Tetrahedron Vol. 34, pp. 1241 to 1245. Pergamon Press 1978. Printed in Great Britain

NITRONES—V[1]

REACTIONS OF SOME NITRONES WITH PHOSPHINOXY YLIDS

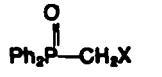
SHMUEL ZBÁIDA and ELI BREUER*
Department of Pharmaceutical Chemistry, The Hebrew University School of Pharmacy, Jerusalem, Israel

(*Received in UK 30 September 1977; Accepted for publication 13 October 1977*)

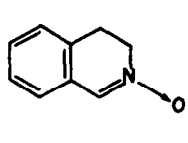
Abstract—Reactions of 3,4-dihydroisoquinoline N-oxide (1) with carbomethoxymethyldiphenylphosphine oxide (13) and cyanomethyldiphenylphosphine oxide (14) lead both in 1,2-dimethoxyethane (DME) and in t-BuOH mostly to enamines 6 and 7 respectively. In contrast reactions of 5,5-dimethyl-Δ^1-pyrroline N-oxide (2) with 13 and 14 lead to mixtures of aziridines 8 or 9 and of enamines 10 or 11, respectively, in the aprotic solvent DME. These reactions give only aziridines 8 or 9 in t-BuOH. The results obtained are explained in terms of the formation of pentacoordinated phosphorus intermediates.

Recently, we reported that reactions of 3,4-dihydroisoquinoline N-oxide (1)[2] and of 5,5-dimethyl-Δ^1-pyrroline N-oxide (2)[1] with ylids derived from trialkyl phosphonoacetate (3) or diethyl cyanomethylphosphonate (4) lead to aziridines (5, 8 or 9) and/or enamines (6, 7, 10 or 11). The course of these reactions was found to depend upon a number of factors, such as the structure of nitrone and phosphonate and the nature of solvent and of base used in the reaction. The results obtained were rationalized by assuming the formation of an oxazaphospholidine intermediate 12 which can decompose to an aziridine or to an enamine. We assumed that decomposition of this intermediate to aziridine is initiated by the negatively charged exocyclic oxygen.[3] In intermediate 12 interaction with the oxygen lone pairs raises the energy of the phosphorus *d* orbitals, therefore these orbitals are not good acceptors and cannot stabilize the negative charge.[4] We considered that replacement of the OR's by phenyl groups should result in a better ability of the phosphorus to stabilize the negative charge by delocalization and therefore it may be expected that such an intermediate will show less tendency to undergo fragmentation to aziridine than 12. Consequently, in the reactions of nitrones with phosphinoxy ylids more enamine formation should be expected.

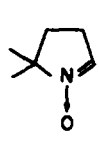
To test the validity of these assumptions, we have studied the reactions of two representative nitrones, 1 and 2 with ylids derived from carbomethoxymethyldiphenylphosphine oxide (13) and cyanomethyldiphenylphosphine oxide (14). The results of this study are the subject of this paper.



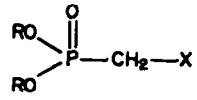
13: X = CO_2CH_3
14: X = CN



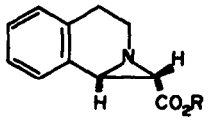
1



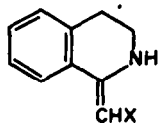
2



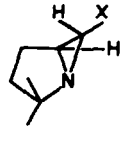
3, X=CO_2R
4, X=CN



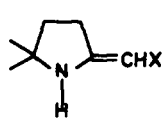
5



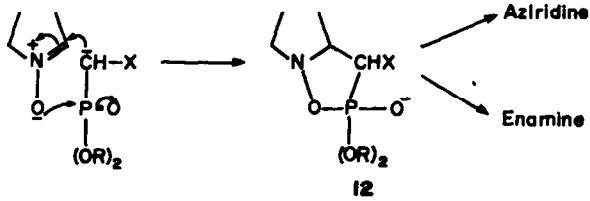
6, X=CO_2R
7, X=CN



8, X=CO_2R
9, X=CN



10, X=CO_2R
11, X=CN



12

RESULTS

The results from the reactions of 3,4-dihydroisoquinoline N-oxide (1) with phosphine oxides 13 and 14 are summarized in Table 1. From this table it can be seen that while the reaction of 1 with 13 using sodium hydride in 1,2-dimethoxyethane (DME) gave rise to equal amounts of aziridine 5 (R = Me) and enaminoester 6 (R = Me) (exp. 1) all other reactions led exclusively to enaminic products, excepting the reaction of 1 with 14 in methanol, from which unreacted starting materials were recovered (exp. 8).

