Synthesis and Rearrangement of 2-Oxo-3-phenylisoxazolo[2,3-*a*]pyrimidines

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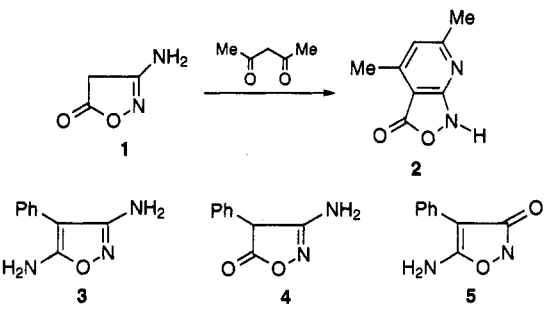
2-Oxo-3-phenylisoxazolo[2,3-*a*]pyrimidine derivatives were synthesized by the reaction of 3-amino-4-phenyl-5-isoxazolone with malonaldehyde tetraacetal, 3-oxobutyraldehyde diacetal, 2,4-pentanedione, and 1-phenyl-1,3-butanedione. The regioselectivity of this reaction was determined by X-ray single crystal structural analysis. Upon heating either in water or in ethanol this bicyclic system underwent a ring opening, followed by decarboxylation to yield phenylpyrimidylmethanol and phenylpyrimidyl methyl ethers. The structures of these 2-oxoisoxazolo[2,3-*a*]pyrimidines and the mechanism of their rearrangement is discussed.

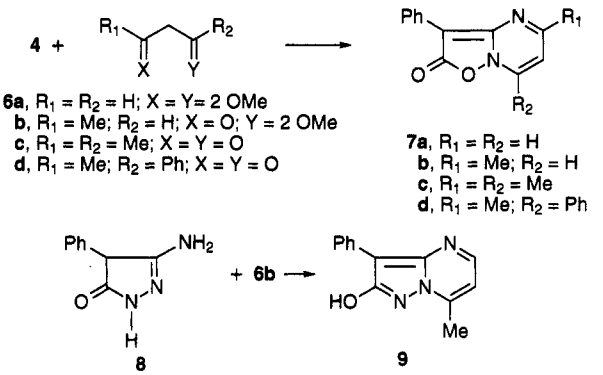
3-Amino-5-isoxazolones and 5-amino-3-isoxazolones were described by Bauer and Nambury.[1] Substituted isoxazolo[2,3-*a*]pyrimidines were prepared previously[2] by the reaction of 3,5-diamino-4-phenylisoxazole (**3**) with 1,3-dicarbonyl compounds. The reaction of 3-amino-5-isoxazolone (**1**) with acetylacetone yielded 4,6-dimethylisoxazolo[3,4-*b*]pyridine[3] (**2**), which is the result of an attack at the amino group and the carbon at position 4. In the present work we wish to report about the preparation of 2-oxo-4-phenylisoxazolo[2,3-*a*]pyrimidines (**7**) from 3-amino-4-phenyl-5-isoxazolone (**4**) and their transformations into derivatives of phenylpyrimidylmethanol by a rearrangement induced by nucleophilic solvents. The reduction of the isoxazole ring in the bicyclic system **7** as well as in the starting material **4** and its isomer **5** is reported.

The condensation of 3-amino-4-phenyl-5-isoxazolone (**4**) with 1,3-dicarbonyl compounds was carried out under acid catalysis. Malonaldehyde tetraacetal (**6a**), 3-oxobutyraldehyde diacetal (**6b**), 2,4-pentandione (**6c**), and 1-phenyl-1,3-butandione (**6d**) were condensed with the aminoisoxazolone derivative **4**, in the presence of ethanolic hydrogen chloride, to yield 2-oxo-3-phenylisoxazolo-[2,3-*a*]pyrimidine (**7a**), its methyl derivative (**7b**), its dimethyl derivative (**7c**), and its methylphenyl derivative (**7d**), respectively. Except for the methylphenyl derivative (**7d**) which has orange color, all the other isoxazolopyrimidine derivatives (**7a–c**) are yellow. However, on exposure to light they change their color to pink-purple, probably due to some decomposition on the surface of the crystals. They are stable at room temperature when protected from light. The reaction is regioselective since in the condensation of both unsymmetrical dicarbonyl compounds **6b** and **6d** only one isomer is obtained. The determination of the isomeric structure was accomplished by single crystal X-ray analysis.[10] In contrast with an earlier observation[4] where the 7-methyl derivative **9** was the major product obtained in the reaction of the pyrazole analog **8** with the diacetal **6b**, the 5-methyl derivative **7b** was the sole product in the present case. One simple

Scheme 1



Scheme 2



explanation for this difference in the regioselectivity of the two reactions is that the relative reactivity of the two nucleophilic centers is different in the heterocyclic starting materials, due to the replacement of oxygen by nitrogen.

