Studies on Heterocyclic Compounds. V.[1] Action of Grignard Reagents on 2-Phenyl-5-oxazolone and ω-Benzamidoacetophenone Derivatives

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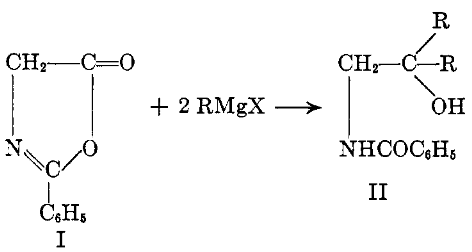
It was reported[2] that 2-phenyl-5-oxazolone (I) reacts with excess ethylmagnesium iodide to give a dimer of the original oxazolone.

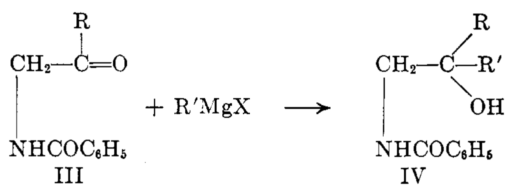
However, ethanol derivatives of type II could be prepared by the action of excess arylmagnesium halides on either I (*cf.* Scheme A), or on the appropriate ω-benzamidoacetophenone derivatives[3] (III)(*cf.* Scheme B). The latter compounds are now easily accessible from the Friedel-Crafts reaction with I as reported in ref. 3.



IIa. R = C_6H_5; IIb, R = $C_6H_4OCH_3$ (*o*); IIc. R = $C_6H_4CH_3$(*p*)

Scheme A

In Scheme A the two aryl radicals introduced by the Grignard reagents are the same. Different radicals (including aliphatic ones) can be introduced when the Grignard reagent is allowed to react with III (*cf.* Scheme B).



IIIa. R = C_6H_5
IIIb. R = $C_6H_4CH_3$(*p*)
IIIc. R = $C_6H_3(CH_3)_2$(3,5)
IVa. (IIa). R = R′ = C_6H_5
IVb. (IIc). R = R′ = $C_6H_4CH_3$(*p*)
IVc. R = $C_6H_4CH_3$(*p*), R′ = CH_3
IVd. R = $C_6H_4CH_3$(*p*), R′ = C_6H_5
IVe. R = $C_6H_3(CH_3)_2$(3,5), R′ = CH_3
IVf. R = $C_6H_3(CH_3)_2$(3,5), R′ = $C_6H_4OCH_3$(*o*)

Scheme B

(1) W. I. Awad and Abd El-Aziz Ali Gadallah, *J. Org. Chem.*, **26**, 591 (1961).
(2) *The Chemistry of Penicillin,* Princeton University Press, Princeton, N. J., 1949, p. 738.
(3) Studies of the Friedel-Crafts reaction on Unsaturated Azlactones, W. I. Awad and M. S. Hafez, *J. Org. Chem.*, **26**, 2055–2057 (1961).

TABLE I

$C_6H_5CONHCH_2—C(R')(R)—OH$

R	R′	Method of Preparation	M.P.	Yield,[a] %	Formula[b]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Color with Concd. H_2SO_4	Stretching Frequency, Cm.$^{-1}$ NH (OH)	CH (aromatic)	Amide I	Amide II	C=C (aromatic)
C_6H_5—	C_6H_5—	A	179	47	$C_{21}H_{19}NO_2$	79.49	79.90	5.99	6.03	4.41	4.40	Yellow	3333	3003	1613	1562	1517
o-$CH_3OC_6H_4$—	*o*-$CH_3OC_6H_4$—	A	155	30	$C_{23}H_{23}NO_4$	73.20	73.02	6.1	6.09	3.72	4.01	Permanganate	3448	2985	1695	1626	1550
p-$CH_3C_6H_4$—	*p*-$CH_3C_6H_4$—	A	160	33	$C_{23}H_{23}NO_2$	80.00	79.62	6.66	6.70	4.06	4.24	Orange	3389	2985	1615	1562	1515
p-$CH_3C_6H_4$—	CH_3—	B	89	79	$C_{17}H_{19}NO_2$	75.84	76.00	7.06	6.61	5.20	5.39	No color	3333	2941	1700	1626	1533
p-$CH_3C_6H_4$—	C_6H_5—	B	144	71	$C_{22}H_{21}NO_2$	79.76	79.91	6.34	6.46	4.23	4.24	Orange	3389	2958	1639	1582	1526
3,5-$(CH_3)_2C_6H_3$—	CH_3—	B	126	74	$C_{18}H_{21}NO_2$					4.96	5.19	No color	3448	2941	1642	1610	1526
3,5-$(CH_3)_2C_6H_3$—	*o*-$CH_3OC_6H_4$—	B	212	59	$C_{24}H_{25}NO_3$	76.8	77.22	6.6	6.17			Yellow	3246	2949	1639	1587	1506

[a] Yield is calculated as pure material. [b] All crystals were colorless.

Structure IV was supported by infrared[4] spectra which showed the stretching frequencies characteristic of aromatic CH, C=C, Amide I, and Amide II (*cf.* Table I). The spectra showed one band in the region 3246–3448 cm.$^{-1}$, probably due to an overlap of the OH and NH stretching frequencies.