Table 2 summarizes the results from the reactions of 5,5-dimethyl Δ^1-pyrroline N-oxide (2) with phosphine oxides 13 and 14. From this table it can be seen that reactions that were carried out in the aprotic solvent DME led either partially (exps 1, 5 and 6 or solely exp. 7) to enamines (it is worthy to mention that reactions of 2 with phosphonates 3 and 4 in DME led only to aziridines).[1] In contrast reactions of 2 with 13 and 14 in t-butyl alcohol led only to aziridines (exps 3 and 8). Unreacted starting materials were recovered from reactions that were run in methanol (exps 4 and 9). It is worthy to note the formation of two unexpected products in these reactions.

$$Ph_2P(O)CH_2CO_2CH_3 + Ph_2PO_2^- \longrightarrow$$

13 $$Ph_2P(O)CH_2COOP(O)Ph_2 + OCH_3^- \longrightarrow$$

$$\longrightarrow Ph_2P(O)OCH_3 + Ph_2P(O)CH_2CO_2^-.$$

15

Inherent in this suggestion is partial destruction of the reagent, phosphine oxide 13, which may account for the low yield in this experiment and for the recovery of unreacted 2. In an attempt to overcome this a second experiment, using two equivalents of phosphinoxy ylid, was carried out. This, however, resulted in complete decomposition (exp. 2).

A different type of byproduct was isolated from the reaction of nitrone 2 with cyanomethyldiphenylphosphine oxide (14) using sodium hydride in DME (Table 2, exps 5 and 6). This reaction gave an oily product (16) with a molecular weight of 385, which equals to the sum of two molecules of enaminonitrile 11 plus 1 molecule of nitrone 2. Upon examining the possibilities of obtaining independently the above byproduct, we found that in alkaline conditions, (i) reaction of equimolar amounts of nitrone 2 and enaminonitrile 11 gives mainly a product $C_{14}H_{23}N_3O$ mol. wt. 249, 17 and traces of 16 identifiable by tlc; (ii) reaction of 17 with enaminonitrile 11 gave 16, and (iii) reaction of nitrone 2

Table 1. Results from the reactions of 3,4-dihydroisoquinoline N-oxide (1) with phosphine oxides 13 and 14

No.	Phosphine oxide	Base/Solvent	Temp.	Time (hr)	Products: Aziridine, yield %		Enamine, yield %	
1	13	NaH/DME	25	14	5	17	6	17
2†	13	t-BuONa/t-BuOH	40	1		0	6	20
3†	13	t-BuONa/t-BuOH	40	3		0	6	26
4†	13	t-BuONa/t-BuOH	40	22		0		0
5	13	CH_3ONa/CH_3OH	25	14		0	6	42
6	14	NaH/DME	25	3		0	7	90
7	14	t-BuONa/t-BuOH	40	3.5		0	7	95
8‡	14	CH_3ONa/CH_3OH	Reflux	24		No reaction		

†Enaminoester 6 was found unstable in these conditions, no products of its decomposition were identified.

‡Unreacted starting materials were recovered in this experiment.

Table 2. Results from the reactions of 5,5-dimethyl Δ^1-pyrroline N-oxide (2) with phosphine oxides 13 and 14

No.	Phosphine oxide	Base/Solvent	Temp.	Time (hr)	Products: Aziridine, yield %		Enamine, yield %	
1†	13	NaH/DME	Reflux	24	8	12	10	27
2	13‡	NaH‡/DME	Reflux	24		Decomposition		
3	13	t-BuONa/t-BuOH	Reflux	24	8	20§		0
4¶	13	CH_3ONa/CH_3OH	Reflux	72		No reaction		
5[b]	14	NaH/DME	Reflux	1	9	33	11	33
6[b]	14	NaH/DME	25	3.5	9	33	11	33
7	14‡	NaH‡/DME	25	3		0	11	58
8	14	t-BuONa/t-BuOH	25	3	9	95		0
9¶	14	CH_3ONa/CH_3OH	Reflux	72		No reaction		

†This reaction gave 22% methyl diphenylphosphinate (15).

