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# STUDIES OF ACYL AND THIOACYL ISOCYANATES—XI[1]

## THE REACTIONS OF BENZOYL AND THIOBENZOYL ISOCYANATES WITH 2-THIAZOLINES AND 2-OXAZOLINES*

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**Abstract** - Thiobenzoyl isocyanate adds to 2-thiazoline and its 2-methyl derivative to afford the corresponding (4 + 2) cycloadducts. Reaction of benzoyl isocyanate with 2-methylthiazoline gives 2,3-dihydro-5-phenyl-8-benzoylcarbamoylthiazolo[3,2-c]pyrimidin-7-one. Thiobenzoyl isocyanate reacts with 2-methyl-2-thiazoline and -2-oxazoline at 90° to form the corresponding 8-thiobenzoylcarbamoylthiazolo- and -oxazolo[3,2-c]pyrimidin-7-ones, while reaction of benzoyl isocyanate with 2-methyloxazoline affords a 2:1 adduct, which with acetic acid gives the corresponding oxazolo[3,2-c]pyrimidine. Benzoyl isocyanate reacts with 2-ethyl-2-thiazoline to afford 2,3-dihydro-6-benzoyl-8-methylthiazolo[3,2-c]pyrimidine-5,7-dione and 2,3-dihydro-5-phenyl-8-methylthiazolo[3,2-c]pyrimidin-7-one; their acid and alkaline hydrolyses are described. Formation of these products is shown to proceed *via* attack of both isocyanates on the β-carbon of the tautomeric enamines of 2-alkyl-2-thiazoline and -2-oxazoline.

RECENTLY WE REPORTED the cycloaddition reactions of benzoyl (**1**) and thiobenzoyl isocyanates (**2**) with anils,[2] carbodiimides[3] and benzaldazines.[4] The reactivity of **2** in 1,4-cycloaddition to C=N bonds is somewhat higher than that of **1**; with benzaldazines, **1** gives criss-cross cycloadducts, while (4 + 2) cycloadducts are formed with **2**.

A few studies concerning the cycloadditions to 2-thiazolines and 2-oxazolines have been reported; reaction of diphenylketene with thiazolines and oxazolines gave the 2:1 cycloadducts,[5] while epoxide reacted with the oxazoline to afford the 1:1 cycloadduct.[6] On the other hand, the reaction of phenyl isocyanate with the thiazolines and oxazolines did not give any cycloadducts, instead bis-addition products were obtained.[7] Our interest in the reactions of acyl isocayanate with compounds


having a C=N bond prompted us to investigate the behaviour of both isocyanates **1** and **2** toward cyclic C=N bonds. The present paper describes the reactions of **1** and **2** with 2-alkyl-2-thiazolines (**3**) and -oxazolines (**4**).

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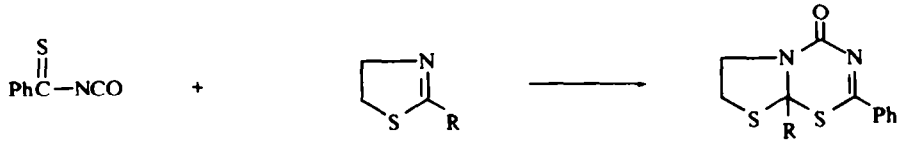
## RESULTS AND DISCUSSION

While benzoyl isocyanate (**1**) does not react with 2-thiazoline (**3a**) under a variety of conditions, thiobenzoyl isocyanate (**2**) reacted easily with **3a** at −70° to afford a 1:1 adduct, whose structure was confirmed to be that of the (4 + 2) cycloadduct **5a** by spectral data. Reaction of **2** with 2-methyl-2-thiazoline (**3b**) gave different products depending on reaction temperature. At room temperature, **2** added to **3b** to give the corresponding (4 + 2) cycloadduct **5b**.



**2** **3** **5**

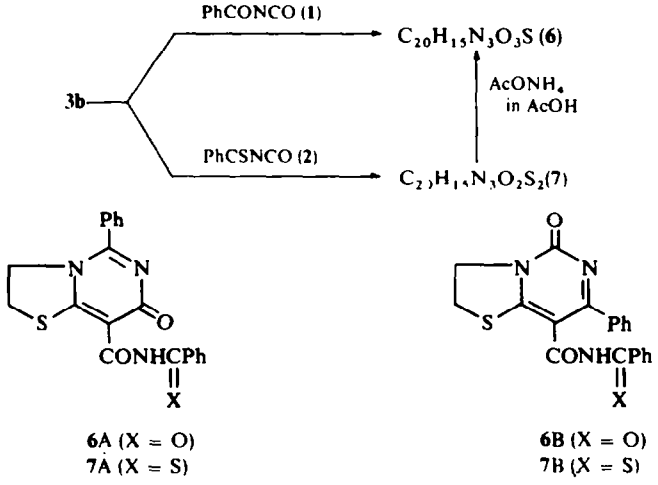
a: R = H
b: R = Me

a: R = H
b: R = Me

Isocyanate **1** reacted with **3b** at room temperature to afford a novel product (**6**) whose molecular formula corresponds to that of a 2:1 adduct with loss of water. As mentioned above, **2** reacted with **3b** at room temperature to form the (4 + 2) cycloadduct **5b**, while at 90–95° a product (**7**) corresponding to a 2:1 adduct with elimination of hydrogen sulfide, was obtained in a low yield.

The IR spectra of **6** and **7** are very similar. Treatment of **7** with $NH_4OAc$ in AcOH yielded **6**, indicating that **6** and **7** have the same ring structure. On the basis of their spectral data and the mode of formation of **6** and **7**, either of two isomers, **6A**, **7A** and **6B**, **7B**, is thought possible for the structures of **6** and **7** respectively (Scheme 1).

Although the spectral data did not present a clear assignment as to which types of structures (A or B) would be more reasonable for **6** and **7**, the results of hydrolytic studies showed **6** and **7** to be 2,3-dihydro-5-phenyl-8-benzoylcarbamoyl- (**6A**) and -8-thiobenzoylcarbamoylthiazolo[3,2-c]pyrimidin-7-one (**7A**).



