A New Synthetic Route to 1,3,4-Oxadiazoles. Pharmacological Study of some New Derivatives

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2-Substituted 1,3,4-oxadiazoles have been examined as possible prodrugs of antidepressant hydrazides. A new method of synthesis of this heterocycle from thionoester and five new oxadiazoles substituted at the 2-position by a 4-pyridyl or 4-aminophenyl group and at the 5-position by a phenyl group are described.

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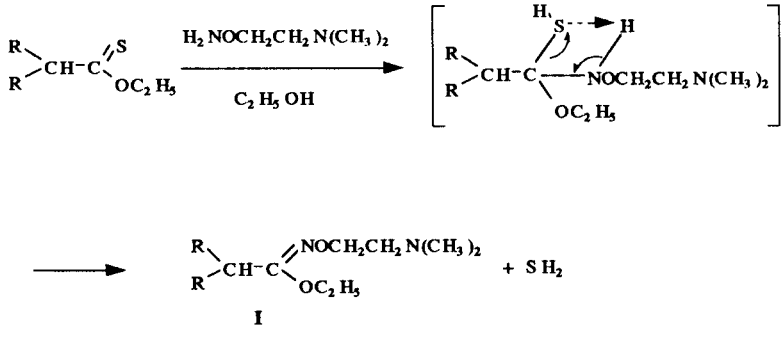
The study of thionoesters that has been conducted for some years in our laboratory led us to examine them as starting materials for the synthesis of 1,3,4-oxadiazoles. Several reviews [1,2] deal with their synthesis, the most recent dating from 1966 [3]. As far as their therapeutic interest is concerned, since the article of Derappe *et al.* [4], various areas of application have been examined. In more than thirty papers, nearly all sections of pharmacology have been covered including their H_2-antihistaminic activity [5]; about fifteen deal with their antimicrobial antiprotozoal and antiviral activities. A large number of patents, too numerous to be cited here, are related to their activities as growth factors of plant cells, herbicides and fungicides; in these cases, the oxadiazole ring usually carries an aryloxy group in position 5 [6]. In the present paper we consider pharmacologically interesting derivatives which are possible prodrugs potentially capable of releasing hydrazides *in vivo*, and which are thus potential antidepressors.

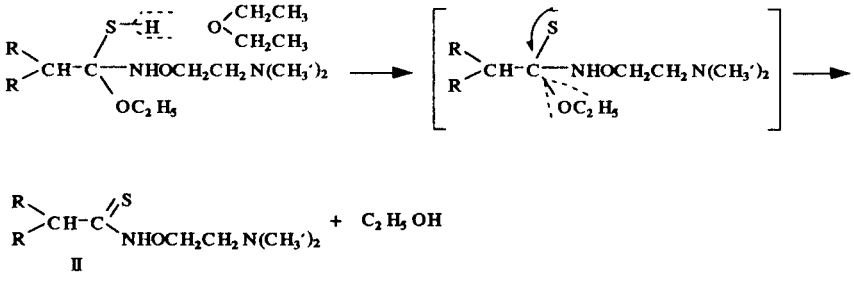
The reaction of thionoesters with amines follows two different pathways according to the conditions, alcoholic or aprotic, employed. Thus in ethanol, dialkylaminoethoxyamines afford *O,N*-dialkylaminoethylhydroximates **I** [7] (Scheme 1). It is probable that in the protic medium, hydrogen sulphide is eliminated from a four centred, cyclic, coplanar transition state intermediate. This four centred,

Scheme 1



I

Scheme 2



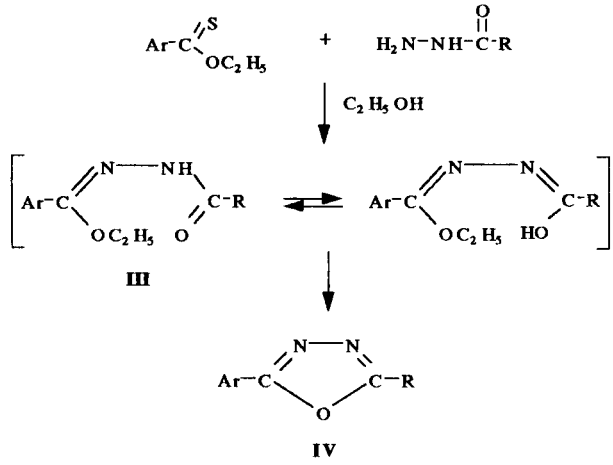
II

concerted mechanism, specific for the sulphur atom, was observed by Schönerg *et al.* a long time ago [8-9] and it was also encountered in our laboratory during the conversion of dialkyaminothionoesters into thioloesters upon heating [10].

In contrast, if the solvent is an ether, in the transition state, the proton attached to the sulphur atom is sufficiently acidic to be captured by either the solvent or by the tertiary nitrogen atom. The alkoxy group is then eliminated and the major product formed is an *N*-(dimethylaminoethoxy)thioamide **II** (Scheme 2).

These observations led us to the conclusion that the ethyl *N*-acylhydrazonate intermediate **III** (Scheme 3) formed from a thionoester and an acid hydrazide in alcoholic medium would afford a 1,3,4-oxadiazole **IV**.

