Synthesis of 1,3,4-Thiadiazolo[3,2-*a*]pyrimidin-5-one and Isomeric 7-one Derivatives

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Continuing preceeding studies, designed to obtain derivatives of 1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one and of the isomeric 7-one of pharmacological interest, some of the above mentioned compounds were prepared. Their structural identification was obtained by mass spectra.

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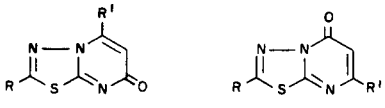
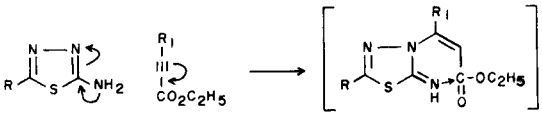
The thiadiazolopyrimidine nucleus and its substituted products, as well as a number of other substances belonging to the pseudopurine class are reported to have interesting biological properties [1-9]. With the aim of extending our research on 1,3,4-thiadiazolo derivatives of pharmacological interest, we synthesized some derivatives of thiadiazolopyrimidine corresponding to the general formulas A and B. Various methods for obtaining this class of compounds have been reported [10-15] and recent studies have emphasized that the reaction of various heterocyclic nitrogens, carrying an α-amino group, with acetylenic compounds can generate both isomers of general formulas A and B [16,17].



A B

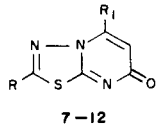
In our case, compounds of type A **7-12** were prepared by reacting 5-substituted-2-amino-1,3,4-thiadiazoles **1-4** respectively with ethyl propiolate **5** or with ethyl phenylpropiolate **6** (Scheme 1), whereas 1,3,4-thiadiazolo[3,2-*a*]-

Scheme 1



1-4 **5-6**

1, R = CH_3 **4**, R = C_6H_5
2, R = C_2H_5 **5**, R_1 = H
3, R = CF_3 **6** R_1 = C_6H_5

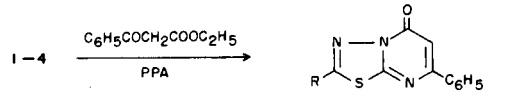


7-12

7, R = CH_3, R_1 = H
8, R = C_2H_5, R_1 = H
9, R = CF_3, R_1 = H
10, R = C_6H_5, R_1 = H
11, R = CF_3, R_1 = C_6H_5
12, R = R_1 = C_6H_5

pyrimidin-5-one isomers, compounds of type B, **13-16** were obtained by reacting compounds **1-4** with ethyl benzoylacetate in heated PPA (Scheme 2).

Scheme 2



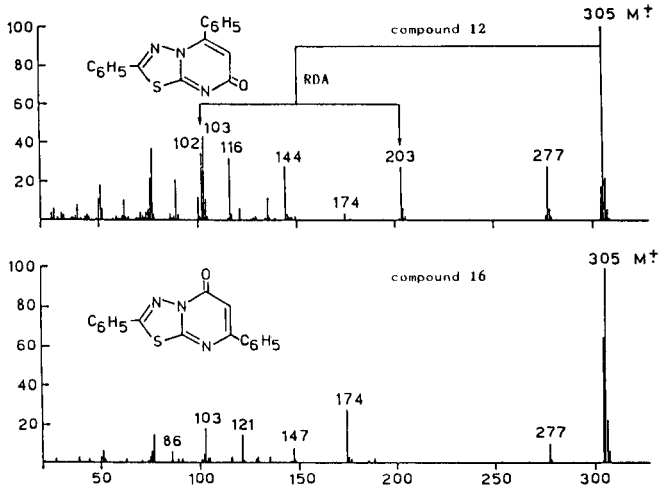
13-16

13, R = CH_3 **15**, R = CF_3
14, R = C_2H_5 **16**, R = C_6H_5

Considering that these reactions could yield both 7-one and 5-one derivatives and because the spectral data uv, ir and ^{1}H-nmr did not always allow us to distinguish between the two isomers, it seemed interesting to undertake an investigation of the ms electron impact behaviour of the synthesized substances **7-16**. The detailed mass spectrometric investigation given by us in a previous paper [18], allowed us to point out that the compounds investigated were stable enough to electron impact and that ring contraction reactions are characteristic of these structures. In fact, a diagnostic retro Diels-Alder process (RDA) has been noticed by us only in the 7-one derivatives **7-12**, while this fragmentation does not occur in the isomeric 5-one derivatives **13-16**, since in these structures the pyrimidine moiety of the molecule contains two conjugated bonds, thus allowing the unequivocal assignment of the structure. This behaviour is illustrated in Figure 1 in which the mass spectra of **12** and of isomeric derivative 5-one **16** are compared.

It can be seen that compound 2,5-diphenyl-7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one (**12**) gives intense ions at m/z 203 and m/z 102 originating from the RDA process; instead these ions are completely absent in isomeric 2,7-diphenyl-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (**16**). Moreover the ir spectrum of thiadiazolopyrimidine derivatives **7-12** (compounds of type A) exhibits an intense absorption at 1660-1630 cm^{-1} due to the carbonyl group. This band is shifted in compounds of type **13-16** to higher frequency.

