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NEW ACTIVATION OF CARBOXYLIC ACIDS BY REACTION WITH N,N-BIS-(2-OXO-3-OXAZOLIDINYL) PHOSPHORODIAMIDIC CHLORIDE (CLSPO)

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Summary: Pentacoordinated and pentavalent phosphorus intermediates, have been isolated by reaction between the title reagent and carboxylic acids, prior to conversion into amides.

Mixed anhydrides, similar to III (scheme) have been prepared by reaction between alkaline or silver salts of partially esterified phosphoric acids with acyl halides.[1]

An alternative procedure is based on the combination of a salt of the carboxylic acid with the phosphoric acid chloride. However, the corresponding acylphosphates were not formed from dibenzyl phosphorochloridate[2]

Acyl phosphates have also been postulated as intermediates in amide preparation with diethyl phosphorobromidate[3] and even isolated in the reaction between diethyl phosphorochloridate and mesitoic acid[4]

We have shown that N,N-bis-(2-oxo-3-oxazolidinyl) phosphorodiamidic acid chloride (I) is an effective reagent for the preparation of amides and esters in the antibiotic field[5,6] Now we report the isolation of the mixed anhydrides (III) (scheme).

Also, pentacoordinated phosphoric compounds of the type II have been invoked as intermediates[7] and we present examples of such intermediates.

When the reactions of phenylmalonic acid hemiesters and hemiamides were studied in the presence of tertiar amines (B), a rapid decarboxylation was observed as expected[8,9], which competes with the formation of mixed anhydrides (III).

The different yields on amides V (table 1) suggest a control through intermediates II. These have been prepared as mixtures (II-M) with I and the pyridinium salts of phenylmalonic hemiesters (mixing 1 mmol of I and pyridinium salt in acetonitrile (30 ml) at -15° for 30 minutes followed by filtration, entries 1 and 2).

When 2,6-dimethoxybenzoic acid triethylammonium salt was chosen as

starting material (entry 3) (reacted with I in methylene chloride/n-hexane at 20º for 30 min), II-M was also isolated. The presence of I and the absence of III in II-M were confirmed through the isolation of the amide of the acid IV, its formation not being possible from III.

II-M from the ardamycin ester (entry 4), decomposes to the ester of phenylacetic acid, even in solution or in solid state at room temperature. It gives silver chloride precipitate when warmed with silver nitrate solution. Its reaction with aniline gives the phenylacetic ester (26%, mp 43-52º), I (10%) and anilide V. With n-butylamine an extensive decarboxylation was observed, and the phenylacetic ester (73%), the amide of n-butylamine with IV (63%) and the butylamide V were produced.

A similar behaviour has been demonstrated for the phenyl hemiester of phenylmalonic acid (entry 2, II-M).

However, II-M with the amines (entry 3) yielded the carboxyamides V, not formation of those corresponding to acid IV being detected. These facts suggest that this reaction proceeds exclusively through III.

Both reactions are competitives in the synthesis of the antibiotics with betalactam nucleus, when amino and/or carboxylic functions present.

The amides derived from acid IV were prepared for characterization purposes from I and the corresponding amines: n-butylamine (Cl_2CH_2, room temp. 45 min, 100%, mp 125-6º from isopropanol); anilide (CH_3CN, room temp., 2h, 70%, mp 204,5-205º from isopropanol).

From 2,6-dinitrobenzoic acid (entry 4) and 2,6-dichloroberzoic acid (entry5), intermediates III could be isolated and converted into the amides V

3,4,5-trimethoxybenzoic and 3,5-dinitrobenzoic acids were also converted into their anilides (95% yield) without isolation of the intermediates III, in a one stape-synthesis.

Therefore, the presence of the amides of the acid IV and the observed decarboxylation suggest a slow formation of II.