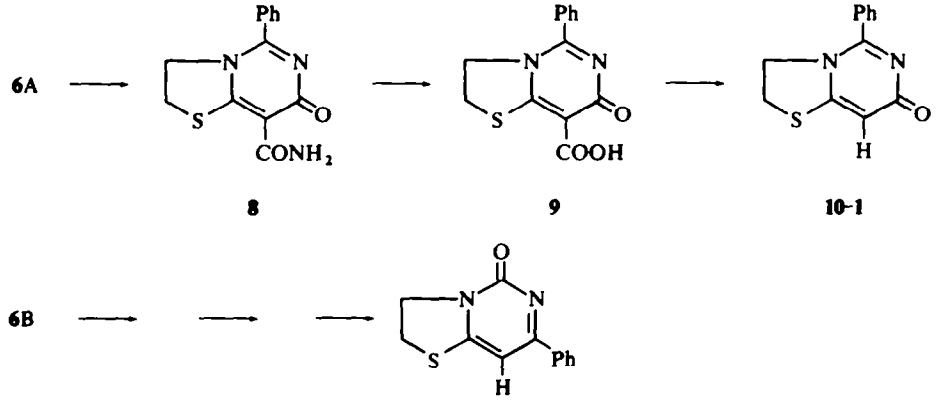

**6A** (X = O)
**7A** (X = S)

**6B** (X = O)
**7B** (X = S)

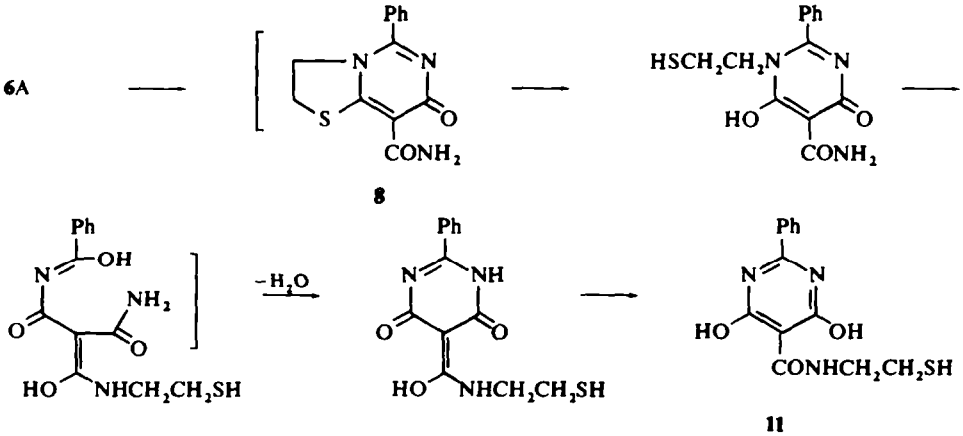
SCHEME 1

Mild hydrolysis of **6** with HCl gave the corresponding carbamoyl derivative (**8**), which on further treatment with acid afforded carboxylic acid **9**. The latter was also obtained directly by the hydrolysis of **6** under forcing conditions. Heating **9** with copper powder in N,N-dimethylaniline gave the decarboxylated product (**10**) in excellent yield. For compound **10**, two structures are possible: one (**10–1**) arising from **6A** and the other (**10–2**) from **6B** (Scheme 2).

The carbonyl band of the (4 + 2) cycloadducts of **1** and **2** (to C=N bonds) appear at 1670–1700 $cm^{-1}$,[2–4] while that of β-amino-α,β-unsaturated ketones appears at 1600–1625 $cm^{-1}$.[8] The IR spectrum of **10** showed the characteristic band at 1615 $cm^{-1}$: which suggests the presence of a β-amino-α,β-unsaturated ketone. Consequently, it seems reasonable to assume that the initial compounds and the degradation products are the corresponding thiazolo[3,2-c]pyrimidin-7-ones **6A**, **7A**, **8**, **9** and **10–1**.



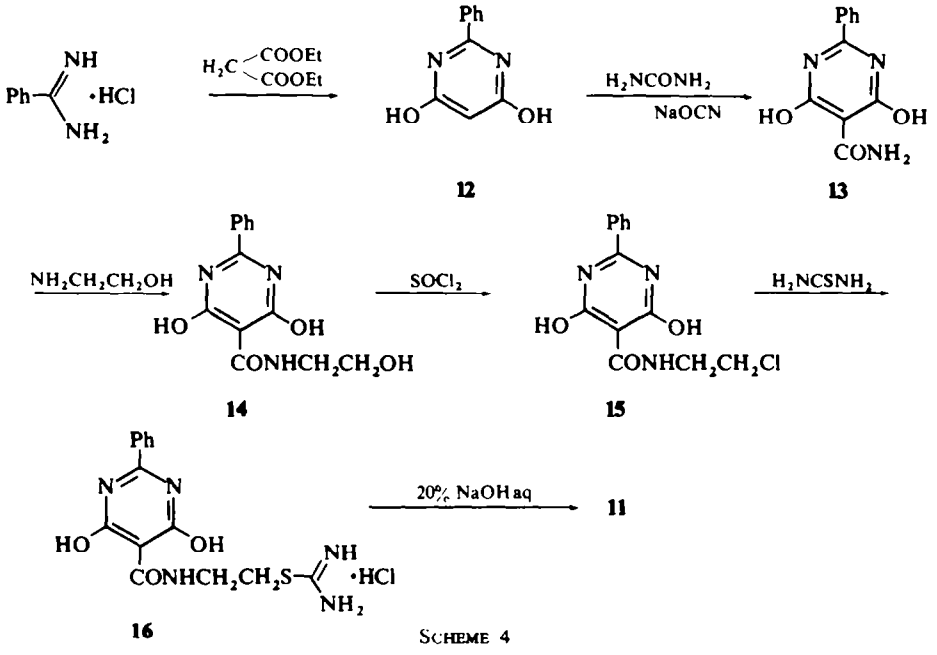

Furthermore, the structure of **6** was more clearly established by alkaline hydrolysis. Treatment of **6** with 20% KOHaq gave 2-phenyl-4,6-dihydroxy-5-β-mercaptoethylcarbamoylpyrimidine (**11**), whose structure was established by spectral data and




SCHEME 3

identification with an authentic sample prepared by the method described below. Although the exact pathway for the formation of **11** is not clear, it can be viewed as arising by initial formation of amide **8**, followed by dihydrothiazole- and pyrimidine-ring openings and subsequent dehydrative ring closure (Scheme 3).*

The pyrimidine **11** was prepared as shown in Scheme 4. 2-Phenyl-4,6-dihydroxypyrimidine (**12**)[9] obtained from benzamidine hydrochloride and diethyl malonate, reacted with urea in the presence of sodium cyanate, by the application of Buděšinský's method,[10] to yield 2-phenyl-5-carbamoyl-4,6-dihydroxypyrimidine (**13**). Reaction of **13** with ethanolamine afforded hydroxyethylcarbamoyl derivative