The pseudoaromatic structure of the 2-oxoisoxazolo-[2,3-*a*]pyrimidine system **7** is demonstrated by the bond distances which were obtained in the X-ray study. The bond lengths in the pyrimidine ring (see Tables 1 and 2) are in agreement with an aromatic six-membered ring system, as shown in the resonance structures in Scheme 3. The nitrogen in position 8 bears, therefore, a partial positive charge. The contribution of the "no bond resonances" which is shown in structures **7γ** and **7δ** provides explanation to the bond distances which are observed in the five-membered ring. The C_1-C_6 and C_1-O_1 bonds are considerably short whereas the C_1-O_2 bond is extremely long (see Tables 1 and 2).

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(1) Bauer, L.; Nambury, C. N. V. *J. Am. Chem. Soc.* **1961**, *26*, 4917.
(2) Zvilichovsky, G.; David, M. *J. Org. Chem.* **1983**, *48*, 575.
(3) Ali Khan, M.; Rafla, F. K. *J. Chem. Soc., Perkin Trans. 1* **1975**, 693.
(4) Zvilichovsky, G.; Gurvich, V. *J. Chem. Soc., Perkin Trans. 1*, accepted for publication.

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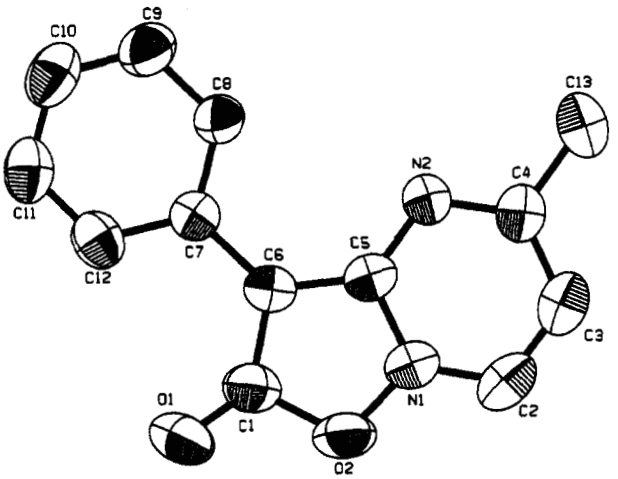
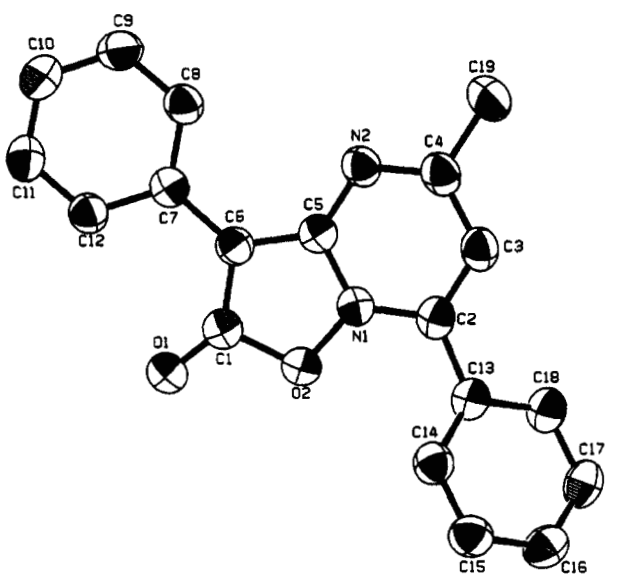
Table 1. Bond Lengths (Å) in 2-Oxo-3-phenyl-5-methylisoxazolo[2,3-*a*]pyrimidine (7b)