These results have been extended to the synthesis of n-acyl derivatives of 6-aminopenicillanic acid (6-APA) by a two-steps procedure. I (0,5 cmol) was reacted with the triethylamonium salt of the carboxylic acid (1,0 cmol) in methylene chloride (room temp.,30-45 min). This mixture was added to a suspension of 6-APA (0,5 cmol) in triethylamine (1 cmol) and methylene chloride. The mixture was stirred at 0-5º for 100 minutes. The isolation was carried out by conventional procedures.[10]

A mixture of I (0,5 cmol) and the triethylammonium salt of the 3-(2-

SCHEME

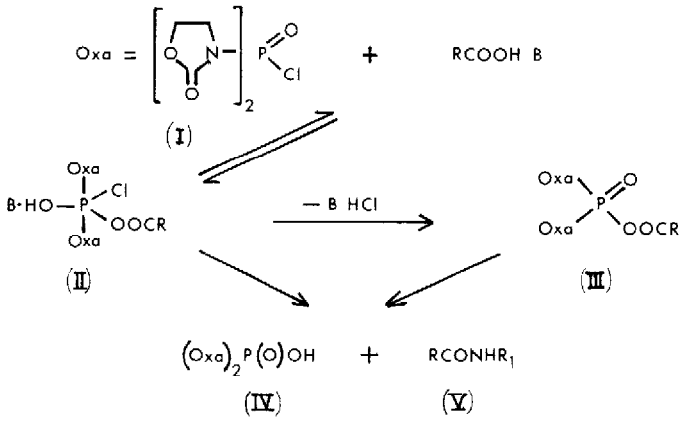
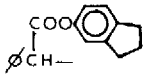
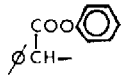
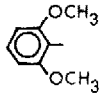
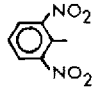
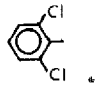


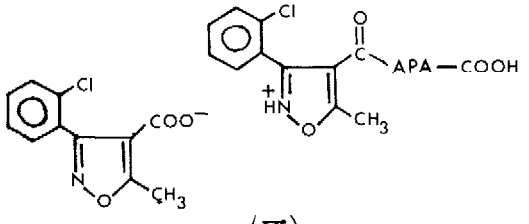
Table 1: [illegible] Intermediates and amides

Entry	R	T	II-M [ref]	[illegible] ld (%)	m.p. (dec.)	IR(KBr) ν (cm⁻¹)	V	Yie (%)	m.p. (solvent)
1		PYR	II-Ma	95	78-80º	1775 1750	n-but.[1]	26	92-95º (isop./H_2O)
							Anil.[2]	73	147-8º[2] (isop.)
2		PYR	II-M	9[illegible]	71-73º	1775 1750	o-Tolu.[3]	70	130,5-134,5º
3		TEA	II-Mc	97	60-70º	1775 1754	Anil.	91	169-71º (benc.)
							n-But	93	100-104º (n-hept./acet.)
4		TEA	III	90	175-6º	1782 1750	Anil.	100	218-20º (ethan.)
5		NEP	III	98	145-6º	1786 1768 1750	2,6-Xily[4]	90	253,5 (acetonitrile)

IR(KBr) max.: (1) 3325,1760,1650. (2) 3310,1769,1657. (3) 3292,1777,1649. (4) 3230,3195,1662. PYR(Pyridine), TEA(Triethylamine), NEP(N-Ethylpiperidine).

chlorophenyl)-5-methyl-isoxazole-4-carboxylic acid (1,0 mmol) in methylene chloride (7 ml) was added to a solution of 6-APA trimethylsilyl ester (prepared from 6-APA (0,5 mmol), TEA (0,7 ml), 3-trimethylsilyl-2-oxazolidinone (1,1 ml) in Cl_2CH_2 (5 ml)). The mixture was kept at 0-5º for 100 min, diluted with water (40 ml). NaCl and n-hexane (10 ml) were added and the ph adjusted at 1,0-1,5 with HCl.

The organic solvents were evaporated and the precipitate was filtered, washed with water and n-hexane, and dried and in vacuum to afford 3,00g (89%) of VI, (mp 170-180ºC with decomposition). IR (KBr): 1785, 1730 and 1682cm^{-1}. All new compounds gave correct elemental analysis.



(VI)

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