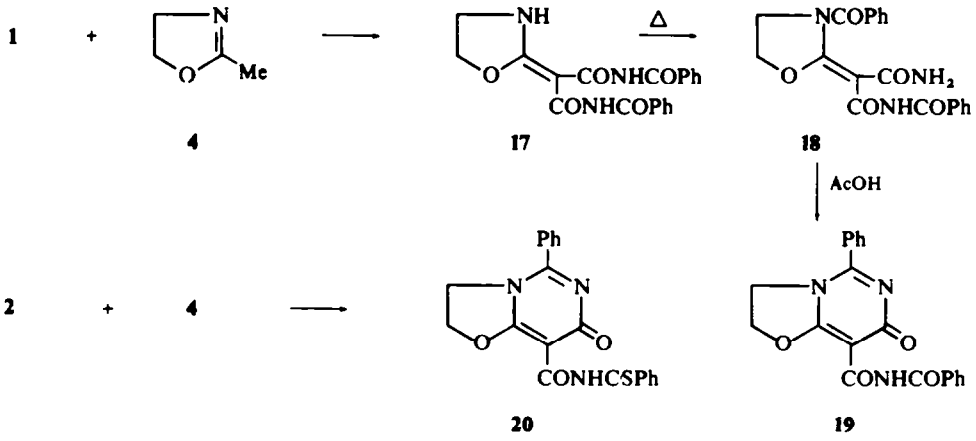



SCHEME 4

**14**, which on treatment with $SOCl_2$ was transformed to the chloroethylcarbamoyl compound **15**. In the final step, the expected pyrimidine (**11**) was obtained by reaction of **15** with thiourea, followed by the treatment with 20% NaOH aq. The structures of pyrimidines **13**–**15** shown in Scheme 4 were confirmed by their spectral data and microanalyses.

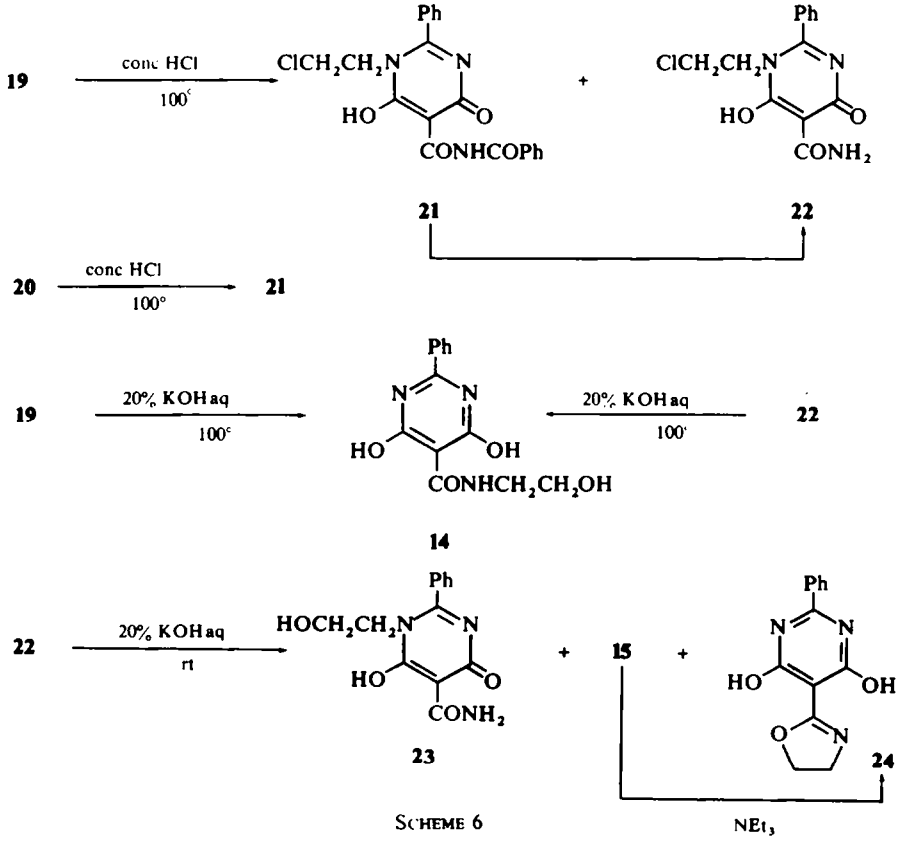
Similarly, reactions of **1** and **2** with 2-methyl-2-oxazoline (**4**) were investigated. Isocyanate **1** reacted with **4** at room temperature to give a thermally unstable 2:1 adduct whose structure was tentatively assumed to be 2-bis(benzoylcarbamoyl)-methyleneoxazolidine (**17**) by its IR spectral data. When a benzene or acetone solution of **17** was refluxed, **17** was transformed into isomer **18**, which on treatment with AcOH was converted into the oxazolo[3,2-c]pyrimidin-7-one **19**. On the other hand, **2** reacted with **4** at 90° to form directly the oxazolo[3,2-c]pyrimidin-7-one **20** in a low yield (Scheme 5). The structures of **19** and **20** were confirmed by their spectral data and chemical conversions.

* 2,4-Dihydroxy-6-phenyl-5-β-mercaptoethylcarbamoylpyrimidine would be expected to form by the hydrolysis of **6B**



SCHEME 5

Under acidic conditions, **19** behaved differently from its thiazole analogue **6**. Hydrolysis of **19** with HCl gave two products, 1-chloroethyl-5-benzoylcarbamoylpyrimidine (**21**) and 1-chloroethyl-5-carbamoylpyrimidine (**22**). Compound **22** was obtained on further treatment of **21** with HCl in a good yield; similarly, **20** was also hydrolyzed to **21**. This indicates that both products **19** and **20** have the same ring structure (Scheme 6).

