Synthesis of Some 1,2-Oxazoles bearing a Fused Heterocyclic Ring from α-Acetylhomotetronic Acids

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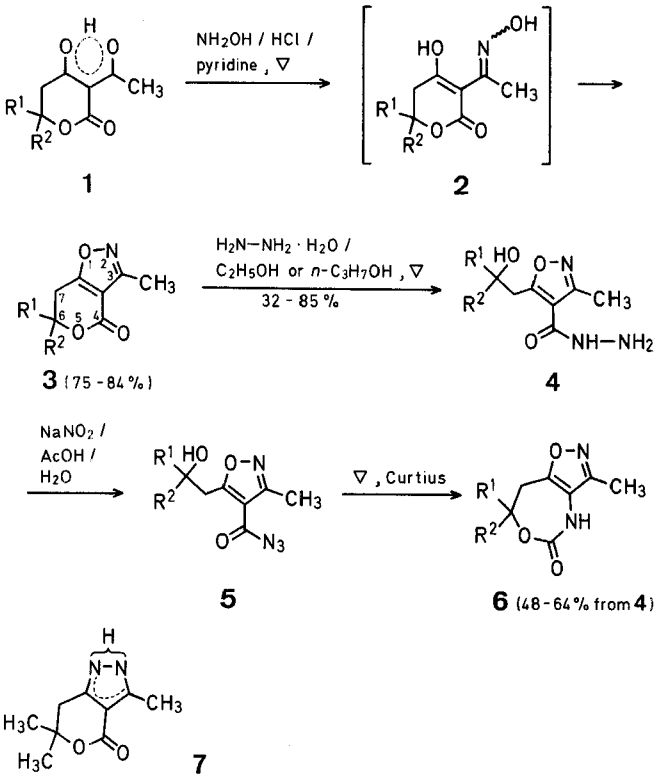
In continuation of our work on the synthesis of heterocyclic-fused compounds[1], we report here the preparation of 3-methyl-4-oxo-6,7-dihydro-4*H*-pyrano[3,4-*d*][1,2]oxazoles **3** and 3-methyl-5-oxo-4,5,7,8-tetrahydro[1,2]oxazolo[4,5-*d*][1,3]oxazepines **6** from α-acetylhomotetronic acids[2] **1** as starting material.



Treatment of **1** with hydroxylamine hydrochloride in boiling pyridine leads to the exclusive formation of the fused isoxazole **3**. This reaction involves the oximes **2** as intermediates, in agreement with the preferred orientation in the reactions of nucleophiles onto cyclic tricarbonylic substrates[3]. For **3a**, the structure is further corroborated by the ^{13}C-N.M.R. spectrum (Table). The carbon lines are assigned from the obtained signal multiplicities in the off resonance spectrum and from the coupled spectrum. Thus, the upfield triplet (^2J = 7 Hz) at 176.4 ppm is assigned to C-8; this carbon atom is coupled with the H-7 protons and the quartet (^2J = 6.5 Hz) at 158.0 ppm is assigned to C-3 which is coupled with the methyl protons. These values are consistent with previous findings concerning some other isoxazole derivatives[4].

Hydrazinolysis of the lactone ring of compounds **3a** and **b** (R^1 = H, CH_3; R^2 = H) affords the pure hydrazides **4a, b**. In the case of **3c** ($R^1 = R^2 = CH_3$), most hindered, the cleavage of the carboxyl group takes place only at higher temperature to give **4c** and it competes with the opening of the isoxazole ring to yield the pyrazole **7**. However, the hydrazide **4c** is easily purified by recrystallization.

Treatment of hydrazides **4** in aqueous acetic acid with sodium nitrite affords the stable azides **5**. Curtius rearrangement of **5**, followed by *in situ* reaction of the resultant isocyanates with the