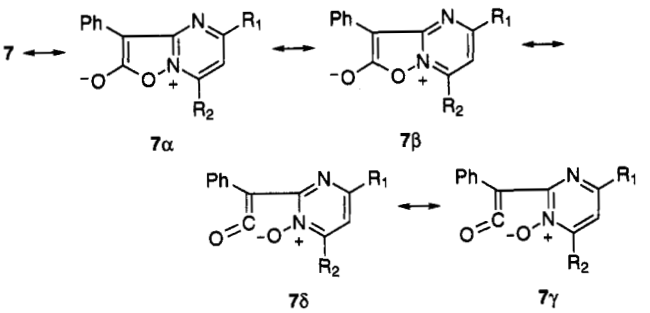
atom	atom	distance	atom	atom	distance
O(1)	C(1)	1.204(3)	C(4)	C(13)	1.500(3)
O(2)	N(1)	1.364(2)	C(5)	C(6)	1.393(3)
O(2)	C(1)	1.445(3)	C(6)	C(7)	1.460(3)
N(1)	C(2)	1.339(3)	C(7)	C(8)	1.397(3)
N(1)	C(5)	1.367(3)	C(7)	C(12)	1.396(3)
N(2)	C(4)	1.324(3)	C(8)	C(9)	1.385(3)
N(2)	C(5)	1.342(3)	C(9)	C(10)	1.366(4)
C(1)	C(6)	1.411(3)	C(10)	C(11)	1.376(4)
C(2)	C(3)	1.346(4)	C(11)	C(12)	1.372(3)
C(3)	C(4)	1.398(3)			

Table 2. Bond Lengths (Å) in 2-Oxo-3-phenyl-5-methyl-7-phenylisoxazolo[2,3-*a*]-pyrimidine (7d)

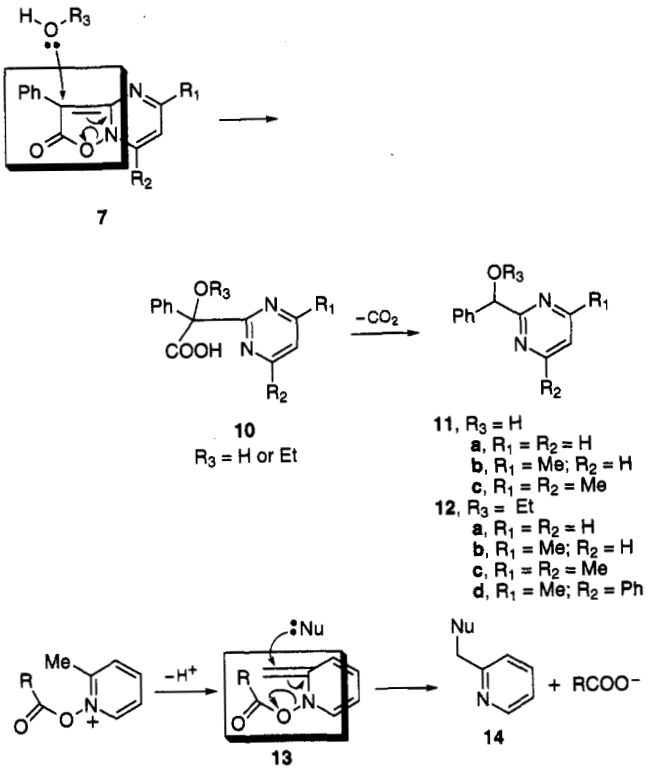


atom	atom	distance	atom	atom	distance
O(1)	C(1)	1.197(2)	C(6)	C(7)	1.464(2)
O(2)	N(1)	1.369(2)	C(7)	C(8)	1.395(2)
O(2)	C(1)	1.451(2)	C(7)	C(12)	1.404(2)
N(1)	C(2)	1.350(2)	C(8)	C(9)	1.383(2)
N(1)	C(5)	1.371(2)	C(9)	C(10)	1.383(3)
N(2)	C(4)	1.325(2)	C(10)	C(11)	1.371(3)
N(2)	C(5)	1.342(2)	C(11)	C(12)	1.375(2)
C(1)	C(6)	1.413(2)	C(13)	C(14)	1.388(2)
C(2)	C(3)	1.368(2)	C(13)	C(18)	1.396(2)
C(2)	C(13)	1.473(2)	C(14)	C(15)	1.376(2)
C(3)	C(4)	1.405(3)	C(15)	C(16)	1.382(3)
C(4)	C(19)	1.490(3)	C(16)	C(17)	1.373(3)
C(5)	C(6)	1.402(2)	C(17)	C(18)	1.375(3)

