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REACTIONS WITH AZIRIDINES XXI [1].

THE (MICHAELIS-)ARBUSOV REACTION WITH N-ACYL AZIRIDINES AND OTHER AMIDOETHYLATIONS AT PHOSPHORUS.

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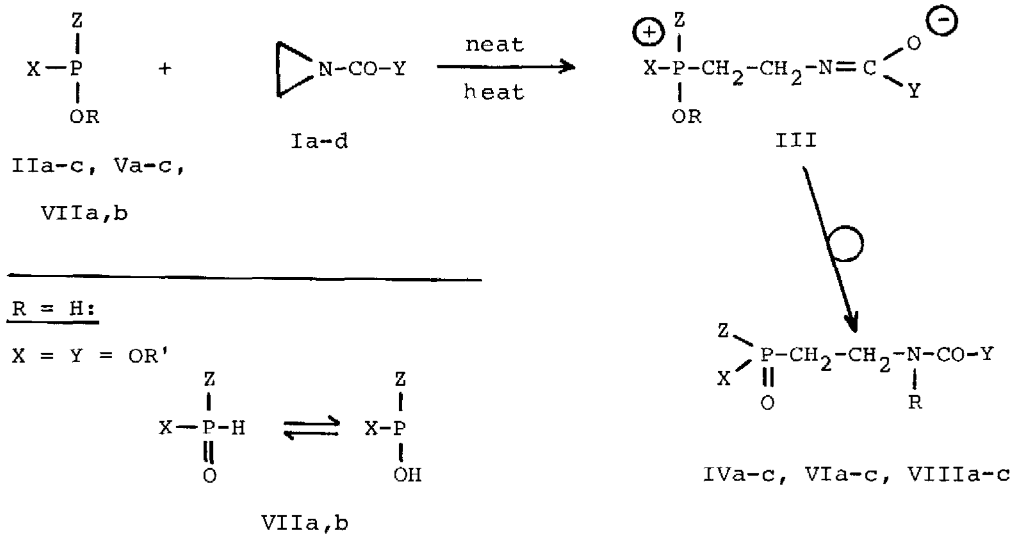
Summary: Heating trialkyl phosphites with N-acyl aziridines produces dialkyl 2-amidoethyl-phosphonates bearing one of the phosphite alkyl groups on nitrogen. Other alkoxy phosphines behave analogously. Dialkyl phosphites furnish the same type of products devoid of the N-alkyl group.

The well known (Michaelis-)Arbusov reaction[2] of trialkyl phosphites with alkylating agents yields dialkyl alkylphosphonates by nucleophilic displacement of one alkyl group from the intermediate phosphonium ion. By substituting N-acyl aziridines Ia-c for the usual alkyl halides we have obtained compounds IVa-c. By analogy, we assume that formation of IV proceeds via the intermediate zwitterions III. IVa-c were formed by heating equimolar parts of I and II without solvent, see table 1.



	IVa	IVb	IVc	IVd	IVe	IVf	IVg
Y	OEt	OMe	Ph	OEt	OEt	OEt	OCH_2Ph
R	Et	Me	Et	CH_2Ph	Et	CH_2Ph	Et
X	OEt	OMe	OEt	OEt	OEt	OEt	OEt
Z	OEt	OMe	OEt	OCH_2Ph	OCH_2Ph	OEt	OEt

VIa-c: Y = OEt; Z = Ph;

	VIa	VIb	VIc
R	Et	Et	Me
X	OEt	Ph	Ph

VIIIa-c: R = H; Y = OR';

	VIIIa	VIIIb	VIIIc
Y	OEt	Ph	$OCHMe_2$
R'	Et	Et	$CHMe_2$

Table 1.

Reaction		Yields, based on consumed I [a]
Ia + IIa	2 h 140-145°C	28 % IVa, by distillation, b.p. 120°C/0.03 mm Hg
Ia + IIa	57 h 100°C	(65 %) IVa
Ib + IIb	2 h 140-150°C	38 % IVb, by distillation, b.p. 121°C/0.02 mm Hg
Ic + IIc	15 h 110°C	(66 %) IVc
Ia + IId	6 h 100°C	mixture of IVd-g + IVa, see text
Ia + Va	8 d 65°C	33 % VIa, by column chromatography
Ia + Vb	7 d 50°C	21 % VIb, by column chromatography
Ia + Vc	4 h 100°C	14 % VIc, by short way distillation at 160-180°C/0.005 mm Hg
Ia + VIIa	5 h 150°C	42 % (66 %) VIIIa, b.p. 137°C/0.001 mm Hg
Ic + VIIa	64 h 100°C	(77 %), identified by comp. with auth. sample
Id + VIIb	70 h 100°C + 40 h 120°C	52 % (60 %) VIIIc [b]

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[a] Yields in parentheses are determined by ^{1}H-NMR of the reaction mixture.

