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# INTRAMOLECULAR CYCLIZATION OF HYDRAZIDES OF (2-ALKYLTHIO-3,4-DIHYDRO-6-METHYL-4-OXO-3-PYRIMIDINYL)ACETIC ACIDS TO 1,2,3,4-TETRAHYDROPYRIMIDO[2,1-c]-1,2,4-TRIAZINE-3,6-DIONES

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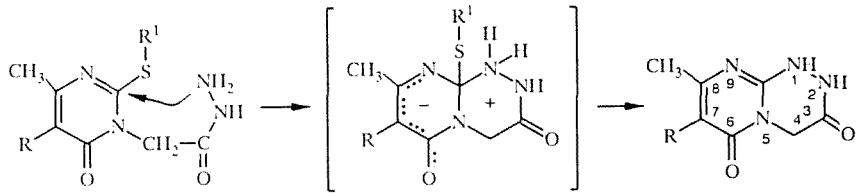
*A method has been developed for the synthesis of 1,2,3,4-tetrahydropyrimido[2,1-c]-1,2,4-triazine-3,6-diones by intramolecular cyclization of hydrazides of (2-alkylthio-3,4-dihydro-6-methyl-4-oxo-3-pyrimidinyl)acetic acids in benzylamine.*

Two methods are known for the preparation of derivatives of pyrimido[2,1-c,d]-1,2,4-triazine. The first method [1] is based on recyclization of thiazolo- or oxazolo[3,2-a]pyrimidin-5-ones, in which, under the action of hydrazine, the azole ring is converted to an azine ring, and pyrimido[2,1-c]-1,2,4-triazines are formed. The second method [2] is based on intramolecular cyclization of 3-(3-chloropropylamino)-6-methyl-1,2,4-triazin-5-one. In the literature available to us, we have not been able to find any information on methods for constructing pyrimido[2,1-c]-1,2,4-triazine on the basis of pyrimidine derivatives.

In view of the high sensitivity of derivatives of (3,4-dihydro-6-methyl-2-methylthio-4-oxo-3-pyrimidinyl)acetic acids to nucleophilic attack at position 2 [3], it appeared likely that hydrazides of these acids (I-III) having a nucleophilic nitrogen atom in the hydrazide fragment, could be used for the synthesis of pyrimido[2,1-c]-1,2,4-triazines (IV-VI).



I–III IV–VI

I,IV R = H; II,V R = $C_2H_5$; III,VI R = $(CH_3)_2CH$; I,II $R^1$ = $CH_3$; III $R^1$ = $C_2H_5$

In the example of the hydrazide I, we tested various conditions for the cyclization (Table 1). Initially, we carried out the reaction by boiling the hydrazide I in DMF. After refluxing for 10 h, the yield of compound IV was only 10%. Thin-layer chromatography established that the initial hydrazide I remained in the reaction mixture. Apparently, the methyl mercaptan that is liberated during the reaction, being a nucleophile, shifts the equilibrium toward the initial hydrazide I. In order to test this hypothesis, we removed the methyl mercaptan from the reaction medium as it was formed, by passing gaseous nitrogen through the reaction mixture. With this modification of the reaction conditions, we were able to bring the yield of IV up to 52%.

On the assumption that a two-stage mechanism of bimolecular nucleophilic substitution may be realized in this reaction [4], we used as basic catalysts various amines, which should have a favorable effect on decomposition of the intermediate [4]. The experiments demonstrated (Table 1) that the highest yield, 63% after 10-h refluxing, was obtained when using a primary

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TABLE 1. Influence of Reaction Conditions on Yield of 8-Methyl-1,2,3,4-tetrahydropyrimido[2,1-c]-1,2,4-triazine-3,6-dione (IV)

| Reaction conditions (and synthesis method) | Yield, % | Reaction conditions (and synthesis method) | Yield, % |
|---|---|---|---|
| DMF, 10-h refluxing (A) | 10 | DMF, morpholine, 10-h refluxing (C) | 35 |
| DMF, 10-h refluxing with nitrogen bubbling (B) | 52 | DMF, triethylamine, 10-h refluxing (C) | 33 |
| DMF, diethylamine, 10-h refluxing (C) | 39 | DMF, benzylamine, 10-h refluxing (C) | 63 |

amine (benzylamine); the yields were much lower when using secondary amines (diethylamine or morpholine) or a tertiary amine (triethylamine). The benzylamine apparently serves not only as a basic catalyst, but also as an acidic catalyst owing to the formation of hydrogen bonds.