Scheme 3



III

IV

Indeed, condensation of isoniazide and of *p*-aminobenzoylhydrazide with various ethyl thionobenzoates produced six 1,3,4-oxadiazoles substituted in positions 2 and 5 (Table I). Compound **1** excepted [11], they are all new derivatives. In one case (compound **1**), the intermediate *N*-acylhydrazonate was isolated. None of the six oxadiazoles described form stable salts in solution.

EXPERIMENTAL

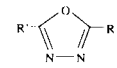
Boiling points are represented by the symbol E_{torr}°. Melting points (mp°) were measured with a Buchi-Tottoli apparatus. Molecular weights are represented by the symbol MW. The ^1H nmr spectra were recorded with a Varian T60 spectrometer (solutions in deuteriochloroform or dimethyl sulfoxide-d_6 with internal tetramethylsilane as the standard). Chemical shifts are given in ppm; s, t, q, m, se designated singlet, triplet, quartet, multiplet and broad singlet, respectively.

Iminoesters **7-9**.

General Procedure for the Preparation of Ethyl Benzimidate.

A solution of nitrile (0.15 mole), anhydrous ethanol (17 ml) and dry chloroform (70 ml) cooled to −5° was saturated with dry gaseous hydrogen chloride and then placed in a refrigerator for one week. The mixture was diluted with anhydrous ether (600 ml) and cooled to −15°, which led to precipitation of the imino chloride. This suspension was maintained at −15° and a large excess of dry gaseous ammonia was bubbled into it. Ammonium chloride was then rapidly filtered off, the filtrate was concentrated to dryness and the oily residue was distilled.

Table I : 1, 3, 4-Oxadiazoles **1-6**

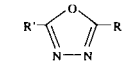


n°	R'	R		Yield (%)	Molecular Formula Mr	Analytical Data Calc. % Found % C	H	N	mp
1			(a)	80	$C_{11}H_8N_3OCl$	60.59	3.12	16.30	176
					257.67	60.58	3.23	16.24	
2			(a)	76	$C_{14}H_8N_3F_3O$	57.73	2.76	14.42	164
					291.23	57.70	2.86	14.46	
3			(a)	72	$C_{14}H_8N_3F_3O$	57.73	2.76	14.42	193
					291.23	57.74	2.91	14.42	
4			(b)	74	$C_{14}H_{10}N_3OCl$	61.88	3.70	15.46	199
					271.70	61.82	3.90	15.42	
5			(b)	79	$C_{15}H_{10}N_3OF_3$	59.01	3.30	13.76	189
					305.25	59.14	3.45	13.66	
6			(b)	73	$C_{15}H_{10}N_3OF_3$	59.01	3.30	13.76	223
					305.25	59.15	3.43	13.72	

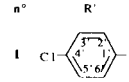
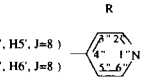
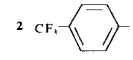
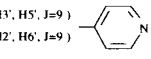
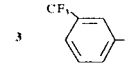
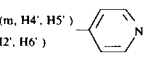
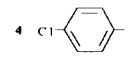
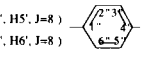
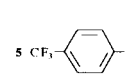
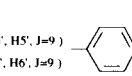
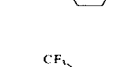
Solvent used in the reaction (a) : ethanol ; (b) : ethyleneglycol.

Table II

1, 3, 4-oxadiazoles : ^1H Nmr Data



1 - 6

n°	R'	R
1	 7.60 (d, H3', H5', J=8) 8.20 (d, H2', H6', J=8)	 8.10 (d, H3", H5", J=6) 9.00 (d, H2", H6", J=6)
2	 8.00 (d, H3', H5', J=9) 8.50 (d, H2', H6', J=9)	 8.15 (d, H3", H5", J=5) 9.00 (d, H2", H6", J=5)
3	 8.00-8.20 (m, H4', H5') 8.45 (m, H2', H6')	 8.10 (d, H3", H5", J=5) 8.85 (d, H2", H6", J=5)
4	 7.70 (d, H3', H5', J=8) 8.20 (d, H2', H6', J=8)	 5.9 (s.e., NH_2) 6.80 (d, H3", H5", J=9) 7.90 (d, H2", H6", J=9)
5	 7.90 (d, H3', H5', J=9) 8.25 (d ,H2', H6', J=9)	 6.0 (s.e., NH_2) 6.80 (d, H3", H5", J=9) 7.85 (d, H2", H6", J=9)
6	 7.90-8.20 (m, H4', H5') 8.45 (m, H2', H6')	6.1 (s.e., NH_2) 6.90 (d, H3", H5", J=9) 7.90 (d, H2", H6", J=9)

Spectra recorded at 60MHz in $DMSOd_6$; δ (ppm) ; J=Hz. Protons NH_2 exchangeable with D_2O.

O-Ethyl 4-Trifluoromethylbenzimidate (**7**).