Scheme 3



Scheme 4



On heating in nucleophilic solvents (*e.g.*, water and ethanol) the 2-oxoisoxazolo[2,3-*a*]pyrimidine derivatives **7** undergo a ring opening, followed by decarboxylation to yield the pyrimidine alcohols and ethers **11**. Those bicyclic derivatives in which the pyrimidine ring bears substituents undergo this transformation faster than the unsubstituted compound **7a**; the latter (**7a**) decomposes by boiling in ethanol for 24 h, with the formation of only traces of the ether derivative **11a**. An increase in the yield of the ether was observed upon the addition of sodium ethoxide. A possible mechanism for the formation of these products is shown in Scheme 1. It is known that *O*-acyl derivatives of *N*-oxides undergo a rearrangement that involves the intermediate **13** which is converted to the final product **14**. The analogy between the bicyclic system of the oxo derivatives **7** and intermediate **13** is shown in the framed segments (Scheme 4). Except for the alcohol **11a** which was prepared earlier[5] from benzaldehyde, all these alcohols (**11b,c**) and ethers (**12a–d**) were unknown.

It was demonstrated in this work that this bicyclic system **7** could be converted into a benzylpyrimidine

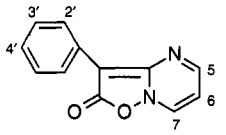
(5) Sandosham, J.; Undheim, K. *Tetrahedron* **1994**, *50*, 275.

Table 3. Crystallographic Data[a]

	7b	7d		7b	7d
formula	$C_{13}H_{10}N_2O_2$	$C_{19}H_{14}N_2O_2$	ϱ_{calcd}, g cm^{-3}	1.37	1.36
space group	$P2_1/n$	$P2_1/c$	μ(Cu K$_\alpha$), cm^{-1}	7.39	6.86
a, Å	15.344(1)	8.704(1)	no. of unique reflections	1725	2318
b, Å	10.093(1)	10.720(1)	no. of reflections with $I \geq 2\sigma_1$	1309	
c, Å	7.060(1)	15.874(2)	no. of reflections with $I \geq 3\sigma_1$		2020
β, deg	90.34(1)	95.94(1)	R	0.044	0.040
v, Å^3	1093.3(3)	1473.2(4)	R_w	0.066	0.075
z	4	4			

[a] Standard calibrations, data formats and positional parameters, structure factors, and U values were submitted to the Editor.

Table 4. Analytical and Spectral Data of 2-Oxo-3-phenylisoxazolo[2,3-*a*]pyrimidines 7