In a further search for optimal conditions of heterocyclization of the hydrazides I-III, we found that when these hydrazides are heated in benzylamine in the absence of dimethylformamide at 160°C, 1,2,3,4-tetrahydropyrimido[2,1-c]-1,2,4-triazine-3,6-diones (IV-VI) are formed. Under these conditions, the reaction time is shortened to 10 min, and the yields of compounds IV-VI are 50-68%. With still shorter reaction times, the yields of the desired product are lower. Extending the reaction time beyond 10 min has virtually no effect on the process of forming the desired product.

In the mass spectra of compounds IV-VI, in the region of greatest values of m/z, the peaks at 180, 208, and 222 correspond to the molecular ions.

In contrast to the IR spectra of the hydrazides I-III, in which we found all of the absorption bands that are characteristic for hydrazides of carboxylic acids [5] as well as for stretching vibrations of the lactam group C=O, we found that the only bands manifested clearly in the spectra of compounds IV-VI are the "amide I" band and the band of the lactam group C=O (Table 2).

In the $^1$H NMR spectra of the 1,2,3,4-tetrahydropyrimido[2,1-c]-1,2,4-triazine-3,6-diones (IV-VI) (Table 3), there are none of the signals from protons of alkylthio groups in the 2.43-2.98 ppm region or of primary amino groups in the 4.15-4.19 region that are characteristic for the original hydrazides I-III; we do observe broadened signals of protons of secondary amino groups in the 10.08-10.26 ppm region. Another distinctive feature of the $^1$H NMR spectra of compounds IV-VI in comparison with the original hydrazides I-III is the upfield shift of the signal of N–$CH_2$ group protons by 0.42-0.45 ppm and the upfield shift of the signal of the proton in position 5 of the pyrimidine ring by 0.99 ppm (for compounds I and IV).

Since the 1,2,3,4-tetrahydropyrimido[2,1-c]-1,2,4-triazine-3,6-diones IV-VI are structural analogs of the natural compound fervenulin and since they have reactive functional groups, these compounds themselves may have biological activity, or they may serve as intermediates for the synthesis of biologically active compounds.

## EXPERIMENTAL

The course of the reaction and the purity of the compounds were monitored on Silufol plates. The UV spectra were measured in a Specord UV-Vis spectrometer, in ethanol. The IR spectra were recorded in a Specord IR-75 spectrometer, in a suspension in white mineral oil. The $^1$H NMR spectra were recorded in a Tesla BS-487C instrument (80 MHz) in DMSO-$d_6$, internal standard HMDS. The mass spectra were taken in a Kratos MS-50 spectrometer (70 eV) with direct introduction of the samples into the ion source.

The results of elemental analyses for C, H, and N matched the calculated values.

TABLE 2. Characteristics of Synthesized Compounds I-VI

| Compound | Empirical formula | mp, °C (and solvent) | UV spectrum, $\lambda_{max}$, nm (and log $\varepsilon$) | IR spectrum, $\nu$, $cm^{-1}$ | | | | | | | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | C=O (lactam) | amide-I | amide-II | amide-III | $\delta NH_2$ | $\tau NH_2$ | $\omega NH_2$ | |
| I* | | | | 1660 | 1687 | 1528 | 1276 | 1624 | 1105 | 1005 | |
| II | $C_{10}H_{16}N_4O_2S$ | 225-227 (ethanol) | 225 p., 242 (3,83), 294 (4,04) | 1650 | 1664 | 1544 | 1256 | 1626 | 1075 | 1005 | 73 |
| III | $C_{12}H_{20}N_4O_2S$ | 147-149 (ethanol) | 225 p., 242 (3,84), 295 (4,06) | 1664 | 1688 | 1536 | 1272 | 1624 | 1100 | 1000 | 65 |
| IV | $C_7H_8N_4O_2$ | 334-336 d. (water) | 212 (3,95), 289 (3,95) | 1644 | 1666 | | | | | | 68 |
| V | $C_9H_{12}N_4O_2$ | 279-281 d. (water) | 221 (3,98), 293 (4,03) | 1636 | 1668 | | | | | | 60 |
| VI | $C_{10}H_{14}N_4O_2$ | 263-265 d. (water) | 222 (3,82), 294 (3,90) | 1648 | 1672 | | | | | | 50 |

*Data on compound I were reported in [3].

