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ARYLAZOMETHYLENETRIPHENYLPHOSPHORANES: INTRA MOLECULAR REACTIONS WITH ALDONITRONYL SUBSTITUENTS IN THE ORTHO POSITION WITH RESPECT TO THE AZOPHOSPHORANE GROUP

A.ALEMAGNA*, P.DEL BUTTERO, E.LICANDRO* and A.PAPAGNI

Dipartimento di Chimica Organica e Industriale dell'Università
Via C. Golgi 19 - 20133 Milano, Italy

M.BALLABIO

Farmitalia-C.Erba, Ricerca e sviluppo Chimico
Via dei Gracchi 35 - 20146 Milano, Italy

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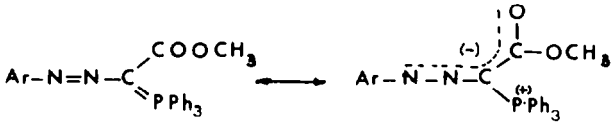
Abstract: The title reactions begin with the attack on the aldonitronyl group by the nitrogen atom α to the ylidic carbon, to give, presumably, a cyclic species, which splits off a nitroso compound to afford indazolyl--2-methylenetriphenylphosphorane. In one case the primarily formed cyclic species underwent a further intra molecular cyclization to imidazo[1,2-b]indazole.

A few years ago we became interested in the chemistry of arylazomethylenetriphenylphosphoranes[1,2,3], a class of compounds whose reactivity was, at the time, practically unknown. Since then, we have investigated the inter and intra molecular reactions of compounds of type (1) with double and triple C-C bonds[4,5] and with electrophilic groups[6,7]. Among the latter , the intra molecular

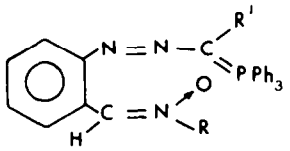


(1)

reactions of C=O groups[6] have shown peculiar and interesting features[6,8].

In this paper we report the results of our research on arylazomethylenetriphenylphosphoranes (2) carrying, in the position ortho to the azophosphorane group, an aldonitronyl substituent. Inter molecular reactions between aldonitrones and alkylidene phosphoranes have been reported[9] to afford

1,2,5-oxaazaphospholes, through a 1,3 dipolar cycloaddition process. Although a preliminary work had shown that azophosphoranes of type (1) do not react intermolecularly with aldonitrones, an analogous intra molecular reaction on compounds of type (2) was, in principle, possible, and would have led to the dihydrooxaazaphospholocinnolines (3).



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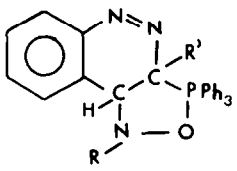
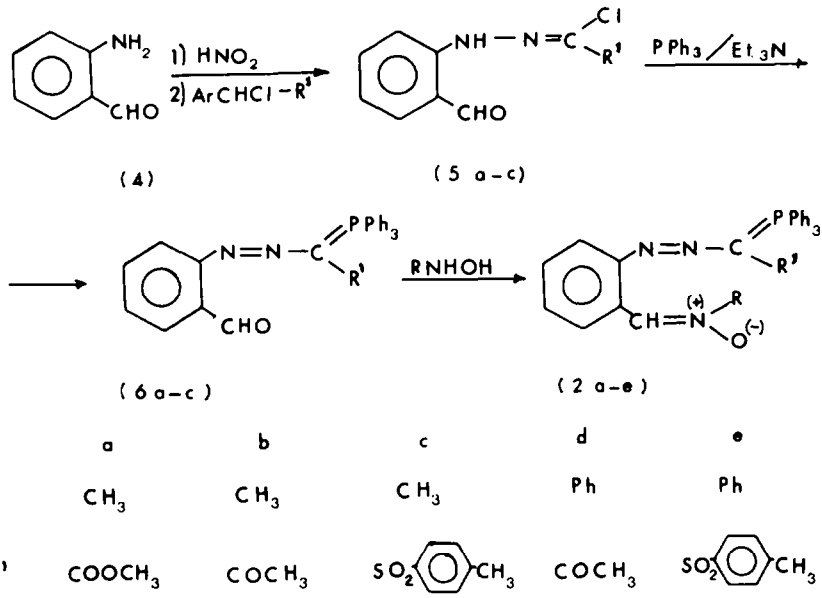