0039-7881/81/0432-0315 $ 03.00

Table. Compounds **3**, **4**, and **6** prepared

Product	R^1	R^2	Yield [%]	m.p. [°C] (solvent)	Molecular formula[a]	I.R. (KBr) $\nu_{C=O}$ [cm^{-1}]	U.V. (C_2H_5OH) λ_{max} [nm] (ε)	^{1}H-N.M.R. (DMSO-d_6) δ [ppm]
3a[b]	H	H	75	87–88° (H_2O)	$C_7H_7NO_3$ (153.1)	1740	218 (4500)	2.40 (s, 3H); 3.30 (t, 2H, J=6 Hz); 4.63 (t, 2H, J=6 Hz)
3b	H	CH_3	83	74–76° (H_2O)	$C_8H_9NO_3$ (167.2)	1740	218 (4300)	1.48 (d, 3H, J=6 Hz); 2.40 (s, 3H); 2.6–3.6 (m, 2H); 4.9 (m, 1H)
3c	CH_3	CH_3	84	136–138° (H_2O)	$C_9H_{11}NO_3$ (181.2)	1740	218 (4400)	1.48 (s, 6H); 2.40 (s, 3H); 3.35 (s, 2H)
4a	H	H	85	176–178° (C_2H_5OH)	$C_7H_{11}N_3O_3$ (185.2)	1670, 1650	212 (8100)	2.31 (s, 3H); 3.07 (t, 2H, J=7 Hz); 3.8 (m, 2H); 4.46 (br. s, 2H); 5.34 (t, 1H, J=5 Hz); 9.38 (br. s, 1H)
4b	H	CH_3	72	128–129° (C_2H_5OH)	$C_8H_{13}N_3O_3$ (199.2)	1660	212 (8200)	1.15 (d, 3H, J=6 Hz); 2.30 (s, 1H); 2.6–3.2 (m, 2H); 4.0 (m, 1H); 4.43 (br. s, 2H); 5.40 (br. s, 1H); 9.43 (br. s, 1H)
4c	CH_3	CH_3	32	154–155° (C_2H_5OH)	$C_9H_{15}N_3O_3$ (213.2)	1660	212 (8400)	1.25 (s, 6H); 2.35 (s, 3H); 3.03 (s, 2H); 4.43 (br. s, 2H); 5.55 (br. s, 1H); 9.80 (br. s, 1H)
6a	H	H	64[c]	238–239° (C_2H_5OH)	$C_7H_8N_2O_3$ (168.2)	1700	216 (5800)	2.25 (s, 3H); 3.15 (t, 2H, J=6 Hz); 4.51 (t, 2H, J=6 Hz); 9.38 (s, 1H)
6b	H	CH_3	50[c]	234–235° (C_2H_5OH)	$C_8H_{10}N_2O_3$ (182.2)	1705	216 (6300)	1.45 (d, 3H, J=6 Hz); 2.25 (s, 3H); 2.7–3.2 (m, 2H); 4.75 (m, 1H); 9.30 (s, 1H)
6c	CH_3	CH_3	48[c]	231–232° (C_2H_5OH)	$C_9H_{12}N_2O_3$ (196.2)	1700	216 (6500)	1.53 (s, 6H); 2.28 (s, 3H); 3.16 (s, 2H); 9.58 (s, 1H)

[a] Satisfactory microanalyses obtained: C ±0.28, H ±0.29, N ±0.30.
[b] ^{13}C-N.M.R. ($CDCl_3$): δ=176.4 (C-8); 161.0 (C-4); 158.0 (C-3); 106.7 (C-9); 66.7 (C-6); 23.3 (C-7); 10.1 ppm (C-10).
[c] Yield based on **4**.

hydroxy group of the alkyl side chain, gives the compound **6** in good yield. Microanalyses and spectral data are consistent with the assigned bicyclic structures, which represent a new class of heterocycle-fused isoxazoles.

3-Methyl-4-oxo-6,7-dihydro-4*H*-pyrano-[3,4-*d*][1,2]oxazoles 3; General Procedure:
Hydroxylamine hydrochloride (2 g, 0.0287 mol) is added to a solution of the α-acetylhomotetronic acid **1** (0.025 mol), in pyridine (50 ml) and the mixture is heated under reflux for 0.5 h. The solvent is then distilled off at reduced pressure and the residual product is recrystallized from water.

4-Hydrazinocarbonyl-5-(2-hydroxyalkyl)-3-methyl-1,2-oxazoles 4; General Procedure:
Hydrazine hydrate (1.5 g, 0.03 mol) is added to a solution of the isoxazole **3** (0.025 mol) in ethanol (50 ml), or propanol (50 ml) in the case of **3c**. The mixture is heated under reflux for 0.5 h, or 2 h for **3c**. The solvent is then distilled off in vacuo and the residual product is recrystallized from ethanol to give pure compounds **4** (Table).

In the case of **3c**, after evaporation in vacuo of the solvent of recrystallization, the residue is recrystallized from water to give the pyrazole **7**; yield: 30%; m.p. 144–146 °C.

$C_9H_{12}N_2O_2$	calc.	C 59.98	H 6.71	N 15.55
(180.2)	found	59.80	6.84	15.45

I.R. (KBr): ν=3220, 3180, 3080 (NH); 1680 cm^{-1} (C=O).

U.V. (ethanol): λ_{max}=230 nm (ε=8400).

^{1}H-N.M.R. (DMSO-d_6): δ=1.46 (s, 6H); 2.52 (s, 3H); 3.00 (s, 2H); 13.2 ppm (br. s, 1H).

4-Azidocarbonyl-5-(2-hydroxyalkyl)-3-methyl-1,2-oxazoles 5; General Procedure:
A cold solution of compound **4** (0.025 mol) in 25% aqueous acetic acid (~160 ml) is treated with sodium nitrite (3.45 g, 0.05 mol) with stirring while the temperature of the reaction mixture is not allowed to exceed 20 °C. After a reaction time of 1 h, the azide **5** is extracted with dichloromethane (3 × 50 ml) and the extracts are successively washed with saturated sodium hydrogen carbonate solution, and water and then dried with anhydrous sodium sulfate. The azides **5** are obtained only as a crude oil after evaporation under reduced pressure of the organic layer. The structures of these compounds are supported by their I.R. spectra which showed the characteristic absorptions of the azidocarbonyl group at $\nu \simeq 2140$ cm^{-1} (N_3) and $\nu \simeq 1700$ cm^{-1} (C=O).

3-Methyl-5-oxo-4,5,7,8-tetrahydro[1,2]oxazolo-[4,5-*d*][1,3]oxazepines 6; General Procedure:
A solution of the crude azide **5** (0.02 mol) in dry 1,2-dimethoxyethane (500 ml) is heated under reflux for 4 h. The solvent is then removed under reduced pressure and the solid residue recrystallized from ethanol.

Received: October 27, 1980

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