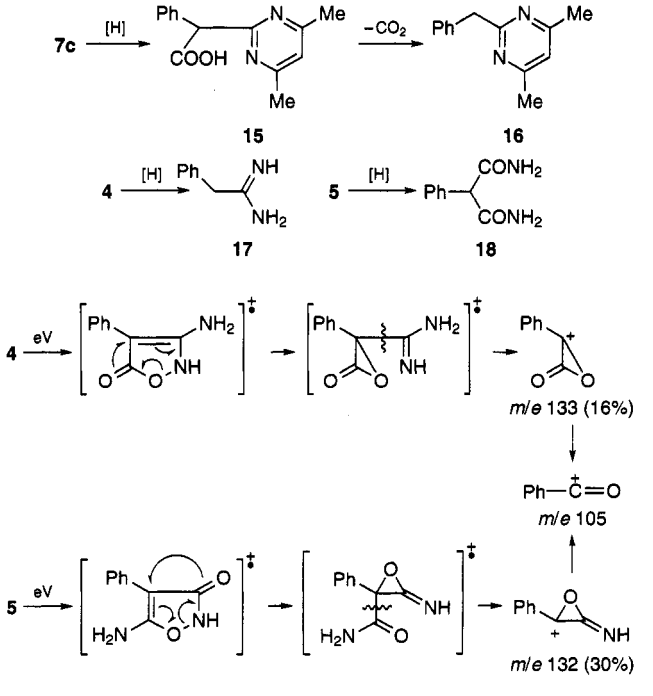


compound	7a	7b	7c	7d
yield, %	70	65	85	90
mp, °C	168	178	180	140
formula	$C_{12}H_8N_2O_2$	$C_{13}H_{10}N_2O_2$	$C_{14}H_{12}N_2O_2$	$C_{19}H_{14}N_2O_2$
found (calcd)				
%C	67.67 (67.92)	69.02 (68.77)	69.61 (69.99)	75.54 (75.48)
%H	3.86 (3.80)	4.46 (4.58)	5.14 (5.03)	4.71 (4.67)
%N	12.92 (13.20)	12.38 (12.23)	11.77 (11.66)	8.98 (9.27)
^{1}H NMR				
solvent	$CDCl_3$	$CDCl_3$	$CDCl_3$	DMSO-d_6
position 5	8.52 (dd, $J_1 = 2.58$, $J_2 = 1.78$)	2.58 (s, Me)	2.52 (s, Me)	2.58 (s)
6	6.54[a] (dd, $J_1 = 4.31$, $J_2 = 2.58$)	6.42[d] (d, $J = 7.04$)	6.31 (s)[f]	7.11 (s)
7	8.19 (m)[b]	8.02[e] (d, $J = 7.04$)	2.54 (s, Me)	7.95 (d, $J = 8.14$, o−Ph), 7.69 (m, m+p-Ph)
2′	8.19 (d)[c]	8.26 (dd, $J_1 = 6.86$, $J_2 = 1.33$)	8.28 (dd, $J_1 = 5.43$, $J_2 = 0.79$)	8.24 (d, $J = 8.28$)
3′	7.42 (t, $J = 7.46$)	7.41 (t, $J = 7.58$)	7.41 (t, $J = 7.51$)	7.40 (t, $J = 7.59$)
4′	7.22 (t, $J = 7.46$)	7.25 (t, $J = 7.58$)	7.20 (dt, $J_1 = 7.51$, $J_2 = 0.79$)	7.16 (t, $J = 7.59$)
UV (MeCN) λ_{max} (ϵ)	310 (20 661)	310 (17 200)	310 (22 500)	411 (1 600) 320 (20 800)
IR (Nujol) ν (C=O) cm^{-1}	1730	1720	1750	1735

[a] In DMSO-d_6: 6.97. [b] Together with 1′, in DMSO-d_6: 9.17 (dd, $J_1 = 5.25$, $J_2 = 1.72$). [c] Together with 7. [d] In DMSO-d_6: 6.87. [e] In DMSO-d_6: 9.01. [f] In DMSO-d_6: 6.76.

derivative **16**, by the reduction of the isoxazole ring by Zn in acetic acid. The intermediate acid **15** which is initially obtained in the reduction is unstable and it undergoes spontaneous decarboxylation. Reduction of the isoxazole derivatives **4** and **5** led to phenylacetamidine (**17**) and phenylmalonamide (**18**), respectively (Scheme 5). Another way to distinguish between these two isomers was the difference in their fractionation under electron impact. The fraction *m/e* 133 which is observed in the MS diagram of isomer **4** is absent in that of isomer **5**. However, isomer **5** gives a fraction of *m/e* 132. A possible mechanism of the formation of these fractions is shown in Scheme 5. Both fractions, probably decompose to the fraction *m/e* 105, which is a major fraction in the MS of both isomers **4** and **5**.

Scheme 5



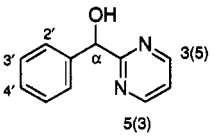
Experimental Section

General Methods. Melting points are uncorrected. Chromatographic separation was carried out with silica gel (230–400 mesh) on a 450 × 10 mm column.

X-ray crystal structure analysis data were measured on a computer-controlled Diffractometer. All non-hydrogen atoms were found by using the results of the SHELXS-86 direct method analysis.[6] After several cycles of refinements[7] the positions of hydrogen atoms were calculated and added to the refinement process. Refinement proceeded to convergence by minimizing the function $\Sigma w(|F_o| - |F_c|)^2$. A final difference

(6) Sheldrick, G. M. *Crystallographic Computing 3*, Oxford University Press: New York, 1985; pp. 175–89.

