

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

El-Sayed A. M. Badawey, Ahmed M. M. Hassan, and Farid S. G. Soliman

Department of Pharmaceutical Chemistry, Faculty of Pharmacy,
University of Alexandria, Alexandria 21521, Egypt

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.:

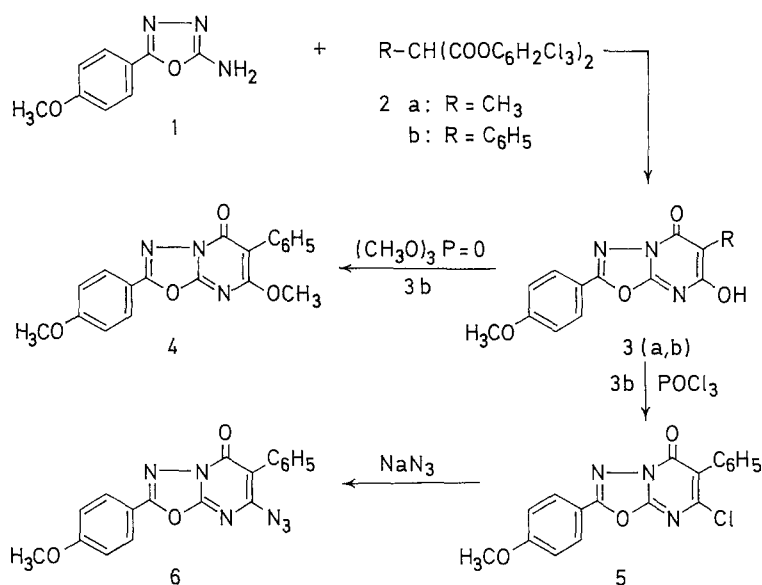
Synthese von 1,3,4-Oxadiazolo[3,2-a]pyrimidin-5-onen als potentiell antimikrobielle Substanzen

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 antimikrobielle 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

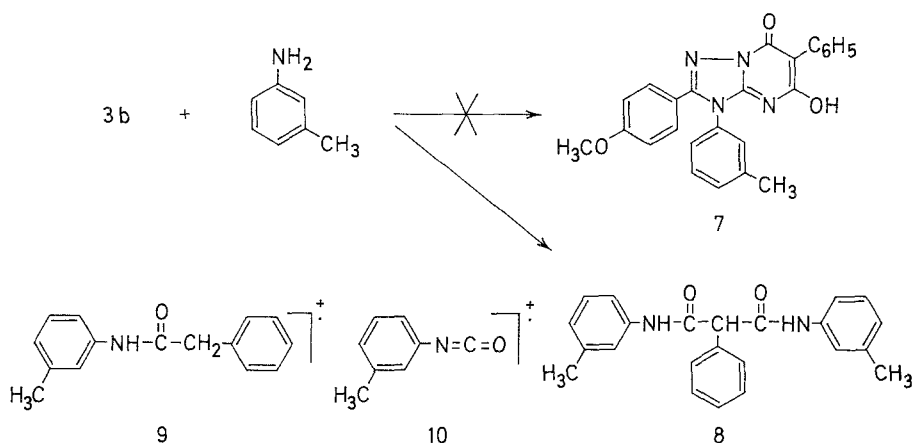
tibacterial screening. It is worth mentioning that pharmacotoxicological properties of this bicyclic system, which possesses certain structural features in common with xanthenes, is still unexplored.

Results and Discussion

Reacting equimolar quantities of 2-amino-5-(4-methoxyphenyl)-1,3,4-oxadiazole (1) with bis(2,4,6-trichlorophenyl) monosubstituted malonates (2a, b) in boiling chlorobenzene afforded high yields of 6-methyl- or 6-phenyl-7-hydroxy-2-(4-methoxyphenyl)-5H-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)-5H-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)-5H-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)-7H-1,3,5-triazolo[1,5-a]pyrimidin-7-one (7).

The exclusion of the latter was based on the ¹H 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-7H-1,3,5-triazolo[1,5-a]pyrimidin-7-ones from 7-methyl-2-phenyl-5H-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. ^1H nmr spectra were recorded on a Varian EM 360 using tetramethylsilane as the internal standard. Mass spectra were measured on A.E.I. (Kratos) MS9 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 $\text{C}_{13}\text{H}_{11}\text{N}_3\text{O}_4$: 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 $\text{C}_{18}\text{H}_{13}\text{N}_3\text{O}_4$: 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 *ArH*), 7.4 (s, 5 *ArH* at C-6), 8.2 (d, 2 *ArH*). Anal. calcd. for $\text{C}_{19}\text{H}_{15}\text{N}_3\text{O}_4$: 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 $\text{C}_{18}\text{H}_{12}\text{ClN}_3\text{O}_3$: 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 $\text{C}_{18}\text{H}_{12}\text{N}_6\text{O}_3$: 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 *ArH*); 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 $\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_2$: C 77.1, H 6.2, N 7.8; found: C 76.7, H 6.1, N 7.7.

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