(3)

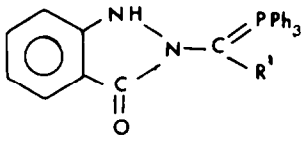
In order to check the possibility of this or different intra molecular reactions, we have prepared several derivatives of type (2), namely (2a-e) (scheme 1), carrying different substituents on the ylidic carbon and on the nitronyl nitrogen.

Scheme 1



The starting material has been, in all cases, the o.aminobenzaldehyde (4), that was diazotized and coupled with the appropriate chloro derivatives, to give the hydrazonoyl halides (5a-c); the latter were transformed into the corresponding phosphoranes (6a-c) by treatment with PPh_3 and a base[3]. The nitronyl derivatives (2a-e) were then obtained in good yields by reaction of the formylphosphoranes (6a-c) with the appropriate N substituted hydroxylamine. Carrying out the reaction in mild conditions (50° C) has allowed to avoid the intra molecular cyclization of compounds (6a-c) to the corresponding indazolinonyl or quinazolinonyl derivatives of types (7) or (8), which are obtained at higher temperatures (70-80° C)[6,8,10].

The phosphoranes (2a-e) have been submitted to thermal treatment in toluene and DMSO as solvents (scheme 2 and table 1). (2a), refluxed in toluene under nitrogen, gave the 3-methoxycarbonyl-imi-



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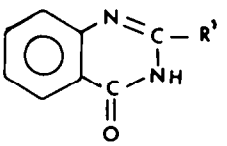
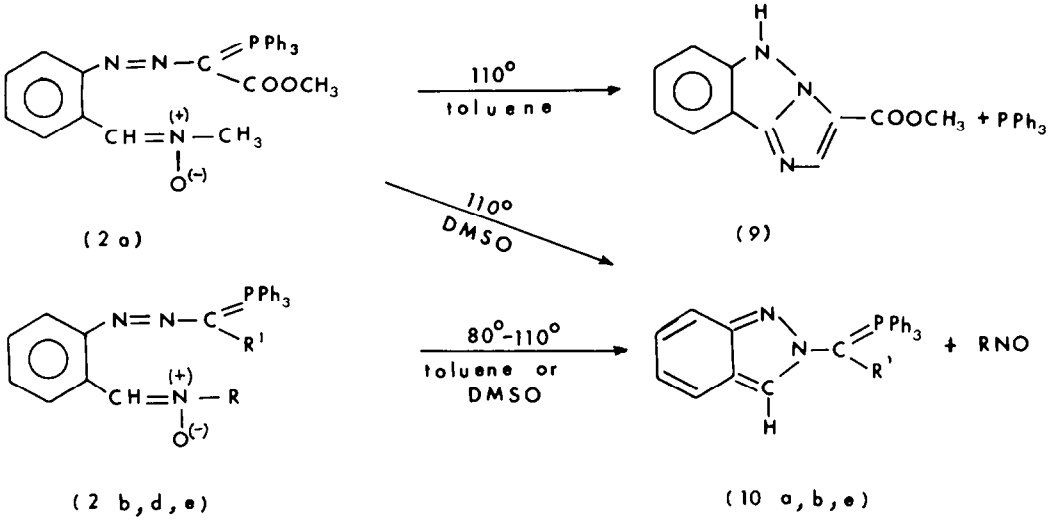


(8)

dazo[1,2-b]indazole (9) and PPh_3. On heating the same compound (2a) at 110° C, under nitrogen, in DMSO, we obtained, instead, the indazol-2-yl-(methoxycarbonyl)methylenetriphenylphosphorane (10a). Carrying out the reaction in toluene in the presence of a trace of Et_3N led to (10a), while in o.dichlorobenzene a mixture of (9) and (10a) was obtained.