‡Two equivalents.

§Contaminated to a large extent by t-butyl ester as evidenced by NMR.

¶Unreacted starting materials were recovered in these experiments.

[b]This reaction gave 16.

with excess of 11 gave directly 16. On the basis of analogies with known reactions[5] of nitrones with enamines, we formulate the reaction of 2 with 11, as follows:

The structures proposed for products 16 and 17 are in agreement with the spectroscopic data obtained (Experimental). The formation of 16 could be suppressed by using an excess of phosphinoxy ylid (Table 2, exp. 7).

DISCUSSION

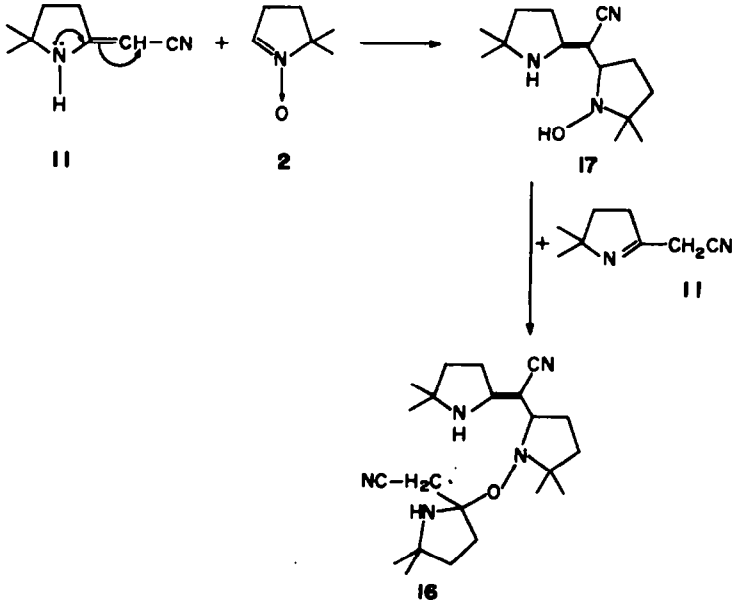
The results that reactions of 1 or 2 with phosphine oxides 13 and 14 using NaH in DME produce considerable amounts of enamines, are in accordance with the expectations that were expressed in the introduction to this paper. However, the other results reported in this paper necessitate further elaboration of the mechanistic picture. It is possible to rationalize all the results summarized in the tables by assuming the initial formation of an oxazaphospholidine intermediate 18. The tendency of 18 to undergo ring opening will be expected to be somewhat lower than that of 12, because of the greater ability of the phosphorus to accommodate the negative charge in 18, therefore, β-elimination leading to enamines will gain greater relative importance. In protic solvents such as alcohols 18 will presumably be in equilibrium with the protonated species 19. This intermediate is expected to undergo permutational isomerization[6] to 20 to bring the OH into apical position since it is a stronger apicophile than the phenyl groups.[7] Examination of molecular model of 20 indicate that flanking of the oxazaphospholidine ring by the two equatorial phenyl groups produces a great deal of steric hindrance to β-elimination, that would lead to enamine, therefore, it is possible by this picture to explain the exclusive formation of aziridines in the reactions of 2 with both phosphinoxy ylids in t-butyl alcohol. The formation of enamines in t-butyl alcohol from 1 with 13 and 14 is presumably due to the much higher acidity of the benzylic H in intermediate 18 than the corresponding hydrogen in 18 derived from 2, therefore β-elimination in the former is much faster.

Further pseudorotation (or turnstile rotation)[6] of 20 may give 21 in which the departing carbon is apical and situated favorably for a base promoted ring fission (indicated in 21) to 22.[8] The behaviour of this will be determined largely by the nature of X and that of the nitrone, and not expected to differ much from the analogous intermediates derived from the phosphonates.[1,2] Thus, 22 may undergo ring closure to aziridine or protonation followed by β-elimination of enamine.