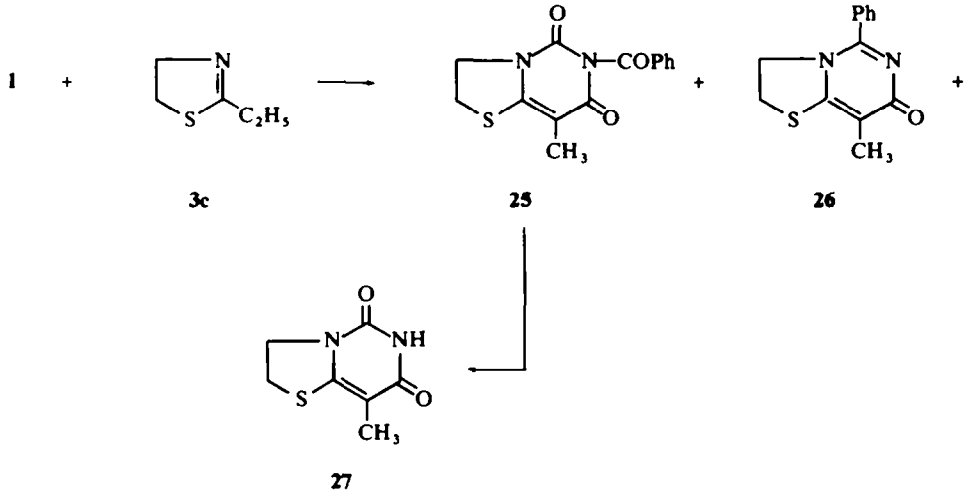


SCHEME 6

Alkaline hydrolysis of **19** was similar to that of **6** as shown in Scheme 6, and gave the hydroxyethylpyrimidine compound (**14**), which was also obtained by treatment of **22** with 20% KOHaq at 100°. However, on alkaline hydrolysis at room temperature, **22** afforded 5-chloroethylcarbamoylpyrimidine (**15**), 1-hydroxyethyl-5-carbamoylpyrimidine (**23**) and 5-oxazolinylpyrimidine compound (**24**). Compound **24** was also obtained by the treatment of **15** with $Et_3N$. Compounds **21–24** were identified by their spectral data and microanalyses.

In order to compare these novel reactions of **1** with **3b** and **4**, the reaction with 2-ethyl-2-thiazoline (**3c**) was investigated. At room temperature, three products were formed (Scheme 7). Spectral data and microanalysis of the main product proved it to be 2,3-dihydro-6-benzoyl-8-methylthiazolo[3,2-c]pyrimidine-5,7-dione (**25**), whose structure corresponds to the compound derived from a 2:1 adduct with elimination of benzamide.

The other products were 2,3-dihydro-5-phenyl-8-methylthiazolo[3,2-c]pyrimidin-7-one (**26**) and 2,3-dihydro-6H-8-methylthiazolo[3,2-c]pyrimidine-5,7-dione (**27**). The former (**26**) corresponds to a 1:1 adduct with dehydration, and the latter (**27**)



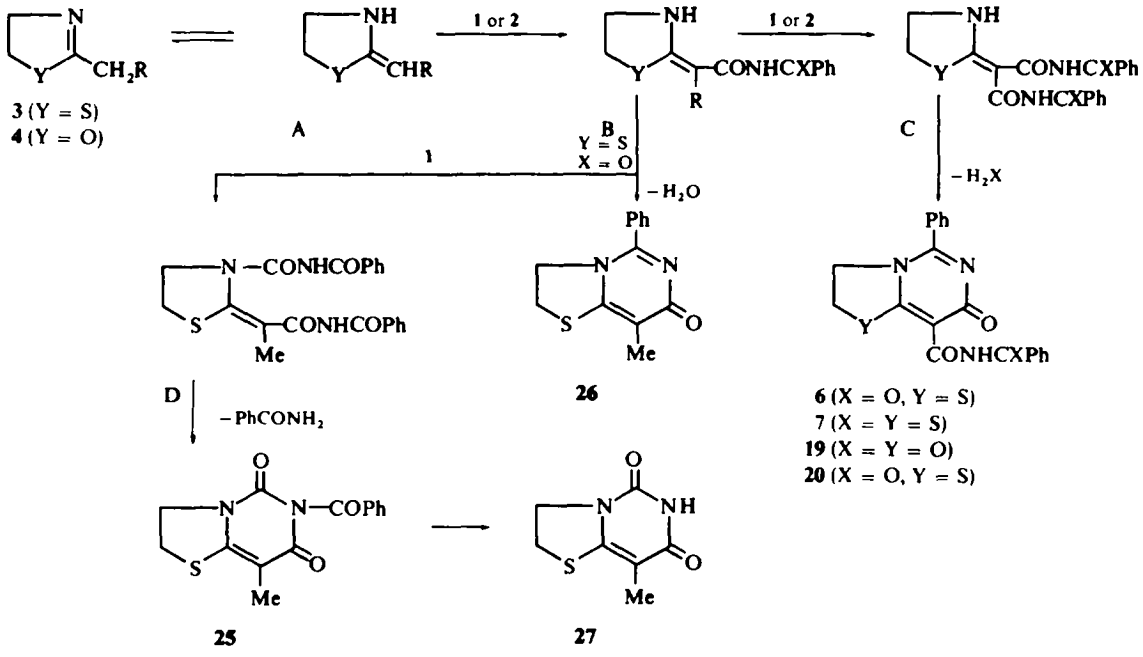

SCHEME 7

to the hydrolyzed product of **25**. In fact, **25** gave an excellent yield of **27** by HCl hydrolysis. Compounds **26** and **27** were identified by their spectral data.

From the structures of the products mentioned above, it is evident that, in the reaction with isocyanates **1** and **2**, 2-alkyl-2-thiazolines (**3b**, **3c**) and 2-methyl-2-oxazoline (**4**) behave as their tautomeric enamines* (Scheme 8).

The formation of novel products **6**, **7**, **19** and **20** from the reactions of isocyanates with 2-methyl derivatives **3b** and **4** can be understood by initial attack of the isocyanate on the β-carbon atom of the tautomeric enamine A to yield the 1:1 adduct B.

* The structures of tautomeric enamines of **3** and **4** could not be recognized by the NMR spectroscopic measurements at various temperatures.




SCHEME 8

This is followed by a second addition of isocyanate to form the 2:1 adduct C. Subsequent cyclization of C with elimination of water or hydrogen sulfide leads to the novel products **6**, **7**, **19** and **20**.

On the other hand, since the 1:1 adduct B (R = Me) formed from **1** and 2-ethyl derivative **3c** does not possess a hydrogen atom on the β-carbon atom, **1** reacts preferentially with the ring NH to give the 2:1 adduct D, followed by ring closure and the elimination of benzamide to give **25**. The formation of **26** can be also understood by the ring closure from the 1:1 adduct B with loss of water.

## EXPERIMENTAL

All m.ps are uncorrected. IR spectra were measured as KBr pellets on a Nippon Bunko IR-S spectrophotometer and the mass spectra were obtained on a Hitachi RMS-4 mass spectrometer with a direct inlet (ionization energy 70 eV). NMR spectra were determined at 60 MHz with a Hitachi R-20 NMR spectrometer with TMS as the internal reference and the microanalyses were performed by Miss M. Akita of our laboratory.