Scheme 2



(2 a)

(9)

(2 b, d, e)

(10 a, b, e)

The structure of 3-methoxycarbonyl-imidazo[1,2-b] indazole has been assigned to (9) on the base of analytical, IR, ^1H and ^{13}C NMR and mass spectral data. The tricyclic structure is well supported by the presence in the ^{13}C NMR spectrum of the signal of C-9b, vicinal to two nitrogen atoms, as a broad singlet at 139.77 δ , and by the broad CH-2 signal of the imidazole moiety at 132.27 δ*. The ester carbonyl is found at 159.00 δ; the high shielding with respect to the α,β unsaturated esters[11] is justified by the high degree of $e^{(-)}$ delocalization present in structure (9). The assignment of the phenyl carbons is in agreement with known substituent effects[12].

Also for (10a) analytical and spectral data are consistent with the given structure, which has been proved also by acid catalyzed hydrolysis to methyl indazol-2-yl-acetate, identical with an authentic sample[13].

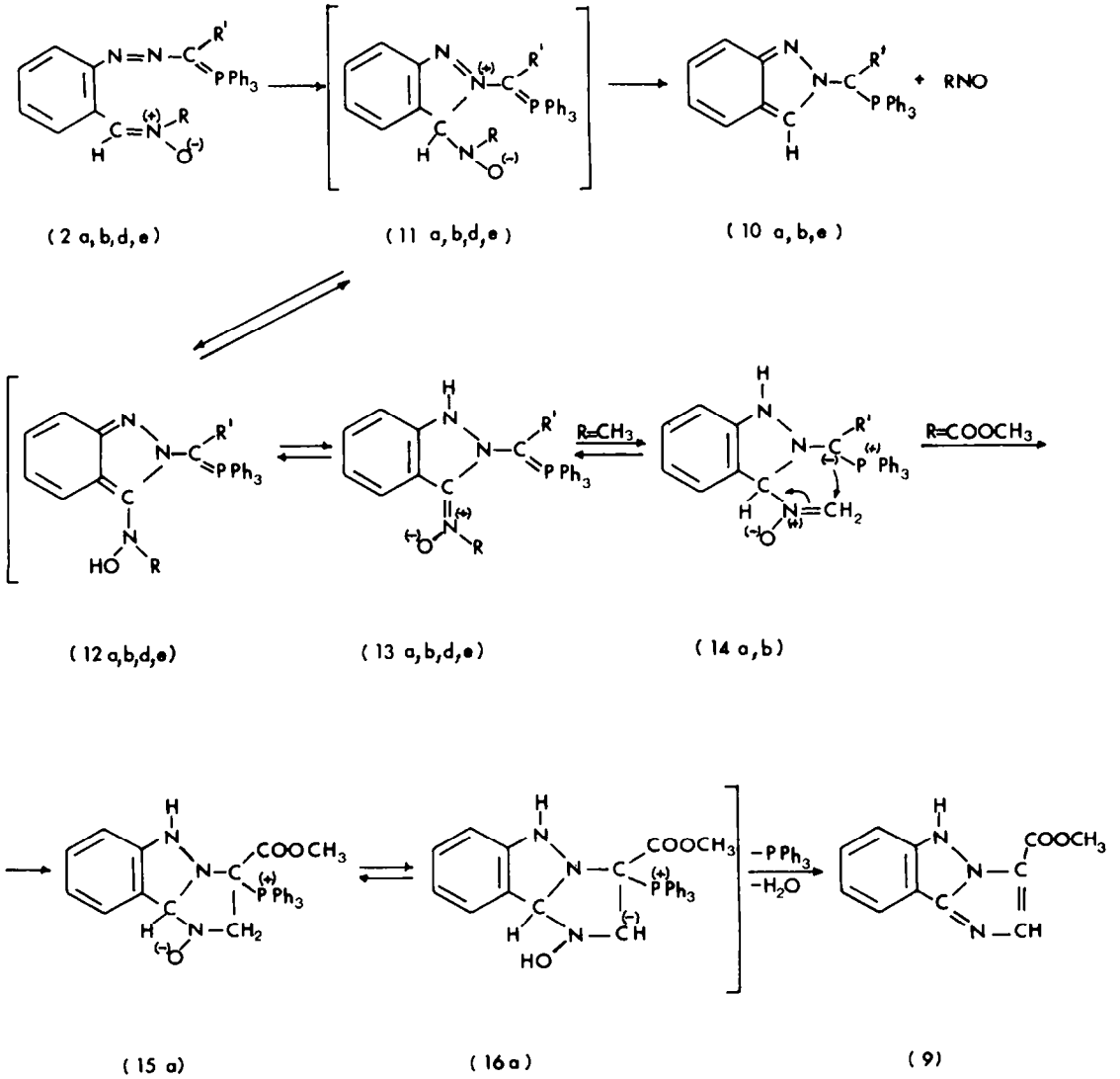
Heating compounds (2b,d) at 110° C, both in toluene and in DMSO, led to the corresponding indazolylphosphoranes (10b,d), whereas (2c,e), in the same conditions gave intractable mixtures;