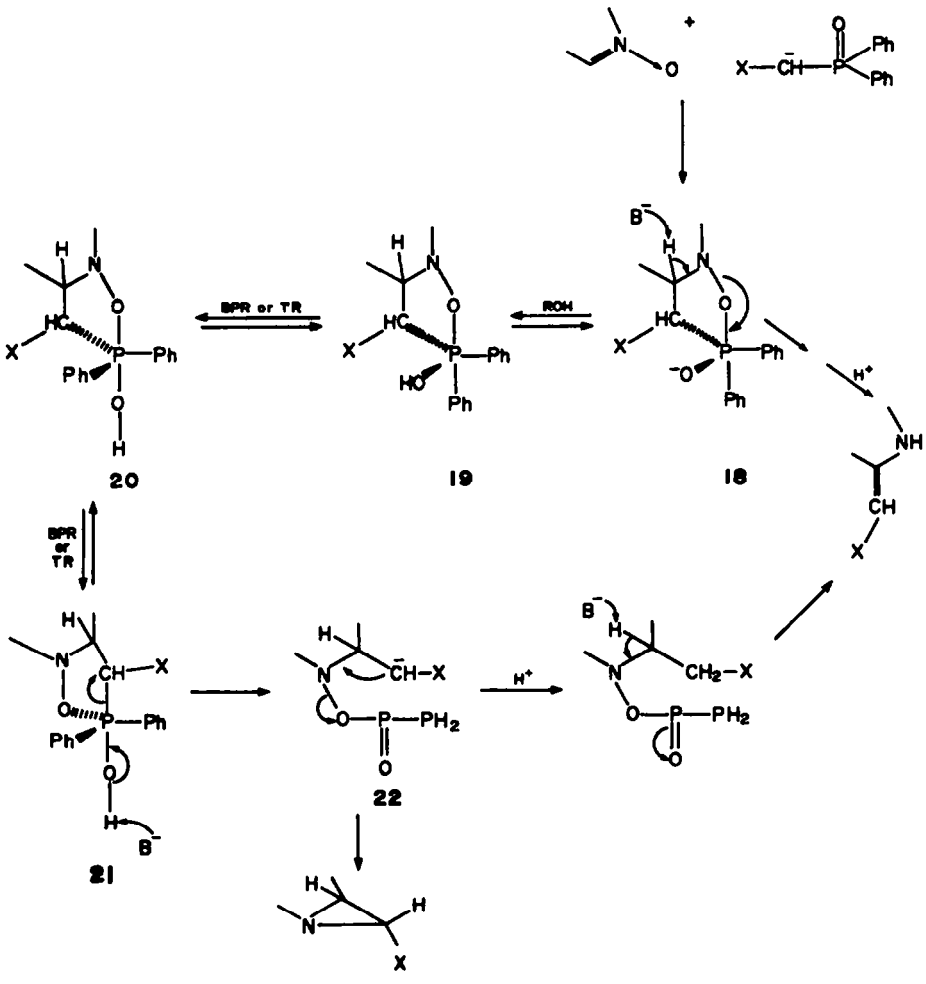
The inhibitory effect of sodium methoxide in methanol upon the reactions is probably due to the fact that these are the weakest basic conditions employed in this work, giving rise to the lowest concentration of phosphinoxy ylids. It is noteworthy that the only combination of nitrone and phosphine oxide that produces reaction in these conditions is that of 1 with 13. In the phosphonate series 4 is considerably more reactive towards aldehydes and ketones than 3.[9] We found similar order of reactivities (4 > 3) towards nitrone 2.[1] From the perturbation theory[10] it is known that ketones react mainly by charge control, the same is expected of aliphatic nitrones. In contrast, an aromatic nitrone such as 1 should be expected to react mainly by frontier orbital control, therefore its reaction with the anion derived from 13, in which the negative charge is better delocalized than that in the ylid of 14[4] indicates the possible applicability of the perturbation theory to correlate reactivities of nitrones with nucleophiles.