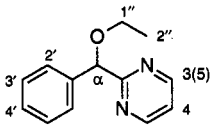
Table 5. Analytical and ^{1}H NMR (in $CDCl_3$) Data of 1-Phenyl-(2-pyrimidinyl)methanols 11



compound	**11a** (lit.[5])	**11b**	**11c**
reaction time, h	5	7	48
yield, %	81	62	56
mp, °C	semisolid	97–9	82–3
formula		$C_{12}H_{12}N_2O$	$C_{13}H_{14}N_2O$
found (calcd)			
%C		71.98 (72.12)	72.87 (73.16)
%H		6.04 (5.73)	6.59 (6.37)
%N		13.99 (13.82)	13.07 (12.94)
^{1}H NMR			
position 3(5)	8.63 (d, J = 4.94)	8.55 (d, J = 5.10)	2.45 (s)
4	7.15 (t, J = 4.94)	7.05 (d, J = 5.10)	6.87 (s)
5(3)	8.63 (d, J = 4.94)	2.54 (s, Me)	2.45 (s)
2	7.23–7.50[a] (m)	7.50 (d, J = 7.71)	7.50 (d, J = 7.77)
3' + 4'	7.23–7.50[b] (m)	7.26–7.33 (m)	7.26–7.31 (m)
α	5.86 (bs)	5.83 (bs)	5.78[c] (bs)
OH		4.45 (bs)	5.12[d] (bs)

[a] Together with 3' + 4'. [b] Together with 2'. [c] In DMSO-d_6: 5.65 (d, J = 5.71). [d] In DMSO-d_6: 5.77 (d, J = 5.71).

Table 6. Analytical and ^{1}H NMR (in $CDCl_3$) Data of 1-Phenyl-(2-pyrimidyl)methyl Ethyl Ethers 12



compound	**12a**	**12b**	**12c**	**12d**
reaction time, h	12	10	12	8
yield, %	59	89	65	60
mp, °C	oil	oil	oil	97–8
formula	$C_{13}H_{14}N_2O$	$C_{14}H_{16}N_2O$	$C_{15}H_{18}N_2O$	$C_{20}H_{20}N_2O$
found (calcd)				
% C	72.87 (72.62)	73.66 (73.42)	74.35 (74.26)	78.92 (78.72)
%H	6.59 (6.39)	7.06 (6.73)	7.49 (7.32)	6.62 (6.40)
%N	13.07 (12.75)	12.37 (12.60)	11.56 (11.62)	9.20 (9.10)
^{1}H NMR				
position 3(5)	8.75 (d, J = 4.90)	8.59 (d, J = 5.12)	2.50(s)	8.01 (m, *o*-Ph)
				7.24–7.49 (m)[a]
4	7.16 (t, J = 4.90)	7.01 (d, J = 5.12)	6.92 (s)	7.24–7.49 (s)[b]
5(3)	8.75 (d, J = 4.90)	2.56 (s, Me)	2.50 (s)	2.57 (s, Me)
2'	7.57 (d, J = 7.76)	7.58 (d, J = 8.11)	7.58 (d, J = 8.12)	7.68 (d, J = 8.27)
3' + 4'	7.29–7.39 (m)	7.25–7.38 (m)	7.22–7.38 (m)	7.24–7.49 (m)[c]
1''	3.60 (q, J = 7.16)	3.59 (q, J = 7.01)	3.65 (q, J = 7.06)	3.64 (q, J = 7.02)
2''	1.29 (t, J = 7.16)	1.30 (t, J = 7.01)	1.33 (t, J = 7.06)	1.31 (t, J = 7.02)
α	5.63 (s)	5.59 (s)	5.61 (s)	5.67 (s)

[a] Together with 4 and 3'+4'. [b] Together with 3'+4' and *m*+*p*-Ph in 3(5). [c] Together with 4 and *m*+*p*-Ph in 3(5).

Fourier synthesis map showed several peaks less than 0.2 e/Å^{-3} for **7b** and 0.17 e/Å^{-3} for **7d** scattered about the unit cell without a significant feature. The discrepancy indices, $R = \sum w(||F_o|F_c||)/\sum|F_o|$ and $R_w = [\sum w(|F_o| - |F_c|^2/\sum|F_o|^2]^{1/2}$ are presented with other pertinent crystallographic data in Table 3.