Benzoyl isocyanate (**1**) was prepared by the method of Speziale *et al.*,[11] b.p. 100°/24 mm, m.p. 28–29°, $\nu_{NCO}$ 2270 $cm^{-1}$; (lit.,[11] b.p. 98°/23 mm, m.p. 25·5–26°, $\nu_{NCO}$ (in $CHCl_3$) 2225 $cm^{-1}$). Thiobenzoyl isocyanate (**2**): a solution of 1·0 g of 2-phenylthiazoline-2,4-dione[12] in 10 ml of xylene was heated at 120°, producing a reddish violet solution of **2**, which was used *in situ*. This solution is referred to as the standard solution of **2**. 2-Thiazolines were prepared from the corresponding β-N-acylaminoethanol and $P_2S_5$, and purified by several distillations. 2-Thiazoline (**3a**), b.p. 138–140° (lit.[13] b.p. 139–140°), 2-methyl- (**3b**), b.p. 141–143° (lit.[13] b.p. 144°), and 2-ethyl-2-thiazoline (**3c**), b.p. 162° (lit.[13] b.p. 162°). 2-Methyl-2-oxazoline (**4**) was prepared by heating of β-N-acetylaminoethanol, b.p. 108–110° (lit.,[13] b.p. 110–111°).

*Reaction of* **2** *with* **3a**. To a solution of **2** in xylene (10 ml) (prepared from 1·6 g of 2-phenylthiazoline-2,4-dione) was added a solution of 0·9 g of **3a** in xylene (10 ml) at −70° (dry ice–acetone bath); crystals

were formed immediately. Filtration gave 1·5 g (65%) of 6,7-dihydro-2-phenylthiazolo-[2,3-b]-1,3,5-thiadiazin-4(8aH)-one (**5a**), pale yellow prisms from benzene, m.p. 140–141° dec. (Found: C, 53·04; H, 3·95; N, 11·11. Calc. for $C_{11}H_{10}N_2OS_2$: C, 52·80; H, 4·03; N, 11·20%). IR $cm^{-1}$: $\nu_{CO}$ 1695.

*Reaction of* **2** *with* **3b** (i) The standard solution of **2** was stirred with 0·6 g of **3b** at room temp for 25 hr. The mixture was evaporated *in vacuo* to leave a viscous oily substance, which solidified on standing overnight. The colourless solid (0·92 g, 67%) of 6,7-dihydro-2-phenyl-8a-methylthiazolo[2,3-b]-1,3,5-thiadiazin-4-one (**5b**) was washed with benzene and ether, m.p. 90–91·5° dec. (Found: C, 54·83; H, 4·42; N, 10·51. Calc. for $C_{12}H_{12}N_2OS_2$: C, 54·54; H, 4·58; N, 10·61%). IR $cm^{-1}$: $\nu_{CO}$ 1660, NMR ($CDCl_3$) $\delta$ ppm: 1·96 (3H, s, C<u>H</u>$_3$), 3·77, 4·63 (each 2H, m, C<u>H</u>$_2$), 7·6 (5H, m, aromatic protons).

(ii) The same reaction was carried out at 90–95° for 4 hr. After cooling, red crystals were filtered, which on recrystallization from $CHCl_3$ afforded 0·17 g (17%) of 2,3-dihydro-5-phenyl-8-thiobenzoylcarbamoylthiazolo[3,2-c]pyrimidin-7-one (**7**), m.p. 223·5 224° dec, as red prisms. (Found: C, 61·04; H, 3·73; N, 10·47. Calc. for $C_{20}H_{15}N_3O_2S_2$: C, 61·07; H, 3·84; N, 10·68%). IR $cm^{-1}$: $\nu_{NH}$ 3200, $\nu_{CO}$ 1690. NMR (TFA) $\delta$: 3·58, 4·75 (each 2H, dd, C<u>H</u>$_2$), 7·76 (10H, m, aromatic protons), 12·74 (1H, broad, N<u>H</u>).

*Reaction of* **1** *with* **3b**. A solution of 1·0 g of **1** and 0·7 g of **3b** in dry benzene (10 ml) was stirred at room temp for 2 hr, and colourless crystals were filtered. Recrystallization from AcOH afforded 0·8 g (66%) of 2,3-dihydro-5-phenyl-8-benzoylcarbamoylthiazolo[3,2-c]pyrimidin-7-one (**6**), m.p. 281° dec, as colourless prisms. (Found: C, 63·79; H, 3·86; N, 11·12. Calc. for $C_{20}H_{15}N_3O_3S$: C, 63·66; H, 4·01. N, 11·14%). IR $cm^{-1}$: $\nu_{NH}$ 3200, $\nu_{CO}$ 1720. NMR (TFA) $\delta$: 3·65, 4·85 (each 2H, dd, C<u>H</u>$_2$), 1·82 (10H, m, aromatic protons), 12·75 (1H, broad, N<u>H</u>).

To a solution of 0·1 g of **7** in 30 ml of AcOH was gradually added 2·0 g of $(NH_4)_2CO_3$. The mixture was refluxed for 2 hr, cooled and poured into water to precipitate a solid, which on recrystallization from AcOH gave 70 mg (73%) of **6**.

2,3-*Dihydro-5-phenyl-8-carbamoylthiazolo*[3,2-c]*pyrimidin-7-one* (**8**). A solution of 1·7 g of **6** in 30 ml of AcOH was heated with 30 ml of conc. HCl at 100° for 1 hr, and then the mixture was evaporated *in vacuo* to leave a viscous oily substance, which solidified on trituration with EtOH aq Filtration gave 0·67 g (54%) of **8**, which on recrystallization from MeOH afforded colourless prisms, m.p. 296–297° dec. (Found: C, 57·17; H, 3·97; N, 15·28. Calc. for $C_{13}H_{11}N_3O_2S$: C, 57·14; H, 4·06; N, 15·38%). IR $cm^{-1}$: $\nu_{NH}$ 3320, 3170; $\nu_{CO}$ 1665.

2,3-*Dihydro-5-phenyl-8-carboxythiazolo*[3,2-c]*pyrimidin-7-one* (**9**). A solution of 0·8 g of **6** in 30 ml of conc. HCl was heated at 100° for 11 hr, and then evaporated *in vacuo* to leave a residue, which was washed with benzene. From the benzene washings, a small amount of benzoic acid was obtained. Recrystallization of the benzene insoluble solid from EtOH afforded 0·4 g (73%) of **9**, m.p 236·5–237°, as colourless prisms. (Found: C, 56·83; H, 3·96; N, 10·06. Calc. for $C_{13}H_{10}N_2O_3S$ C, 56·93; H, 3·68; N, 10·22%). IR $cm^{-1}$: $\nu_{OH}$ 3400–2400; $\nu_{CO}$ 1720. NMR (TFA) $\delta$: 3·83, 5·02 (each 2H, dd, C<u>H</u>$_2$), 7·96 (5H, m, aromatic protons). Mass spectrum *m/e*: 274 ($M^+$), 273 ($M^+$–H), 230 ($M^+$–$CO_2$).

