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# Oxadiazole Condensed Ring Systems, I: Synthesis of 1,3,4-Oxadiazolo[3,2-a]pyrimidin-5-ones as Possible Antimicrobial Agents

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**Summary.** Syntheses of some substituted 7-hydroxy-5*H*-1,3,4-oxadiazolo[3,2-a]pyrimidin-5-ones (**3**) and their 7-methoxy (**4**), 7-chloro (**5**) and 7-azido (**6**) derivatives are described. 2-Phenyl-N,N′-bis(3-tolyl)propanediamide (**8**) was obtained, instead of the expected triazolopyrimidinone **7** upon reacting **3b** with *m*-toluidine. Three compounds were screened for *in vitro* antibacterial and antifungal activities.

**Keywords.** 2-Amino-oxadiazoles; Active malonates; 1,3,4-Oxadiazolo[3,2-a]pyrimidin-5-ones.

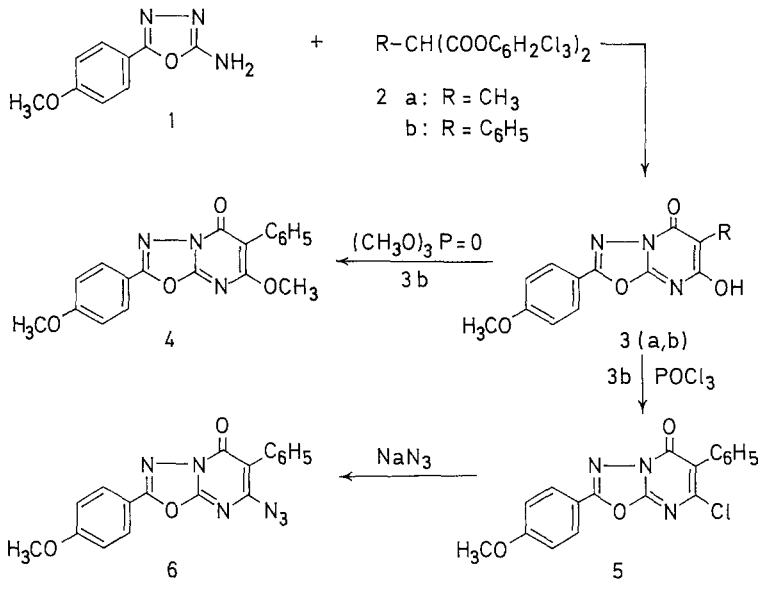
**Kondensierte Ringsysteme des Oxadiazols, 1. Mitt.:**
**Synthese von 1,3,4-Oxadiazolo[3,2-a]pyrimidin-5-onen als potentiell antimikrobielle Substanzen**

**Zusammenfassung.** Die Synthese einiger substituierter 7-Hydroxy-5*H*-1,3,4-oxadiazolo[3,2-a]-pyrimidin-5-one (**3**) und ihrer 7-methoxy (**4**), 7-chloro (**5**) und 7-azido (**6**) Derivate wird beschrieben. Anstelle des erwarteten Triazolo-pyrimidinons **7** entsteht bei der Reaktion von **3b** mit *m*-Toluidin 2-Phenyl-N,N′-bis(3-tolyl)-propandiamid (**8**). Drei Verbindungen wurden auf antimikrobakterielle und fungizide Wirkung geprüft.

## Introduction

Several methods leading to 5*H*-1,3,4-oxadiazolo[3,2-a]pyrimidin-5-ones have been described in the literature. Some substituted 2-amino-1,3,4-oxadiazoles were utilized in such syntheses through reaction with carbon suboxide [1], ethyl ethoxymethylenemalonate [2], ethyl acetoacetate [2] or acetylene-carboxylates [3]. Interaction of N′-2-(5-phenyl-1,3,4-oxadiazolyl)-N,N-dimethylformamidine with diketene provided the 6-acetyl-2-phenyl derivatives of the system [4]. Some 2-azido-1,3,4-oxadiazoles were converted to the 7-carboxy derivatives of the system upon reaction with diethyl fumarate or malonate [5]. Moreover, the synthesis of some 6,7-dihydro derivatives of the system was described either by cyclizing 3-(β-chloropropionyl)-2-imino-5-substituted-1,3,4-oxadiazoles [6] or cycloaddition of diphenyl ketene with 2-arylideneamino-1,3,4-oxadiazoles [7].