This compound [12] was obtained as colorless oil, $E_{0.10}$ = 67°, yield 88%; ^{1}H nmr (DMSO-d_6): δ 1.45 (t, 3H, C*H*$_3$, J = 8), 4.45 (q, 2H, C*H*$_2$, J = 8), 7.80 (d, 2H, 3-, 5-*H*, J = 8), 7.90 (s, 1H, N*H*, deuterium oxide-exchangeable), 8.10 (d, 2H, 2-, 6-*H*, J = 8).

O-Ethyl 3-Trifluoromethylbenzimidate (**8**).

This compound [13] was obtained as colorless oil, $E_{0.05}$ = 76°, yield 84%; ^{1}H nmr (DMSO-d_6): δ 1.45 (t, 3H, C*H*$_3$, J = 8), 4.40 (q, 2H, C*H*$_2$, J = 8), 7.40-8.30 (m, 4H, 2-, 4-, 5-, 6-*H*), 7.80 (s, 1H, N*H*, deuterium oxide exchangeable).

O-Ethyl 4-Chlorobenzimidate (**9**).

This compound [14] was obtained as colorless oil, $E_{0.10}$ = 91°, yield 93%; ^{1}H nmr (DMSO-d_6): δ 1.35 (t, 3H, C*H*$_3$, J = 8), 4.30 (q, 2H, C*H*$_2$, J = 8), 7.30 (d, 2H, 3-, 5-*H*, J = 8), 7.65 (d, 2H, 2-, 6-*H*, J = 8), 7.70 (s, 1H, NH, deuterium oxide-exchangeable).

Thionoesters **10-12**.

General Procedure for the Preparation of Thionoesters.

Hydrogen sulphide was bubbled into a solution of iminoester (0.1 mole) in pyridine (40 ml), contained in a three-necked round bottom flask equipped with a thermometer, a calcium chloride drying tube and a long gas-inlet tube, cooled to 0°. After two hours, the reaction mixture was poured into ice water and the mixture was extracted with ether. The organic phase was washed successively with 0.1 *M* hydrochloric acid until the washings were acid and then with water until the washings were neutral, and was dried with anhydrous sodium sulfate. Solvents were removed under vacuum and the residue was distilled.

O-Ethyl 4-Trifluoromethylbenzothioate (**10**).

This compound is a yellow oil, $E_{0.25}$ = 71°, yield 90%; ^{1}H nmr (DMSO-d_6): δ 1.55 (t, 3H, C*H*$_3$, J = 8), 4.85 (q, 2H, C*H*$_2$, J = 8), 7.80 (d, 2H, 3-, 5-*H*, J = 9), 8.50 (d, 2H, 2-, 6-*H*, J = 9).

O-Ethyl 3-Trifluoromethylbenzothioate (**11**).

This compound is a yellow oil, $E_{0.25}$ = 71°, yield 92%; ^{1}H nmr (DMSO-d_6): δ 1.50 (t, 3H, C*H*$_3$, J = 7), 4.75 (q, 2H, C*H*$_2$, J = 7), 7.35-8.50 (m, 4H, 2-, 3-, 5-, 6-*H*).

O-Ethyl 4-Chlorobenzothioate (**12**).

This compound [15] is a yellow oil, $E_{0.04}$ = 95°, mp 40°, yield 95%; ^{1}H nmr (DMSO-d_6): δ 1.50 (t, 3H, C*H*$_3$, J = 8), 4.70 (q, 2H, C*H*$_2$, J = 8), 7.30 (d, 2H, 3-, 5-*H*, J = 8), 8.00 (d, 2H, 2-, 6-*H*, J = 8).

1,3,4-Oxadiazoles **1-6**.

A solution of thionoester (0.01 mole), hydrazide (isonicotic [16], *p*-aminobenzoïc [17]) (0.02 mole) and acetic acid (0.60 ml) in ethanol or ethyleneglycol (20 ml) (refer to Table I) was heated at 80° for 24 hours (when evolution of hydrogen sulphide ceased). The oxadiazoles crystallised when the solutions were cooled. Yields, melting points and elemental analyses are given in Table I and ^{1}H nmr data in Table II.

Pharmacology.

The three 5-(trifluoromethylphenyl)-1,3,4-oxadiazole derivatives **2**, **3** and **5**, are not very toxic (DL_{50} i.p. greater than 260 mg/kg). Compound **3** is very sedative; it significantly decreases the spontaneous motility of mice [18] and their exploratory behaviour on the "Test de la planche à trous" [19] as well as hypermotility induced by dexamphetamine [20]. Compounds **2** and **5** are not sedative; the former is significantly anxiolytic at doses of 6.25 mg/kg and above in the "Test des 4 plaques" [21]; both decrease significantly the duration of immobility in the "behavioral despair Test" [22], which indicates that they possess an antidepressant effect.

Acknowledgments.

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Résumé.

Les auteurs se sont intéressés aux 1,3,4-oxadiazoles substitués en 2 comme d'éventuelles prodrogues d'hydrazides antidépresseurs. Ils exposent une nouvelle méthode d'accès à cet hétérocycle à partir des thionoesters et décrivent 5 nouveaux oxadiazoles substitués en 2 par un reste 4-pyridyl ou (4-aminophényl) et en 5 par un phényl.