2,3-*Dihydro-5-phenylthiazolo*[3,2-c]*pyrimidin-7-one* (**10**). A solution of 0·8 g of **9** in 6 ml of N,N-dimethylaniline was heated with 0·8 g of copper powder under reflux for 10 hr. The mixture was filtered to remove copper and steam distilled to remove N,N-dimethylaniline; a brown resinous material was left which gave colourless crystals from EtOH (charcoal). Recrystallization from benzene afforded 0·53 g (91%) of **10**, m.p. 208–209° dec, as colourless prisms. (Found: C, 62·89; H, 4·71; N, 11·95. Calc. for $C_{12}H_{10}N_2OS$: C, 62·69; H, 4·38; N, 12·17%). IR $cm^{-1}$: $\nu_{CO}$ 1615. NMR (TFA) $\delta$: 3·73, 4·83 (each 2H, dd, C<u>H</u>$_2$), 6·87 (1H, s, C<u>H</u>=), 7·82 (5H, m, aromatic protons). Mass spectrum *m/e*: 230 ($M^+$), 127 ($M^+$—PhCN, base peak).

*Hydrolysis of* **6** *with aqueous potassium hydroxide*. A suspension of 4·2 g of **6** in 200 ml of 20% KOH aq was heated at 100° for 3·5 hr, giving a clear solution Acidification with HCl precipitated a colourless solid which was recrystallized from benzene giving 1·45 g (47%) of 2-phenyl-4,6-dihydroxy-5-β-mercaptoethylcarbamoylpyrimidine (**11**), m p. 238–238·5° dec, as colourless prisms. (Found: C, 53·78; H, 4·79; N, 14·21. Calc. for $C_{13}H_{13}N_3O_3S$: C, 53·61; H, 4·59; N, 14·43%). NMR $\delta$: ($C_5D_5N$): 2·39 (1H, m, S<u>H</u>), 2·86 (2H, m, C<u>H</u>$_2$), 3·73 (2H, dd, C<u>H</u>$_2$). (TFA): 8·06 (6H, m, aromatic protons), 10·4 (2H, broad, O<u>H</u>). Mass spectrum *m/e*. 291 ($M^+$), 290 ($M^+$ – H), 244 ($M^+$ – $CH_2SH$), 215 ($244^+$ – $CH_2NH$, base peak).

*Preparation of* **11**. (i) 2-Phenyl-5-carbamoyl-4,6-dihydroxypyrimidine (**13**). A mixture of 14 g of 2-phenyl-4,6-dihydroxypyrimidine (**12**),[9] 35 g of urea and 5·0 g of NaNCO was stirred at 150° for 2 hr After cooling to 100°, 100 ml of hot water was added and the resulting solution acidified (HCl) to precipitate colourless crystals, which on recrystallization from AcOH gave 14 g (90%) of **13**, m.p. 315–316° dec, as colourless needles. (Found: C, 57·36; H, 3·68; N, 18·15. Calc. for $C_{11}H_9N_3O_3$: C, 57·14; H, 3·92; N, 18·18%). IR $cm^{-1}$: $\nu_{NH}$ 3440, 3310; $\nu_{CO}$ 1675.

(ii) 2-Phenyl-4,6-dihydroxy-5-β-hydroxyethylcarbamoylpyrimidine (**14**). A solution of 5·0 g of **13** in 25 ml of β-aminoethanol was heated at 180° for 4 hr. After cooling, 100 ml of water was poured into the mixture and the resulting solution acidified with HCl to precipitate colourless crystals. Recrystallization from acetone gave 4·7 g (78%) of **14**, m.p. 249·5° dec, as colourless prisms. (Found: C, 56·84; H, 4·69; N, 15·08. Calc. for $C_{13}H_{13}N_3O_4$: C, 56·72; H, 4·76; N, 15·27%). IR $cm^{-1}$: $\nu_{OH}$ 3500; $\nu_{OH}$ or $\nu_{NH}$ 3270; $\nu_{CO}$ 1645. NMR (TFA) $\delta$: 4·17 (4H, m, C<u>H</u>$_2$), 4·78 (1H, m, O<u>H</u>), 8·07 (6H, m, aromatic protons and N<u>H</u> or O<u>H</u>), 10·23 (2H, broad, O<u>H</u>). Mass spectrum *m/e*: 275 ($M^+$), 245 ($M^+ - CH_2O$), 244 ($M^+ - CH_2OH$), 215 ($244^+ - CH_2NH$, base peak).

(iii) 2-Phenyl-4,6-dihydroxy-5-β-chloroethylcarbamoylpyrimidine (**15**). Four grams of **14** were heated in 25 ml of $SOCl_2$ under reflux for 20 min. After cooling, ether was added to the reaction mixture to precipitate a colourless solid. Recrystallization from benzene afforded 3·8 g (89%) of **15**, m.p. 264·5–265° dec, as colourless prisms. (Found: C, 53·53; H, 4·20; N, 14·08. Calc. for $C_{13}H_{12}N_3O_3Cl$: C, 53·15; H, 4·09; N, 14·31%). IR $cm^{-1}$: $\nu_{NH}$ or $\nu_{OH}$ 3270; $\nu_{CO}$ 1650. NMR (TFA) $\delta$: 3·97 (4H, m, C<u>H</u>$_2$), 8·05 (6H, m, aromatic protons and N<u>H</u> or O<u>H</u>), 10·23 (2H, broad, O<u>H</u>). Mass spectrum *m/e*: 293 ($M^+$), 257 ($M^+ - HCl$), 244 ($M^+ - CH_2Cl$), 227 ($257^+ - C_2H_6$), 215 ($244^+ - CH_2NH$, base peak), 111 ($215^+ - PhCHN$), 104 ($PhC{\equiv}\overset{+}{N}H$).

(iv) 2-Phenyl-4,6-dihydroxy-5-β-mercaptoethylcarbamoylpyrimidine (**11**). A solution of 1·0 g of **15** and 0·26 g of thiourea in 5 ml of pyridine was refluxed for 6 hr. After cooling, filtration gave 0·85 g (68%) of colourless crystals, which on recrystallization from EtOH gave the hydrochloride **16**, m.p. 226–227° dec. A solution of 0·5 g of **16** in 5 ml of 20% NaOH aq was heated at 100° for 1 hr. After cooling, the mixture was acidified with HCl to precipitate a colourless solid, which recrystallized from benzene as 0·23 g (58%) of **11**, m.p. 238–238·5° dec, as colourless prisms.