* The corresponding hydrogen appears as a singlet at 8.18 ppm, probably deshielded by the anisotropic effect of the ester carbonyl group, heavily conjugated with the imidazole ring.

in milder conditions (80° C, toluene), however, the indazolyl derivative (10e) could be obtained from (2e). Starting from (2d) we were able to isolate also nitrosobenzene, in good yield. Therefore we assume that the formation of (10a,b,e) from (2a,b,e) is accompanied by that of the corresponding nitroso compounds RNO, although we did not isolate them. No imidazo 1,2-b indazole derivative analogous to (9) could be detected in the reaction mixture from (2b) and no oxaazaphospholocinnoline derivative of type (3) has been obtained from anyone of compounds (2a-e).

The above results can be rationalized if one assumes that the nitrogen α to the phosphoranyl ylidic carbon attacks the ortho aldonitronyl group at the carbon atom, to give the cyclic species (11a,b,d,e), (scheme 3), which split off RNO, to afford the indazolylmethylenephosphoranes (10a,b, d,e). On the other hand, the cyclic species (11) could rearrange to the hydroxylamino derivative (12),

Scheme 3



which, in turn, should be in prototropic equilibrium with the nitronyl derivative (13). When R = CH_3, the latter may rearrange to a tautomeric compound (14). If the ylidic carbon atom carries enough

negative charge, an intra molecular cyclization may take place. So, when R' = $COOCH_3$ the intermediate (15a) is formed, which rearranges to (16a), which then splits off water and PPh_3 to give the imidazo[1,2-b]indazole (9). The fact that compound (9) is obtained in good yield only in non polar solvents and in the absence of bases and that no analogous tricyclic compound has been obtained from (2b), seems to point out that two steps are critical for its formation: i) the stabilization of intermediates like (12) and (13) (intermediates with higher charge separation as (11) are strongly favoured in highly polar solvents like DMSO, while in solvents of lower polarity like o.dichlorobenzene, an equilibrium between (11) and (12)-(14) is reached, leading to mixtures of (10) and (9)); ii) the following nucleophilic attack of the ylidic carbon on the C-N double bond of (14), that can be hindered by electron withdrawing substituents stronger than $COOCH_3$.

The formation of imidazo 1,2-b indazoles from o.(N-methylaldonitronyl)arylazomethylenetriphenylphosphoranes, although not general, has some synthetic interest, as, to our knowledge, only one example of such heterocycle has been reported in the literature[14].

The reactions described in the present paper are in line with those we have already reported[6,8] on the o.formyl-arylazomethylenetriphenylphosphoranes, and confirm,once again,that in the arylazomethylenetriphenylphosphoranes carrying electron withdrawing substituents on the ylidic carbon, the electrophilic attack does not go on this atom, but rather on the azo group[7], and this could be the key step also in the mechanism of formation of indazolinonylmethylenephosphoranes from isatine derivatives[8].