The reported *in vitro* antibacterial potencies associated with some 1,3,4-oxadiazoles [8, 9] and pyrimidine derivatives [10–12] prompted us to synthesize some 5*H*-1,3,4-oxadiazolo[3,2-a]pyrimidin-5-ones (which comprise both nuclei) for an-




**Scheme 1**

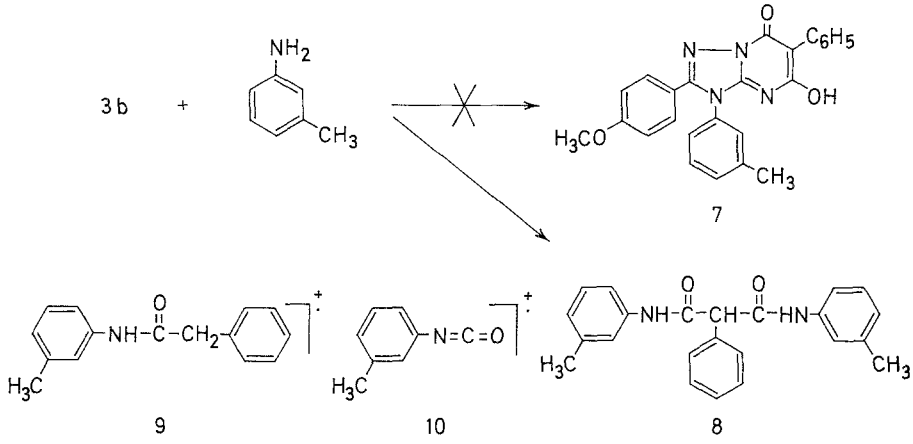
tibacterial screening. It is worth mentioning that pharmacotoxicological properties of this bicyclic system, which possesses certain structural features in common with xanthines, is still unexplored.

## Results and Discussion

Reacting equimolar quantities of 2-amino-5-(4-methoxyphenyl)-1,3,4-oxadiazole (**1**) with bis(2,4,6-tichlorophenyl) monosubstituted malonates (**2a**, **b**) in boiling chlorobenzene afforded high yields of 6-methyl- or 6-phenyl-7-hydroxy-2-(4-methoxyphenyl)-5*H*-1,3,4-oxadiazolo[3,2-a]pyrimidin-5-ones (**3a**, **b**) (Scheme 1). Methylating **3b** with trimethyl phosphate in the presence of sodium carbonate yielded 7-methoxy-6-phenyl-2-(4-methoxyphenyl)-5*H*-1,3,4-oxadiazolo[3,2-a]pyrimidin-5-one (**4**) in high yield. On the other hand, chlorination of **3b** with phosphorus oxychloride gave 7-chloro-6-phenyl-2-(4-methoxyphenyl)-5*H*-1,3,4-oxadiazolo[3,2-a]pyrimidin-5-one (**5**) which was converted to the 7-azido derivative **6** upon treatment with sodium azide at room temperature. Refluxing **3b** with excess *m*-toluidine led to 2-phenyl-N,N′-bis(3-tolyl)-propanediamide (**8**) instead of the expected 5-hydroxy-6-phenyl-2-(4-methoxyphenyl)-3-(3-tolyl)-7*H*-1,3,5-triazolo[1,5-a]pyrimidin-7-one (**7**).

The exclusion of the latter was based on the $^1$H nmr spectrum which showed two methyl groups as a singlet at $\delta = 2.9$ ppm and the acidic malonyl proton at $\delta = 5.4$ ppm. A conclusive proof of the structure was obtained from the mass spectrum which showed an intense molecular ion peak and a base peak at *m/z* 225. The latter ion which might be formulated as **9** is formed through loss of the isocyanate **10** from the parent molecule associated with hydrogen transfer (Scheme 2).

In contrast to our result, Gehlen [13] could prepare some 5-methyl-2,3-disubstituted-7*H*-1,3,5-triazolo[1,5-a]pyrimidin-7-ones from 7-methyl-2-phenyl-5*H*-1,3,4-oxadiazolo[3,2-a]pyrimidin-5-one and primary aromatic or aliphatic amines under similar experimental conditions.




**Scheme 2**

Compounds **3b**, **4**, and **5** were tested for *in vitro* activity against five *Escherichia coli* strains, five *Klebsiella pneumonia* strains, three *Pseudomonas aeruginosa* strains, and two *Candida albicans* strains. The disc method was adopted to determine the inhibition zones and compounds which showed > 8 mm in diameter were evaluated for their minimal inhibitory concentrations (MIC) against the most sensitive organisms. None of the compounds exhibited antimicrobial activity [14].

## Experimental Part

Melting points were determined in open-glass capillaries on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded for nujol mulls, unless otherwise specified, on a Perkin-Elmer 421 spectrophotometer. $^1$H nmr spectra were recorded on a Varian EM 360 using tetramethylsilane as the internal standard. Mass spectra were measured on A.E.I. (Kratos) MS 9 mass spectrometer. Microanalyses were carried out at the microanalytical unit, Faculty of Science, Cairo University.

*7-Hydroxy-6-methyl-2-(4-methoxyphenyl)-5H-1,3,4-oxadiazolo[3,2-a]pyrimidin-5-one* (**3a**)

Bis(2,4,6-trichlorophenyl)methylmalonate (**2a**) [15] (4.77 g, 10 mmol) was added in one portion to a hot suspension of **1** (1.91 g, 10 mmol) in chlorobenzene (15 ml). The mixture was refluxed for 1 h. After cooling, the crystallized solid was filtered, washed with benzene and dried, yield 2.0 g (73.2%), m.p. 262–265° (dimethylformamide). Anal. calcd. for $C_{13}H_{11}N_3O_4$: C 57.1, H 4.1, N 15.4; found: C 56.8, H 4.3, N 14.9.