*Reaction of* **1** *with* **4**. A solution of 1·75 g of **1** and 1·0 g of **4** in 20 ml of dry ether was stirred at room temp for 3 hr, during which time colourless crystals were formed. Filtration gave 1·59 g (58%) of 2-bis(benzoylcarbamoyl)methyleneoxazolidine (**17**), m.p. 163–168° dec. (Found: C, 63·19; H, 5·12; N, 11·53. Calc. for $C_{20}H_{17}N_3O_5$: C, 63·32; H, 4·52; N, 11·08%). IR $cm^{-1}$: $\nu_{NH}$ 3440; $\nu_{CO}$ 1735, 1710, 1680. **17** was easily transformed into 3-benzoyl-2-carbamoyl-benzoylcarbamoylmethyleneoxazolidine (**18**), m.p. 206·5–207° dec, by refluxing in benzene or acetone. Yield, 48%. An analytical sample was prepared by washing with hot $CHCl_3$. (Found: C, 62·94; H, 4·62; N, 10·96. Calc. for $C_{20}H_{17}N_3O_5$: C, 63·32; H, 4·52; N, 11·08%). IR $cm^{-1}$: $\nu_{NH}$ 3440, 3280; $\nu_{CO}$ 1715.

2,3-*Dihydro-5-phenyl-8-benzoylcarbamoyloxazolo*[3,2-c]*pyrimidin-7-one* (**19**). A solution of 1·57 g of **18** in 20 ml of AcOH was stirred at 100° for 20 min. The mixture was evaporated *in vacuo* to leave a residue, which on recrystallization from acetone gave 1·31 g (88%) of **19**, m.p. 247–248° dec, as colourless prisms. (Found: C, 66·69; H, 4·18; N, 11·34. Calc. for $C_{20}H_{15}N_3O_4$: C, 66·47; H, 4·18; N, 11·64%). IR $cm^{-1}$: $\nu_{CO}$ 1740. NMR (TFA) $\delta$: 5·0, 5·43 (each 2H, dd, C<u>H</u>$_2$), 8·02 (10H, m, aromatic protons), 12·56 (1H, broad, N<u>H</u>).

*Reaction of* **2** *with* **4**. The standard solution of **2** was stirred with 0·45 g of **4** at 90° for 1 hr during which time red crystals were formed; recrystallization from acetone gave 0·12 g (10%) of 2,3-dihydro-5-phenyl-8-thiobenzoylcarbamoyloxazolo[3,2-c]pyrimidin-7-one (**20**), m.p. 220·5–221° dec, as red prisms. (Found: C, 63·72; H, 3·78; N, 11·13. Calc. for $C_{20}H_{15}N_3O_3S$: C, 63·66; H, 4·01; N, 11·14%). IR $cm^{-1}$: $\nu_{CO}$ 1720. NMR (DMSO-$d_6$) $\delta$: 4·45, 4·95 (each 2H, dd, C<u>H</u>$_2$), 7·85 (10H, m, aromatic protons), 15·0 (1H, broad, N<u>H</u>).

*Hydrolysis of* **19** *with hydrochloric acid*. A solution of 1·31 g of **19** in 30 ml of conc. HCl was heated at 100° for 10 min. After cooling, filtration gave 0·79 g (55%) of colourless crystals, which on recrystallization from MeOH afforded 1-β-chloroethyl-2-phenyl-5-benzoylcarbamoyl-6-hydroxypyrimidin-4-one (**21**), m.p. 235° dec, as colourless prisms. (Found: C, 60·87; H, 4·41; N, 10·49. Calc. for $C_{20}H_{16}N_3O_4Cl$: C, 60·38; H, 4·03; N, 10·57%). IR $cm^{-1}$: $\nu_{CO}$ 1720. NMR $\delta$: (TFA): 3·95, 4·76 (each 2H, dd, C<u>H</u>$_2$), 7·87 (10H, m, aromatic protons). (DMSO-$d_6$): 13·04, 13·90 (each 1H, broad, N<u>H</u> or O<u>H</u>).

The filtrate was evaporated *in vacuo* to leave a residue, which solidified on trituration with water. Filtration gave 0·24 g (23%) of 1-β-chloroethyl-2-phenyl-5-carbamoyl-6-hydroxypyrimidin-4-one (**22**), which recrystallized from EtOH as colourless prisms, m.p. 201·5–202·5°. (Found: C, 53·42; H, 4·20; N, 13·95. Calc. for $C_{13}H_{12}N_3O_3Cl$: C, 53·15; H, 4·09; N, 14·31%). IR $cm^{-1}$: $\nu_{NH}$ 3300, 3170; $\nu_{CO}$ 1650. NMR ($CDCl_3$) $\delta$: 3·73, 4·47 (each 2H, dd, C<u>H</u>$_2$), 7·57 (5H, s, aromatic protons), 6·08, 10·85, 15·96 (each 1H, broad, N<u>H</u> or O<u>H</u>). Mass spectrum *m/e*: 293 ($M^+$), 276 ($M^+ - OH$), 258 ($M^+ - Cl$), 241 ($276^+ - Cl$, base peak), 214 ($241^+ - C_2H_3$). **22** was also obtained by the treatment of **21** with conc. HCl at 100° for 1 hr. Yield, 94%.

Similarly, 10 mg of **20** was heated with 5 ml of conc. HCl at 100° for 5 min. The mixture was evaporated *in vacuo* to yield 9 mg (90%) of **21**.

*Hydrolysis of* **19** *with aqueous potassium hydroxide.* A suspension of 0·5 g of **19** in 20 ml of 20% KOH aq was stirred at 100° for 30 min, giving a clear solution which was acidified (HCl) to precipitate a colourless solid. Recrystallization from acetone gave 0·18 g (48%) of **14**, m.p. 249·5° dec, as colourless prisms (identical with an authentic sample prepared from **13** and β-aminoethanol).

*Hydrolysis of* **22** *with aqueous potassium hydroxide.* A suspension of 1·0 g of **22** in 10 ml of 20% KOH aq was stirred at room temp for 1·5 hr, giving a clear solution which was acidified (HCl) to precipitate a colourless solid. The solid was filtered and washed with hot benzene to leave 0·14 g (16%) of 2-phenyl-4,6-dihydroxy-5-oxazolinylpyrimidine (**24**), which recrystallized from EtOH as colourless prisms, m.p. 276° dec. (Found: C, 60·68; H, 4·24; N, 16·05. Calc. for $C_{13}H_{11}N_3O_3$: C, 60·69; H, 4·31; N, 16·34%). IR $cm^{-1}$: $\nu_{OH}$ 3200–2900; $\nu_{C=N}$ 1667. Mass spectrum *m/e*: 257 ($M^+$, base peak).