EXPERIMENTAL

M.p.s were taken by means of a Büchi apparatus and are uncorrected . IR spectra were recorded by a Perkin-Elmer X98 spectrophotometer. ^1H NMR spectra were taken at 90 MHz with a Varian EM-390 spectrometer. Chemical shifts are expressed as δ values ($SiMe_4$ as internal standard). Coupling constants are given in Hz. ^{13}C NMR spectra were recorded with a Varian XL-100 spectrometer. Mass spectra were taken with a Varian MAT 311-A spectrometer, equipped with a combined E.I.-F.I.-F.D. ion source. Silica gel 60 (Merck, 70-230 mesh) was used for column chromatography. T.l.c.s were performed on Merck precoated silica gel 60F-254 plates. M.p.s, crystallization solvents and analytical data of new compounds are reported in table 2; spectral data are collected in table 3.

o.Formyl-phenylhydrazonoyl chlorides (5a-c)

The hydrazonoyl chlorides (5a-c) have been prepared, following standard procedures[15], from o.aminobenzaldehyde, by diazotization and coupling with methyl 2-chloroacetacetate for (5a), 3-chloroacetylacetone for (5b) and crude 1-chloro-1-p.toluensulphonylacetone[16] for (5c). (5a), (5b) and (5c) were obtained in 77%, 75% and 38% yield, respectively.

o.formyl-phenylazomethylenetriphenylphosphoranes (6a-c)

These compounds were prepared from the corresponding hydrazonoyl chlorides (5a-c), PPh_3 and Et_3N in CH_3CN, following the method previously described[3]. Crude (6a), dissolved at room temperature in EtOH, crystallized on scratching the pot walls and was recovered in 49% yield. Crude (6b) was washed with light petroleum and employed without further purification (89% yield). For analytical purposes a sample was crystallized from i.PrOH. (6c) was obtained, practically pure, in 86% yield.

o.(N-methyl)aldonitronyl-phenylazomethylenetriphenylphosphoranes (2a-c)

To a solution of the appropriate o.formyl-phenylazomethylenetriphenylphosphorane (6a-c) ($2.04 \cdot 10^{-3}$ moles) in EtOH (30 cm^3) equimolar amounts of $CH_3NHOH.HCl$ and $NaHCO_3$ were added at room temperature.

TABLE 1

Thermal treatment of compounds (2a-e)

Comp.	Solvent	Reaction temperature (°C)	Reaction time (h)	Products	Yields (%)
(2a)	toluene	110	5	(9)	63
(2a)	o.dichlorobenzene	110	5	(9) + (10a)	55 , 30
(2a)	toluene + Et_3N*	110	6	(10a)	80
(2a)	DMSO	110	3	(10a)	22
(2b)	toluene	110	6	(10b)	47
(2b)	DMSO	110	8	(10b)	35
(2c)	toluene	110	6	intractable mixture	
(2c)	DMSO	110	5	intractable mixture	
(2c)	toluene	80	6	no reaction	
(2c)	DMSO	90	4	no reaction	
(2d)	toluene	110	7	(10b) + PhNO	54 , 55
(2d)	DMSO	110	4	(10b)	40
(2e)	toluene	110	4	intractable mixture	
(2e)	toluene	80	10	(10e)	60
(2e)	DMSO	80	4	intractable mixture	

*A trace.