Figure 1



EXPERIMENTAL

Melting points were determined on a Büchi 510 apparatus and are uncorrected. Elemental analyses were performed on a Carlo Erba 1006 elemental analyzer. The ir spectra were recorded using a Perkin-Elmer 281 Spectrophotometer for potassium bromide mulls. The ^{1}H-nmr spectra were recorded in deuteriochloroform on a Bruker WP-80 spectrometer operating at 80 MHz. Chemical shifts are reported in ppm from TMS as an internal standard and are given in units δ. Mass spectra are run on a Jeol JMS 015G-2 double focusing mass spectrometer with a 10 KV accelerating voltage and 75 eV electronic beam energy.

General Procedure for the Reaction of 5-Substituted-2-amino-1,3,4-thiadiazoles with Ethyl Propiolate, **7-10** or With Ethyl Phenylpropiolate, **11**, **12**.

A solution of 5-substituted-2-amino-1,3,4-thiadiazole **1-4** (0.01 mole) and ethyl propiolate (**5**) or ethyl phenylpropiolate (**6**) (0.01 mole) in 40 ml of absolute ethanol was refluxed for 14 hours. In most cases, after cooling the precipitate was filtered and crystallized from appropriate solvent. If the product did not precipitate, the solution was concentrated and allowed to stand overnight. The precipitate was crystallized from ethanol. Analytical data and the characteristics of the products **7-12** are reported in Table I and Table II.

Synthesis of 2-Alkyl and Aryl-7-phenyl-5-oxothiadiazolo[3,2-*a*]pyrimidine, **13-16**.

A mixture of 2-amino-5-alkyl or aryl-1,3,4-thiadiazole **1-4** (0.01 g), ethyl benzoylacetate (0.013 mole) and PPA (10.6 g) was heated on an oil bath at 130-140° for 1 hour. The cooled reaction mixture was treated with ice water, stirred at room temperature for 1 hour. The crystals formed were collected by filtration, washed with water and recrystallized from appropriate solvent.

Compound **15** was chromatographed on silica gel and elution with benzene-ethyl acetate (80:20). The major product was separated and crystallized from cyclohexane.

Analytical data and the characteristics of the products **13-16** are reported in Table I.

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Table I

Fused Pyrimidine Compounds **7-16**

Compound	Mp, °C (colour)	Solvent of Recrystallization	Molecular Formula	IR (cm^{-1})	Analysis % Calcd./Found C	H	N
7 [a]	207-208 (white)	Ethanol	$C_6H_5N_3OS$	1640	43.10 42.92	2.99 2.90	25.14 25.11
8	142-143 (white)	Ethanol	$C_7H_7N_3OS$	1638	46.40 46.28	3.86 4.05	23.20 23.11
9	176-178 (white)	Ethanol	$C_6H_2F_3N_3OS$	1655	32.57 32.76	0.90 0.97	19.00 18.97
10	220-223 (orange)	Ethanol	$C_{11}H_7N_3OS$	1642	57.60 57.51	3.00 3.02	18.30 18.35
11 [b]	241-243 (white)	Ethanol	$C_{12}H_6F_3N_3OS$	1670	48.48 48.56	2.03 1.91	14.14 13.95
12 [b]	211-213 (yellow)	Ethanol	$C_{17}H_{11}N_3OS$	1655	66.87 66.70	3.63 3.51	13.76 13.58
13 [c]	196-198 (yellow)	Ethanol	$C_{12}H_9N_3OS$	1690	59.25 59.40	3.70 3.64	17.28 17.15
14 [c]	144-145 (orange)	Ethanol-water	$C_{13}H_{11}N_3OS$	1680	60.70 60.93	4.28 4.20	16.34 16.25
15	154-155 (white)	Cyclohexane	$C_{12}H_6F_3N_3OS$	1700	48.48 48.60	2.03 2.10	14.14 13.95
16 [b]	210-213 (white)	Ethanol-dioxane	$C_{17}H_{11}N_3OS$	1692	66.87 66.64	3.63 3.60	13.76 13.69

[a] Lit [16]. [b] Lit [1]. [c] Lit [19].

Table II

^{1}H-NMR Spectral Data δ (ppm) of 2-Substituted Fused Pyrimidin-7-one Compounds **7-10**

Compound	C_5-H	C_6-H	Other Protons
7	8.05 (d, 1H, $J_{5,6}$ = 7.8 Hz)	6.35 (d, 1H, $J_{5,6}$ = 7.8 Hz)	2.64 (s, 3H, C_2-CH_3)
8	8.05 (d, 1H, $J_{5,6}$ = 7.7 Hz)	6.36 (d, 1H, $J_{5,6}$ = 7.7 Hz)	2.96 (q, 2H, C_2-CH_2-CH_3) 1.40 (t, 3H, C_2-CH_2-CH_3
9	8.17 (d, 1H, $J_{5,6}$ = 7.7 Hz)	6.48 (d, 1H, $J_{5,6}$ = 7.7 Hz)	—
10	8.17 (d, 1H, $J_{5,6}$ = 7.9 Hz)	6.41 (d, 1H, $J_{5,6}$ = 7.9 Hz)	7.60 (m, 5H, C_2-C_6H_5)

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