EXPERIMENTAL[5]

A. *General procedure for the reaction of 2-phenyl-5-oxazolone*[6] (I) *with arylmagnesium halides.* To an ethereal solution of the arylmagnesium halide (3 moles) was added a solution of the oxazolone (I) (1 mole) in dry ether. The reaction mixture was refluxed for 2 hr. and left overnight. It was hydrolyzed with a saturated ammonium chloride solution, dried over anhydrous sodium sulfate, and evaporated on a water bath nearly to dryness. The oily residue thus obtained was triturated with petroleum ether (b.p. 40–60°) and allowed to cool. The product was filtered and crystallized from benzene. (*cf.* Table I).

B. *General procedure for the reaction of ω-benzamidoacetophenone derivatives* (III) *with aryl- or alkylmagnesium halides.* To an ethereal solution of the aryl- or alkylmagnesium halide (2 moles) was added a solution of the ω-benzamidoacetophenone derivative (III) (1 mole) in dry benzene. The reaction mixture was refluxed for 2 hr. and left overnight. It was hydrolyzed with a saturated ammonium chloride solution, dried over anhydrous sodium sulfate, and evaporated on a water bath nearly to dryness. The oily residue thus obtained was triturated with petroleum ether (b.p. 40–60°) and allowed to cool. The product was filtered and crystallized from benzene. (*cf.* Table I).

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(4) The infrared spectra were carried out by potassium bromide wafer technique using a Perkin-Elmer Infracord Model 137.

(5) Microanalysis were carried out by Alfred Bernhardt im Max-Planck Institut Mülheim (Ruhr), Germany. The melting points are not corrected.

(6) *The Chemistry of Penicillin*, Princeton University Press, Princeton, N. J., 1949, p. 778.

Potential Anticancer Agents: Some New *O*-Alkyl and *O*-Aryl *N,N'*-Diethylene Phosphorodiamidothionates

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N,N',N''-Triethylenephosphorotriamidothionate (TSPA) or Thio-TEPA, considered a standard anticancer alkylating agent[1] and preferred to its less stable oxygen analog, *N,N',N''*-triethylenephosphorotriamide (TEPA) has been shown to be of value in treating a wide variety of human neoplastic conditions including some solid tumors.[1,2]

(1) *Chem. & Eng. News*, special report, Oct. 12, 1959, 53–71.

(2) Ross, R. B., *J. Chem. Ed.*, **36**, No. 8, 368–377 (1959).

In view of this activity we undertook the synthesis of some *O*-alkyl and *O*-aryl *N,N'*-diethylene phosphorodiamidothionates. By substituting an *O*-alkyl or an *O*-aryl group for one of the ethylenimine groups of Thio-TEPA we retained its polyfunctional alkylating properties, anticipating that the new structure would demonstrate improved anticancer activity and reduced toxicity.

The compounds which have been synthesized are now being screened[3] in mice for anticancer activity by the three tumor system, namely, sarcoma-180, adenocarcinoma-755 and leukemia-1210. Some of these compounds have also been tested in the Dunning rat leukemia system. Eleven of the compounds tested in the above systems showed activity in at least one tumor system.

The series of diethylenimine derivatives of monosubstituted *O*-alkyl or *O*-aryl phosphorodichloridothionates prepared in our laboratory are listed in Table I in which some of their physical properties and yields are given and synthetic procedures indicated. Water was used as the reaction medium in the esterification of the phosphorodichloridothionates while in some cases, a water-acetone solution was used. Good yields of relatively pure products were thus obtained. The use of an organic solvent afforded somewhat lower yields and a less pure product due to some polymerization, but cases in which the intermediate phosphorodichloridothionates are sensitive to water, the organic solvent was preferred. When substituted ethylenimines such as 2,2-dimethylethylenimine were used, an organic solvent was also preferred, for it was found that the reaction did not go to completion in water. In general, these compounds are very sensitive to heat and in order to avoid decomposition during distillation, high vacuum and low temperatures have been applied by use of a molecular still. The same synthetic procedures were used in preparing two *O,O'*-dialkyl *N*-ethylene phosphoroamidothionates (I, II) and *N,N'*-diethylenebenzene thiophosphonamide (XVI). No effort was made to obtain maximum yields (Table I).

EXPERIMENTAL

The intermediate *O*-alkyl and *O*-arylphosphorodichloridothionates were prepared by treating thiophosphoryl chloride with the corresponding alkanols or phenols. *O*-Ethyl and *O*-*n*-propyl phosphorodichloridothionates were prepared by modifying the directions given by Pishchimuka[4] in that the reaction mixtures were heated under slight vacuum. The *O*-*n*-butyl and *O*-isoamyl phosphorodichloridothionates were prepared by the procedure given by Manske.[5] A molar excess of the alcohols was heated under reflux with thiophosphoryl chloride in benzene solution.

(3) Screening is being carried out by Cancer Chemotherapy National Service Center NIH, Department of Health, Education and Welfare.

(4) P. S. Pishchimuka, *Ber.*, **41**, 3854–3857 (1908); *J. Russ. Phys. Chem. Soc.*, **44**, 1406–1554 (1912).

(5) R. H. F. Manske, R. W. Beattie, and M. Kulka, U. S. Patent **2,575,224**.