-methyl, N-[2-(methylcarbamoyl)ethyl]carbamate (IX) was thiated for 30 minutes to crystalline product (61%). It crystallized as colourless prisms, m. p. 71—72 °C (ether—hexane). UV spectrum: $\lambda_{max}$ 202.8 and 264.9 nm, log ε 3.93 and 4.11 and $\lambda_{min}$ 230.4 nm, log ε 3.20. IR spectrum: 3268, 3030, 2899, 1616, 1550, and 1481 $cm^{-1}$.

*Anal.* $C_7H_{14}N_2O_2S$ (190.27) calc'd.: C 44.19; H 7.41; N 14.73; S 16.85%
found: C 44.36; H 7.66; N 14.95; S 17.06%

*Methyl N-[2-(thiocarbamoyl)ethyl]thiocarbamate (XVIII)*

Methyl N-[2-(carbamoyl)ethyl]thiocarbamate (X) was thiated to thiocarbamoyl derivative (60%). It crystallized as prisms, m.p. 90—91 °C (water). UV spectrum: $\lambda_{max}$ 245.5 and shoulder at 263 nm, log ε 4.25 and 4.14 and $\lambda_{min}$ 222 nm, log ε 3.59. IR spectrum: 3333, 3215, 2959, 1639, 1563, and 1536 $cm^{-1}$.

*Anal.* $C_5H_{10}N_2OS_2$ (178.27) calc'd.: C 33.68; H 5.65; N 15.72; S 35.97%
found: C 33.73; H 5.63; N 15.91; S 35.71%

*Methyl N-Methyl, N-[2-(thiocarbamoyl)ethyl]thiocarbamate (XIX)*

Methyl N-methyl, N-[2-(carbamoyl)ethyl]thiocarbamate (XI) was thiated to crystalline compound (52%), m.p. 87—88 °C (methylene chloride—ether) as needles. UV spectrum: $\lambda_{max}$ 250 and shoulder at 268.5 nm, log ε 4.31 and 4.12 and $\lambda_{min}$ 223 nm, log ε 3.55. IR spectrum: 3333, 3155, 2924, 1629, and 1495 $cm^{-1}$.

*Anal.* $C_6H_{12}N_2OS_2$ (192.30) calc'd.: C 37.48; H 6.29; N 14.57; S 33.34%
found: C 37.26; H 6.31; N 14.50; S 33.18%

*Methyl N-Methyl, N-[2-(methylthiocarbamoyl)ethyl]thiocarbamate (XXI)*

Methyl N-methyl, N-[2-(methylcarbamoyl)ethyl]thiocarbamate (XIII) was converted to a crystalline compound (61%). It crystallized as colourless plates, m.p. 77—78 °C (methylene chloride—ether). UV spectrum: $\lambda_{max}$ 251 nm, log ε 4.36 and $\lambda_{min}$ 223.5 nm, log ε 3.56. IR spectrum: 3226, 3067, 2924, 1653, and 1502 $cm^{-1}$.

*Anal.* $C_7H_{14}N_2OS_2$ (206.32) calc'd.: C 40.75; H 6.84; N 13.58; S 31.08%
found: C 40.95; H 6.78; N 13.86; S 31.11%

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## IZVOD

### Zaustavljene rotacije u derivatima karbamoiletil-tiokarbamata

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Opisana je sinteza metil N-[2-(karbamoil)etil]karbamata i njihovih tio-analogona. NMR-spektri tio-karbamata otkrivaju zaustavljene rotacije oko C—N vezova i odjeljivanje dvaju geometrijskih izomera.


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