TABLE 2

Melting points, crystallization solvents and analytical data of new compounds

Comp.	M.p. (°C) (cryst. solvent)	Formula	Found %			Required %		
			C	H	N	C	H	N
(2a)	191 (i.PrOH)	$C_{29}H_{26}N_3O_3P$	70.44	5.23	8.62	70.30	5.25	8.49
(2b)	193-194 (i.PrOH)	$C_{29}H_{26}N_3O_2P$	70.40	5.24	8.31	70.65	5.42	8.76
(2c)	190-191 (MeOH)	$C_{34}H_{30}N_3O_3PS$	69.09	5.11	7.12	69.03	5.07	7.10
(2d)	202-203 (CH_3CN)	$C_{34}H_{28}N_3O_2P$	74.46	5.25	7.78	75.41	5.17	7.76
(2e)	197 (C_6H_6)	$C_{39}H_{32}N_3O_3PS$	71.26	4.96	6.47	71.66	4.90	6.43
(5a)	130 (EtOH)	$C_{10}H_9ClN_2O_3$	54.12	3.97	12.75	54.44	4.08	12.70
(5b)	172 (EtOH)	$C_{10}H_9ClN_2O_2$	52.99	4.17	12.35	53.07	4.01	12.50
(5c)	158 (EtOH)	$C_{14}H_{13}ClN_2O_3S$	53.63	4.03	8.36	53.49	3.86	8.32
(6b)	141-142 (i.PrOH)	$C_{27}H_{23}N_2O_2P$	73.50	4.98	6.13	74.66	5.11	6.22
(6c)	178 (iPrOH)	$C_{33}H_{27}N_2O_3PS$	70.57	4.85	4.78	70.46	4.80	4.98
(9)	238-240(dec) (AcOH)	$C_{11}H_9N_3O_2$	61.17	4.49	19.33	61.39	4.19	19.53
(10a)	231 (MeOH)	$C_{28}H_{23}N_2O_2P$	74.32	5.23	6.21	74.66	5.11	6.22
(10b)	208-209 (C_6H_6)	$C_{28}H_{23}N_2OP$	77.69	5.36	6.41	77.41	5.29	6.45
(10e)	207-208 (i.PrOH)	$C_{33}H_{27}N_2O_2PS$	72.62	5.06	5.16	72.52	4.94	5.12

TABLE 3

Spectral data of new compounds

Comp.	ν_{max} (cm^{-1}) (nujol)	N.M.R. ($CDCl_3$, if not otherwise stated)
(2a)	1670	^1H: 3.15(3H,s), 3.60(3H,s), 7.00-7.80(19H,m), 9.00(1H,s)
(2b)	1610, 1345	^1H: 2.70(3H,s), 3.20(3H,s), 7.00-7.80(19H,m), 9.05(1H,d,J=9*)
(2c)	1350, 1140	^1H: 2.35, 2.42(3H,2s**), 3.18, 3.92(1H,2s**), 6.50-8.00(24H,m), 9.04(1H,d,J=7.5*)
(2d)	1620, 1582, 1325	^1H: 2.80(3H,s), 6.85-7.85(24H,m), 9.30(1H,d,J=9*)
(2e)	1350, 1135	^1H ($CDCl_3$+DMSO): 2.20, 2.45(3H,2s**), 6.65-8.10(28H,m), 9.28 (1H,d,J=9*)
(5a)	3230, 1735, 1670	^1H: 3.95(3H,s), 7.00-7.80(4H,m), 10.00(1H,s), 11.90(1H,s)
(5b)	3190, 3180, 1683, 1650	^1H: 2.60(3H,s), 7.10-7.80(4H,m), 10.05(1H,s)
(5c)	3205, 1665, 1335, 1150	^1H: 2.50(3H,s), 7.00-8.00(8H,m), 9.95(1H,s), 11.80(1H,s), 12.00 (1H,s)
(6b)	1680, 1615, 1587, 1330	^1H: 2.70(3H,s), 6.90-7.90(19H,m), 9.37(1H,s)
(6c)	1680	^1H: 2.33, 2.40(3H,2s**), 6.43-8.10(23H,m), 9.27, 10.86(1H,2s**)
(9)†	3150, 1720	^1H: 3.88(3H,s)(CH_3), 7.09, 7.37(2H, 2td, J=7.5, 1.5)(H-7, H-8), 7.52, 7.83(2H,2dd,J=7.5, 1.5)(H-6, H-9), 8.18(1H,s)(H-2) ^{13}C: 51.35(CH_3O), 107.84(C-5a), 113.31(C-3), 113.54(C-6), 118.9 119.45(C-7, C-8), 126.66(C-9), 132.27(C-2), 139.77(C-9b), 148.77(C-9a), 159.00(C=O)
(10a)††	1630, 1310	^1H: 3.50(3H,s), 6.80-7.80(20H,m) ^{13}C: 50.43(CH_3O), 60.09(C-α, $^1J_{CP}$=160), 117.51(C-7), 119.82(C-4) 120.66(C-3), 121.46(C-3a), 124.89(C-1', $^1J_{CP}$=93), 125.07 (C-5), 128.47(C-3', $^3J_{CP}$=12.7), 130.44(C-6), 132.11(C-4', $^4J_{CP}$=3), 133.28(C-2', $^2J_{CP}$=10), 148.87(C-7a)
(10b)	1625, 1500	^1H: 1.90(3H,s), 6.80-7.80(21H,m)
(10e)	1370, 1270, 1120	^1H: 2.35(3H,s), 6.65-7.80(24H,m)