[b] Chromatography: silicagel, eluent acetone (forerun with dichloromethane). Eluted VIIIc was separated from polar byproducts by dissolution in ligroin.

$P(OCH_2Ph)_3$ [3] could not be amidoethylated with Ia at 105°C (5 hours), the only reaction observed being an about 30 % exchange of EtO in Ia by $PhCH_2O$: ^1H-NMR shows benzyl singlet at 5.17 ppm, aziridine singlet at 2.06 ppm (Ia 2.00 ppm). After 3 days (105-120°C) an unidentifiable mixture was obtained which contained neither IV nor aziridine compounds.
Heating of the mixed phosphite $(EtO)_2P(OCH_2Ph)$ (IId) with Ia (6 days at 100°C) produced a mixture which could be separated into three fractions by column chromatography. These were analysed by elemental analysis and by ^1H-NMR. Fraction 1 (2 %) consisted of a mixture of those products of type IV which contain two benzyl groups per molecule, i.e. IVd and (probably) isomers with $N-COOCH_2Ph$ structure. Fraction 2 (13 %) consisted of IVe and IVf (main product) and probably a small quantity of IVg. Fraction 3 (16 %) was rather pure IVa.
The hypophosphite Va as well as the alkoxy diphenylphosphines Vb,c undergo the same reaction with Ia (under N_2) even at lower temperatures producing compounds VI a-c, see table 1.
The isolated products VIa-c were accompanied by the corresponding N dealkylated products in total yields of 6 %, 4.5 % and about 1 %. VIa was separated from its NH homologue by distillation (VIa b.p. 167°C/0.005 mm Hg), VIb by preparative tlc. The yields of VIa,b in table 1 refer to the NH free products.

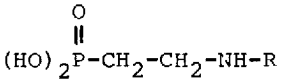
At least in the case of VIa,b these NH byproducts must have formed by dealkylation of the intermediate zwitterions III since the only other conceivable origin of them requires a rather high and therefore detectable contamination of the educts Va,b with their homologues VII (R = H). A very plausible way of dealkylation of III would be an elimination of ethene. - The phosphonates IVa-c were far less contaminated by their NH homologues.

The new products show ir absorption for P = O near 1250 cm^{-1} (IVa-c), 1230 cm^{-1} (VIa), and 1190 cm^{-1} (VIb,c). The most characteristic ^1H-NMR data concern the $P-CH_2-CH_2-N$ structure. The CH_2-N multiplets are found near 3.4 ppm (3.7 if Y = Ph) ($CDCl_3$). The $P-CH_2$ multiplets are duplicated by coupling with ^{31}P: shifts (pairs of multiplets) near 1.94/2.24 ppm for IVa-c, 2.12/2.35

ppm for VIa, 2.52/2.70 ppm for VIb,c. The P-C-H- couplings are 18.5 Hz (IVa-c), 15.6 Hz (VIa) and ca. 10 Hz (VIb,c).

In separate experiments the dialkyl phosphites VIIa,b could be amidoethylated in fair yields [4] in spite of the predominance of the phosphonate tautomer of VIIa,b. We assume that the formation of VIIIa-c follows the same reaction mechanism, the phosphorus atom of the phosphite tautomer of VII serving as nucleophilic centre in the first ring opening step. - The most characteristic NMR-data differ from those of IVa-c by a broad NH signal near 6 ppm (8 ppm if Y = Ph) and by the P-couplings: both P-C-H and P-C-C-H cause splitting by ca. 17 Hz.

Boiling conc. hydrobromic acid hydrolyzes VIIIa and IVa to aminoethylphosphonic acid (ciliatin) IXa and its N-ethyl derivative IXb, isolated as their hydrobromides:



$$(HO)_2\overset{\overset{O}{\|}}{P}\text{-}CH_2\text{-}CH_2\text{-}NH\text{-}R$$

IXa: R = H

IXb: R = Et

ACKNOWLEDGMENT

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REFERENCES and NOTES

[1] Part XX: H. Stamm and J. Budny, J. Chem. Research (S) 1979, 368, (M) 4501.

[2] Compare e.g.: R. G. Harvey and E. R. DeSombre in: Topics in Phosphorus Chemistry, vol. 1, Ed. by M. Grayson and E. Griffith, John Wiley & Sons, New York 1964.

[3] Previously to this experiment the contaminating dibenzyl phosphite had been removed by treatment with an excess of NaH followed by filtration. Tribenzyl phosphite could not be purified by column chromatography (hydrolysis ?) and was remarkable thermostable (after 40 hours at 140°C only 40 % was isomerized.

[4] T. Baumann in our laboratory obtained VIII (R = H, X = Z = OCH_2Ph, Y = OEt) only in 11 % yield from dibenzylphosphite and Ia (24 h 110°C).

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