The benzene washings was evaporated *in vacuo* to leave 0·12 g (12%) of crystals, which on recrystallization from benzene gave **15**, m.p. 264·5–265° dec, as colourless prisms.

The filtrate was neutralized with HCl and the solftion evaporated *in vacuo*. The residue was washed with a small amount of water to remove KCl and the residue was recrystallized from MeOH to give 0·45 g (48%) of 1-β-hydroxyethyl-2-phenyl-5-carbamoyl-6-hydroxypyrimidin-4-one (**23**), m.p. 205–206° dec, as colourless prisms. (Found: C, 56·74; H, 4·59; N, 15·00. Calc. for $C_{13}H_{13}N_3O_4$: C, 56·72; H, 4·76; N, 15·27%). IR $cm^{-1}$: $\nu_{OH}$ 3340; $\nu_{NH}$ 3390, 3230; $\nu_{CO}$ 1672, 1638. NMR (TFA) $\delta$: 4·0 (2H, m, C<u>H</u>$_2$), 4·73 (3H, m, C<u>H</u>$_2$ and O<u>H</u>), 7·86 (6H, m, aromatic protons and N<u>H</u> or O<u>H</u>), 9·6, 10·3 (each 1H, broad, N<u>H</u> or O<u>H</u>). **24** was also obtained by reaction of **15** with $Et_3N$: a solution of 50 mg of **15** and 5 drops of $Et_3N$ in 10 ml of MeOH was refluxed for 10 min. The mixture was evaporated *in vacuo* to leave 44 mg (100%) of **24**.

*Reaction of* **1** *with* **3c**. A solution of 2·6 g of **1** and 2·0 g of **3c** in 30 ml of dry benzene was stirred at room temp for 8 hr. The mixture was evaporated *in vacuo* to leave a resinous material, which solidified on trituration with EtOH aq. Filtration gave 0·78 g (31%) of 2,3-dihydro-6-benzoyl-8-methylthiazolo[3,2-c]-pyridimidine-5,7-dione (**25**), which recrystallized from EtOH as colourless prisms, m.p. 162·5°. (Found: C, 58·52; H, 4·22; N, 9·70. Calc. for $C_{14}H_{12}N_2O_3S$: C, 58·33; H, 4·20; N, 9·72%). IR $cm^{-1}$: $\nu_{CO}$ 1740, 1695, 1645. NMR ($CDCl_3$) $\delta$: 1·92 (3H, s, C<u>H</u>$_3$), 3·36, 4·30 (each 2H, dd, C<u>H</u>$_2$), 7·62 (5H, m, aromatic protons). Mass spectrum *m/e*: 288 ($M^+$), 260 ($M^+ - CO$, base peak). The filtrate was evaporated *in vacuo*. The residue was separated into acetone soluble and insoluble parts. The acetone soluble substance was recrystallized from EtOAc to give 0·51 g (12%) of 2,3-dihydro-5-phenyl-8-methylthiazolo[3,2-c]pyrimidin-7-one (**26**), m.p. 165°, as colourless prisms. (Found: C, 63·90; H, 5·14; N, 11·19. Calc. for $C_{13}H_{12}N_2OS$: C, 63·92; H, 4·95; N, 11·47%). IR $cm^{-1}$: $\nu_{CO}$ 1610. NMR ($CDCl_3$) $\delta$: 2·05 (3H, s, C<u>H</u>$_3$), 3·39, 4·39 (each 2H, dd, C<u>H</u>$_2$), 7·48 (5H, m, aromatic protons). Mass spectrum *m/e*: 244 ($M^+$, base peak), 216 ($M^+ - CO$).

Recrystallization of the insoluble substance from acetone gave 80 mg (5%) of 2,3-dihydro-6H-8-methyl-thiazolo[3,2-c]pyrimidine-5,7-dione (**27**), m.p. 305–306° dec, as colourless prisms. (Found: C, 45·91; H, 4·49; N, 15·42. Calc. for $C_7H_8N_2O_2S$: C, 45·65; H, 4·38; N, 15·21%). IR $cm^{-1}$: $\nu_{NH}$ or $\nu_{OH}$ 3150, 3010; $\nu_{CO}$ 1690, 1655. NMR (TFA) $\delta$: 2·08 (3H, s, C<u>H</u>$_3$), 3·62, 4·60 (each 2H, dd, C<u>H</u>$_2$). Mass spectrum *m/e*: 184 ($M^+$, base peak), 141 ($M^+ - HNCO$), 113 ($141^+ - CO$). **27** was also obtained by hydrolysis of **25**: 90 mg of **25** was heated with 10 ml of conc. HCl at 100 for 30 min, and the solution was evaporated *in vacuo* to leave residue, which on recrystallization from EtOH gave 55 mg (95%) of **27**.

## REFERENCES


1 Part X: O. Tsuge and S. Kanemasa, *Bull. Chem. Soc. Japan* **45**, in press (1972)
2 O. Tsuge, M. Tashiro, R. Mizuguchi and S. Kanemasa, *Chem. Pharm. Bull. (Tokyo)* **14**, 1055 (1966); O. Tsuge and S. Kanemasa, *Bull. Chem. Soc. Japan* **45**, in press (1972)
3 O. Tsuge and K. Sakai, *Bull. Chem. Soc. Japan* **45**, 1534 (1972)
4 O. Tsuge and S. Kanemasa, *Ibid.* **45**, in press (1972)
5 R. D. Kimbrough, Jr., *J. Org. Chem.* **29**, 1242 (1964)
6 R. Feinauer and W. Seeliger, *Liebigs Ann. Chem.* **698**, 174 (1966)
7 R. Nehring and W. Seeliger, *Ibid.* **698**, 167 (1966)
8 N. J. Leonard and J. A. Adamcik, *J. Am. Chem. Soc.* **81**, 595 (1959)
9 G. W. Kenner, B. Lythgoe, A. R. Todd and A. Tophan, *J. Chem. Soc.* 388 (1943)
10 Z. Buděšinský and J. Kopecký, *Chem. Listy.* **48**, 1364 (1954)
11 A. J. Speziale and L. R. Smith, *J. Org. Chem.* **27**, 4361 (1962)
12 J. Goerdeler and H. Schenk, *Chem. Ber.* **98**, 2954 (1965)
13 H. Wenker, *J. Am. Chem. Soc.* **57**, 1079 (1935)