*7-Hydroxy-6-phenyl-2-(4-methoxyphenyl)-5H-1,3,4-oxadiazolo[3,2-a]pyrimidin-5-one* (**3b**)

It was similarly prepared from **1** (4.8 g, 25 mmol) and **2b** (13.5 g, 25 mmol); yield 7.6 g (90.7%), m.p. 273–275° (aqueous dimethylformamide); ir: 3 400–2 600 bm, 1 660 s (CO), 1 620 w, 1 590 s, 1 520 cm$^{-1}$. Anal. calcd. for $C_{18}H_{13}N_3O_4$: C 64.5, H 3.9, N 12.5; found: C 64.8, H 4.0, N 12.4.

*7-Methoxy-6-phenyl-2-(4-methoxyphenyl)-5H-1,3,4-oxadiazolo[3,2-a]pyrimidin-5-one* (**4**)

This was prepared by refluxing **3b** (2.0 g, 6 mmol) with trimethyl phosphate (10 ml) for 30 min in presence on anhydrous sodium carbonate (0.2 g). The product was obtained after cooling and addition

of excess water, yield 2.0 g (96.2%), m.p. 265–268° (aqueous dimethylformamide); ir: 3 000 w, 1 700 m (CO), 1 620 m, 1 520 w $cm^{-1}$; $^1H$ nmr ($CF_3COOH$): 4.0 (s, $OCH_3$), 4.2 (s, $OCH_3$ at C-7), 7.1 (d, 2 *Ar*H), 7.4 (s, 5 *Ar*H at C-6), 8.2 (d, 2 *Ar*H). Anal. calcd. for $C_{19}H_{15}N_3O_4$: C 65.3, H 4.3, N 12.0; found: C 65.4, H 3.9, N 12.4.

*7-Chloro-6-phenyl-2-(4-methoxyphenyl)-5H-1,3,4-oxadiazolo[3,2-a]pyrimidin-5-one* (**5**)

Compound **3b** (1.7 g, 5 mmol) was refluxed with phosphorus oxychloride for 1 h. Subsequently, the excess phosphorus oxychloride was distilled under vacuum and the residue was stirred with ice-water. After neutralization with saturated sodium hydrogen carbonate, the product was filtered, washed with water and dried, yield 0.7 g (39.5%); m.p. 220–221° (aqueous dimethylformamide); ir: 3 400 w, 2 700 w, 1 685 s (CO), 1 640 m, 1 600 s, 1 565 m, 1 500 w $cm^{-1}$. Anal. calcd. for $C_{18}H_{12}ClN_3O_3$: C 61.1, H 3.4, N 11.9; found: C 61.5, H 3.5, N 11.6.

*7-Azido-6-phenyl-2-(4-methoxyphenyl)-5H-1,3,4-oxadiazolo[3,2-a]pyrimidin-5-one* (**6**)

Sodium azide (0.2 g, 3 mmol) was added to a stirred cold solution of **5** (0.71 g, 2 mmol) in dimethylformamide (10 ml). After stirring for 30 min, water was added and the precipitated product was filtered, washed with water and air dried, yield 0.4 g (55.5%); m.p. 223–228° (dimethylformamide – ethanol); ir (KBr): 3 000 s, 2 200 s ($N_3$), 1 700 s, 1 650 s (CO), 1 620 s, 1 580 m, 1 520 m $cm^{-1}$. Anal. calcd. for $C_{18}H_{12}N_6O_3$: C 60.0, H 3.6, N 23.3; found: C 60.4, H 3.8, N 22.9.

*2-Phenyl-N,N'-bis(3-tolyl)-propanediamide* (**8**)

Compound **3b** (1.0 g, 3 mmol) was refluxed with *m*-toluidine (5 ml) for 1 h. Excess *m*-toluidine was removed under reduced pressure and the residue was treated with ether to obtain a white crystalline product, yield 0.8 g (74.8%); m.p. 178–182° (ethanol); ir (KBr): 3 000 s, 1 950 m, 1 880 m, 1 820 m, 1 750 m, 1 670 m (CO), 1 610 s, 1 600 m, 1 500 s $cm^{-1}$; $^1H$ nmr ($CDCl_3$): 2.35 (s, 2 $CH_3$), 6.8–7.8 (m, 8 *Ar*H); MS: *m/z* (relative abundance %); 359 ($M^+ + 1$, 57), 358 ($M^+$, 86), 226 (73), 225 (100), 207 (13), 196 (36), 179 (9), 146 (42), 134 (41), 118 (73), 108 (90). Anal. calcd. for $C_{23}H_{22}N_2O_2$: C 77.1, H 6.2, N 7.8; found: C 76.7, H 6.1, N 7.7.

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