TABLE 3. $^1H$ NMR Spectra of Compounds II-VI in DMSO-$d_6$

| Compound | Chemical shifts, δ, ppm | | | | | |
|---|---|---|---|---|---|---|
| | $CH_3$ (3H, s) | R | $R^1$ | $NCH_2$ (2H, s) | NH | $NH_2$ (2H, s) |
| II | 2,15 | 2,25 (2H, m, $CH_2$), 0,91 (3H, t, $J$ = 7 Hz, $CH_3$) | 2,44 (3H, s, $SCH_3$) | 4,51 | 9,15 (1H, s) | 4,15 |
| III | 2,18 | 2,98 (1H, m, CH), 1,16 (6H, m, $CH_3$) | 2,98 (2H, m, $CH_2$), 1,16 (3H, m, CH) | 4,43 | 9,18 (1H, s) | 4,19 |
| IV | 1,95 | 4,96 (1H, s, CH) | | 4,06 | 10,26 (2H, s) | |
| V | 1,93 | 2,10 (2H, q, $J$ = 7 Hz, $CH_2$), 0,85 (3H, t, $J$ = 7 Hz, $CH_3$) | | 4,06 | 10,09 (2H, s) | |
| VI | 1,94 | 2,64 (1H, q, $J$ = 7 Hz, CH), 1,06 (6H, d, $J$ = 7 Hz, $CH_3$) | | 4,01 | 10,08 (2H, s) | |

The hydrazides of (5-alkyl-2-alkylthio-3,4-dihydro-6-methyl-4-oxo-3-pyrimidinyl)acetic acids (II, III) were synthesized in the same manner as the hydrazide of (3,4-dihydro-6-methyl-2-methylthio-4-oxo-3-pyrimidinyl)acetic acid (I) [3]. The characteristics of compounds II and III are listed in Tables 2 and 3.

**8-Methyl-1,2,3,4-tetrahydropyrimido[2,1-c]-1,2,4-triazine-3,6-dione (IV). A.** A solution of 1 g (0.0044 mole) of the hydrazide I in 3 ml of dimethylformamide was refluxed for 10 h. After cooling, the precipitate was filtered off and recrystallized.

**B.** A solution of 1 g (0.0044 mole) of the hydrazide I in 3 ml of dimethylformamide was refluxed for 10 h while bubbling gaseous nitrogen through the reaction mixture.

**C.** A solution of 1 g (0.0044 mole) of the hydrazide I and 0.0088 mole of the appropriate amine, in 3 ml of DMF, was refluxed for 10 h.

The yields of compound IV that were obtained using methods A, B, and C, are listed in Table 1.

**1,2,3,4-Tetrahydropyrimido[2,1-c]-1,2,4-triazine-3,6-diones (IV-VI).** A mixture of 0.0044 mole of a hydrazide I-III and 1 ml of benzylamine was heated for 10 min in an oil bath at 160°C and then cooled to 80°C; 5 ml of absolute ethanol was added, and the mixture was refluxed for 5 min and cooled. The precipitate was filtered off, washed with absolute ethanol, and recrystallized.

The characteristics of compounds IV-VI are listed in Tables 2 and 3.

## REFERENCES


1. D. W. Dunwell and D. Evans, J. Chem. Soc. C, No. 9, 1615 (1971).
2. Gy. Hornyak, K. Lempert, and K. Zauer, Acta Chim. Acad. Sci. Hung., **61**, 81 (1969).
3. P. Vainilavichyus, V. Syadyaryavichyute, and S. Motsishkite, Khim. Geterotsikl. Soedin., No. 12, 1655 (1992).
4. V. P. Mamaev, O. A. Zagulyaeva, and S. M. Shein, Khim. Geterotsikl. Soedin., No. 6, 723 (1973).
5. V. P. Sinditskii, M. D. Dutov, and A. E. Fogel'zang, Khim. Geterotsikl. Soedin., No. 1, 72 (1991).