EXPERIMENTAL[11]

General procedure for the reactions of nitrones with phosphine oxides using sodium hydride in 1,2-dimethoxyethane. 0.25 g (5 mmol) of 50% dispersion of NaH in mineral oil was washed with petroleum-ether 40–60° (3 × 5 ml) in an inert atmosphere. After evaporation of the residual petroleum-ether 5 ml of 1,2-dimethoxyethane (DME, freshly distilled from LAH) was injected, followed by 5 mmol of phosphine oxide 13[12] or 14[13] dissolved in 10 ml DME. After the liberation of H_2 ceased, 5 mmol of nitrone 1[14] or 2[15] dissolved in 5 ml of DME was introduced. The mixture was stirred under the conditions (time and temp.) indicated in the tables. These were determined by monitoring the progress of the reactions by tlc using alumina plates of 0.25 mm thickness. The residue obtained after evaporation of the DME was dissolved in chloroform and passed through a column of 50 g alumina to remove sodium diphenylphosphinate, which was retained on the column. The mixture eluted was further separated to components by preparative thick layer



11 2 17 11 16



chromatography using 1 mm thick plates of alumina G.F.$_{254}$ and mixtures of chloroform petroleum-ether 40–60°, 3:2. The properties and physical constants of the aziridine and enamine derivatives formed in these reactions were described previously.[1,2]

The by-product of the reactions, sodium diphenylphosphinate could be obtained in all experiments by elution of the column with MeOH. 60 MHz ^{1}H NMR in D_2O: δ 7.60–7.00 m, aromatic, δ 4.66 s, P–OH.

Methyl diphenylphosphinate **15**. This compound was isolated in 22% yield from the mixture obtained in exp. 1, Table 2 by preparative thin layer chromatography. Mol.wt. Calc.: 232, found 232 by MS. Other peaks in mass spectrum: m/e = 201 (M–OCH_3), m/e = 155 (M–C_6H_5). ^{1}H NMR ($CDCl_3$) δ 8.20–7.25 5H m, δ 3.70 3H d (J = 11.0 Hz). This spectrum is in accordance with that published.[16]

Isolation of product **16** *from the reaction of* **2** *with* **14**. This compound was isolated in a quantity of 210 mg (0.55 mmol, 11%) from the mixture obtained in exps 5 and 6 in Table 2, by tlc being the most polar component in the mixture. Mol.wt. found (MS) 385. Calc. for $C_{22}H_{35}N_5O$, 385. IR (neat): 3300, 2960, 2240, 2180, 1600, 1430 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.98 1H bs, 7.60 1H bs, 3.70–3.20 3H m, 2.91–2.40 2H m, 2.30–1.55 10H m, 1.50–1.10 18H (6 × CH_3).

Preparation of **17** *by reaction of* **2** *with* **11**. A soln containing 0.28 g (5 mmol) of KOH, 0.565 g (5 mmol) of **2** and 0.68 g (5 mmol) of **11** in 15 ml t-BuOH was kept overnight at room temp. After removal of the solvent the residue was separated by preparative scale tlc. Recrystallization from MeOH gave m.p. 157–8°. UV (MeOH) 268 nm (16,860). IR (nujol): 3280, 2900, 2160, 1600, 1435 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 7.31 1H bs, 6.99 1H bs, 3.72–3.20 3H m, 1.90–1.30 6H m, 1.18 3H s, 1.16 3H s, 1.03 3H s, 1.00 3H s. M.S. m/e = 249 (M^+), m/e = 231 (M–H_2O), m/e = 223 (M–CN), m/e = 216 (M–CN–CH_3), m/e = 205 (M–CN–H_2O). Mol.wt. calc. 249. (Found: C, 67.00; H, 9.29; N, 16.86. Calc. for $C_{14}H_{23}N_3O$: C, 67.47; H, 9.24; N, 16.8%).

Isolation of **16** *from the reaction of* **17** *with* **11**. A soln of 0.5 mmol t-BuOK 0.5 mmol of **17** and 0.5 mmol **11** in 10 ml of t-BuOH was kept overnight at room temp. Product **16** was isolated as above and was found identical in all spectral and chromatographic properties with the product isolated previously.