*Coupled with an aromatic H.

**Mixture of cis-trans isomers.

†Mass spectrum: m/z 215 (M^+)

††Mass spectrum: m/z 550 (M^+)

The mixture was heated 3 h at 50° C under nitrogen. The solvent was evaporated at reduced pressure and the residue was treated with water and extracted with CH_2Cl_2. The organic solution was dried over Na_2SO_4, the solvent evaporated *in vacuo* and the residue purified by crystallization. (2a), (2b) and (2c) were obtained in 88%, 74% and 92% yield , respectively.

o.(N-phenyl)aldonitronyl-phenylazomethylenetriphenylphosphoranes (2d,e)

These compounds were prepared with a procedure analogous to that described for the corresponding N-methyl derivatives (2a-c) (see above), with the difference that, N-phenylhydroxylamine beeing available as free base, no $NaHCO_3$ was added. As a consequence, work up was simpler, because (2d,e), practically pure, crystallized from the reaction mixture on simple concentration. (2d) and (2e) were obtained in 84% and 93% yield, respectively.

Thermal treatment of o.aldonitronyl-phenylazomethylenetriphenylphosphoranes (2a-e)

a) In toluene or o.dichlorobenzene

Compounds (2a-e) ($3.5 \cdot 10^{-3}$ moles) were heated in 50 cm^3 of solvent until reaction completion (t.l.c., eluent: $CHCl_3$-EtOAc 9:1). The solvent was evaporated under reduced pressure and the residue was either washed with Et_2O (case of (2a)), or column chromatographed (eluent: $CHCl_3$-EtOAc 9:1 to 3:7 for (2b,d); Et_2O-light petroleum 1:1 for (2e)). The products were then crystallized from suitable solvents. Reaction solvents, times, temperature and products yields are shown in table 1.

b) In DMSO

Compounds (2a-e) ($0.3 \cdot 10^{-3}$ moles) were heated in DMSO (5 cm^3) until reaction completion (see above). The mixture was poured in water and extracted with $CHCl_3$. The organic layer, dried over Na_2SO_4, was evaporated to dryness under reduced pressure and the residue was washed with Et_2O in the case of (2a), submitted to thick layer chromatography (eluent: $CHCl_3$-EtOH 3/7) in the other cases. The products were then crystallized. Reaction times, temperatures and products yields are shown in table 1.

Hydrolysis of (10a)

(10a) (0.65 g) was added to an ice cold solution of H_2SO_4 (2.8 cm^3) in MeOH (21 cm^3) and water (2.1 cm^3). The mixture was stirred three days at room temperature, under nitrogen, poured in water and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and the solvent evaporated at reduced pressure. From the residue, treated with a small amount of Et_2O, $Ph_3P{\rightarrow}O$ (0.165 g) was filtered off. The Et_2O solution was distilled; the fraction boiling at 160-180° C/0.5 mm (0.101 g) was recognized as methyl indazol-2-yl-acetate by comparison with an authentic sample[13].

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