2-Oxo-3-phenylisoxazolo[2,3-*a*]pyrimidines (7). To a solution of 3-amino-4-phenylisoxazol-5-one (**4**, 0.05 mol) and a 1,3-dicarbonyl compound **6**, 0.15 mol) in ethanol (10 mL) was added 10 N ethanolic HCl (1 mL), and the solution was refluxed for 1 min. The products started to separate after a few minutes and were collected after leaving at room temperature for 1 h, protected from light. The colored products were recrystallized from acetonitrile and kept in light protected bottles. In the preparation of the isoxazolopyrimidine **7d**, the yield was improved by increasing the amount of ethanolic HCl to 4 mL. The analytical and spectral data are summarized in Table 4.

1-Phenyl-(2-pyrimidinyl)methanols 11. 2-Oxo-3-phenylisoxazolo[2,3-*a*]pyrimidines **7** (0.001 mol) was dissolved in water (100 mL). The mixture was refluxed under nitrogen and protected from light. The solvent was evaporated under reduced pressure. The residue was chromatographed with ethyl acetate–petroleum ether 1:1. The analytical and ^{1}H NMR data are summarized in Table 5.

The product **11a** was identified by ^{1}H NMR as 1-phenyl-(2-pyrimidinyl)methanol which was previously described.[5]

1-Phenyl-(2-pyrimidyl)methyl Ethyl Ethers 12. 2-Oxo-3-phenylisoxazolo[2,3-*a*]pyrimidines **7** (0.001 mol) were dissolved in ethanol (10 mL). The mixture was refluxed under nitrogen with protection from light. The solvent was evaporated under reduced pressure. The residue was chromato-

(7) All crystallographic computing was done on a VAX9000 computer at The Hebrew University of Jerusalem, using the TEXAN Structure Analytical Software.

graphed with ethyl acetate–petroleum ether 1:1. The analytical and ^{1}H NMR data are summarized in Table 6. Ether **12a** was obtained by using 1 N EtONa/EtOH instead of ethanol.

Reduction of 2-oxo-3-phenyl-5,7-dimethylisoxazolo-[2,3-*a*]pyrimidine (7c). 2-Oxo-3-phenyl-5,7-dimethylisoxazolo[2,3-*a*]pyrimidine (**7c**, 0.4 g) was dissolved in acetic acid (50 mL), Zn powder (0.7 g) was added and the mixture stirred for 5 h at room temperature. The mixture was filtered and the solvent removed under reduced pressure. The residue was chromatographed with ethyl acetate-petroleum ether (2:3), m.p. 80–1 °C (lit.[8] 80–1 °C).

Reduction of 3-amino-4-phenylisoxazol-5-one (4). 3-Amino-4-phenylisoxazol-5-one (**4**, 0.25 g) was dissolved in ethanol (50 mL), 10% Pd/C (0.1 g) was added and the stirred mixture was treated with hydrogen for 3 hrs. Then the catalyst was filtered off and the solvent removed under reduced pressure. The residue [phenyl acetamidine **17**, ^{1}H NMR (DMSO-d_6 + CF_3COOH) δ: 8.1–9.0 (bs, 4 H, NH_2), 7.10–7.32 (m, 5 H, Ph), 3.67 (s, 2 H, CH_2)] was dissolved in ethanol (20 mL) and excess of picric acid (0.5 g) was added. The solution was stirred for 5 min while the picrate of **17** precipitated, m.p. 225–30 °C (lit.[9] 227–8 °C).

Reduction of 5-amino-4-phenylisoxazol-3-one (5). 5-Amino-4-phenylisoxazol-3-one (**5**, 0.15 g) was dissolved in acetic acid (20 mL) in the presence of 10% Pd/C (0.1 g). The solution was treated with hydrogen for 3 h. The catalyst was filtered and the solvent removed under reduced pressure. The product **18** precipitated on evaporation. The product was compared with an authentic sample prepared from diethyl α-phenylmalonate (mp, IR, NMR).

Acknowledgment. We wish to thank Dr. Shmuel Cohen for his dedication in carrying out the X-ray diffraction analysis.

JO950446B

(8) Pinner, A. *Ber.* **1894**, 2124.

(9) Partridge, M. W.; Short, W. F. *J. Chem. Soc.* **1947**, 390.

(10) The author has deposited atomic coordinates for **7b** and **7d** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.