Isolation of **16** *from the reaction of* **2** *with excess* **11**. A soln of 1 mmol t-BuOK, 1 mmol of **2** and 2 mmols of **11** in 15 ml of t-BuOH was kept overnight at room temp. Workup of the reaction gave samples of **16** and of **17** identical in all spectral and chromatographic properties with the samples isolated in previous experiments.

General procedure for the reactions of nitrones with phosphine oxides using sodium alkoxides in alcohols. t-BuONa was prepared from 0.25 g (5 mmol) 50% dispersion of NaH in mineral oil, to which 10 ml of t-BuOH was added after washing with petroleum-ether (3 × 5 ml). NaOMe was prepared by dissolving Na in MeOH. To the soln of the NaOR in alcohol was added a soln of 5 mmol of the phosphine oxide in 10 ml of alcohol followed by a soln of 5 mmol of the nitrone in 5 ml of alcohol (all operations were performed in an inert atmosphere). The reaction mixture was stirred under the conditions (time and temp.) indicated in the tables which were determined by monitoring the progress of the reaction by thin layer chromatography. After evaporation of the solvent workup was identical with the reactions carried out in DME.

REFERENCES

[1]Part IV: E. Breuer and S. Zbaida, *J. Org. Chem.* **42**, 1904 (1977).
[2]E. Breuer, S. Zbaida, J. Pesso and I. Ronen-Braunstein, *Tetrahedron* **33**, 1145 (1977).

[3]E. Breuer and I. Ronen-Braunstein, *J. Chem. Soc.* Chem. Comm., 949 (1974).
[4]M. Crossentini, B. Deschamps, Nguyen Trong Anh and J. Seyden-Penne, *Tetrahedron* **33**, 490 (1977).
[5]A. R. Katritzky and J. M. Lagowski, *Chemistry of the Heterocyclic N-oxides*, pp. 317–9. Academic Press, London (1971).
[6]R. Luckenbach, *Dynamic Stereochemistry of Pentacoordinated Phosphorus and Related Elements*. G. Thieme, Stuttgart (1973).
[7]P. Gillespie, F. Ramirez, I. Ugi and D. Marquarding, *Angew. Chem.* Int. Ed. **12**, 91 (1973).
[8]Similar explanations were given for ring opening in phospholanes: D. W. Allen and I. I. Millar, *J. Chem. Soc.* (C), 252 (1969); J. R. Corfield, N. J. De'ath and S. Trippett, *Ibid.* (C), 1930 (1971); See also Ref. 6, pp. 156–167.
[9]J. Boutagy and R. Thomas, *Chem. Rev.* **74**, 87 (1974); and refs cited.
[10]R. F. Hudson, *Angew. Chem.* Int. Ed. **12**, 36 (1973).
[11]All b.ps and m.ps are uncorrected, NMR Spectra were measured by a Jeol C-60H instrument, all chemical shifts are given in ppm downfield from TMS. IR Spectra were measured on a Perkin Elmer Model 237 Spectrophotometer. Mass spectra were obtained by Varian MAT CH5 mass spectrometer at 70 eV using a direct inlet system. Microanalyses were carried out by the Hebrew University Microanalytical Laboratory.
[12]O. A. Mukhacheva, S. A. Gor'kova, U. G. Nikolaeva and A. I. Razumov, *J. Gen. Chem., U.S.S.R.* English translation **40**, 1991 (1970).
[13]A. N. Pudovik, G. E. Yastrebova, L. M. Leont'eva, T. A. Zyablikova and V. I. Nikitina, *J. Gen. Chem., U.S.S.R.* English Translation **39**, 1200 (1969); M. Regitz and W. Anschuetz, *Chem. Ber.* **102**, 2216 (1969).
[14]A. Reiche and E. Schmitz, *Ibid.* **91**, 1488 (1958).
[15]R. Bonnett, R. F. C. Brown, V. M. Clark, I. O. Sutherland and A. Todd, *J. Chem. Soc.* 2094 (1959).
[16]K. D. Berlin, T. H. Austin and M. Nagabhushanam, *J. Org. Chem.* **30**, 1267 (1965).