375. *Some Transformations of* N-*Alkyl*-N-*nitrosophosphoramidates.*

By N. K. Hamer.

Preparations of some salts of mono-esterified *N*-alkyl-*N*-nitrosophosphoramidic acids are reported. The possibility of transforming these compounds into phosphate diesters is investigated, and, whilst the free acids can be so transformed, evidence is presented which suggests that the mechanism of this reaction is different from that with the *N*-alkyl-*N*-nitroso-amides. Phenyl hydrogen *N*-benzyl-*N*-nitrosophosphoramidate undergoes photochemical decomposition in neutral aqueous solution to give benzaldehyde and phenyl hydrogen phosphoramidate.

The *N*-nitroso-derivatives (I) and (II) of *N*-alkylacylamines and *N*-alkylsulphonamides eliminate nitrogen on mild thermal treatment, to give, respectively, the esters $R{\cdot}CO_2R'$ and $R{\cdot}SO_2{\cdot}OR'$,[1,2] often in good yield. Recently, the *N*-nitroso-derivatives of diphenyl *N*-arylphosphoramidates have been reported [3] and shown to decompose initially into the

$R{\cdot}CO{\cdot}N(NO){\cdot}R'$ (I)
$R{\cdot}SO_2N(NO){\cdot}R'$ (II)

$(RO)_2PO{\cdot}N(NO){\cdot}R'$ (IV)

$RO{\cdot}(HO)PO{\cdot}N(NO){\cdot}R'$
(IIIa) R = Ph, R′ = $PhCH_2$
(IIIb) R = Ph, R′ = Et
(IIIc) R = Ph, R′ = cyclohexyl
(IIId) R = $PhCH_2{\cdot}O{\cdot}CH_2{\cdot}CH_2$, R′ = cyclohexyl

corresponding diazonium salt of diphenyl hydrogen phosphate. It seemed possible, therefore, that the esterified *N*-alkyl-*N*-nitrosophosphoramidates (III) and (IV) might be induced to undergo similar transformations, giving di- and tri-esters of phosphoric acid.

Attempts to nitrosate the fully esterified *N*-alkylphosphoramidates by the usual methods [1-3] gave viscous yellow oils which evolved nitrogen when warmed. Owing to the labile nature of these oils and the complex nature of their decomposition products a proper characterisation was impossible and they were, therefore, not studied further. In contrast, the sodium salts of mono-esterified *N*-alkylphosphoramidic acids reacted with nitrous acid under very mild conditions to give readily isolable nitroso-derivatives in good yield. The ultraviolet spectra of these compounds show a characteristic absorption band, $\lambda_{max.}$ 375—380 mμ (ε 55—60), which may be compared with similar bands in the spectra of dialkylnitrosamines [4] and *N*-nitrosoacylamines.[5] Further proof of their structure is afforded by catalytic hydrogenation, which reduces them to the parent *N*-alkylphosphoramidate and ammonia.

The salts of (III) evolve nitrogen slowly when heated in dioxan or dimethyl sulphoxide solution at 100°, giving, as the principal phosphorus-containing compounds, the phosphate monoester (V), the symmetrical pyrophosphate diester (VI), and some inorganic phosphate; no trace of the phosphate diester (VII) was detected. Not unexpectedly, the partly esterified acids were extremely unstable, the *N*-cyclohexyl compounds decomposing

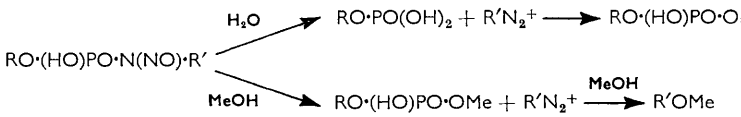
$RO{\cdot}PO(OH)_2$ (V)
$RO{\cdot}(HO)PO{\cdot}O{\cdot}PO(OH){\cdot}OR$ (VI)
$RO{\cdot}(HO)PO{\cdot}OR'$ (VII)

immediately with the evolution of nitrogen when aqueous solutions of their salts were acidified, giving the monoester (V), cyclohexene, and cyclohexanol. The esters (IIIa) and (IIIb) were, however, sufficiently stable at 0° to permit a partial extraction into ether, in which they decomposed smoothly at 30° to give mixed phosphate diesters (VII; R = Ph) in about 50% yield. In this reaction the remainder of the phosphorus appeared as phenyl dihydrogen phosphate together with small amounts of the phenyl hydrogen *N*-alkylphosphoramidate and P^1P^2-diphenyl dihydrogen pyrophosphate. The production of

[1] White, *J. Amer. Chem. Soc.*, 1955, **77**, 6008.
[2] Huisgen and Reimlinger, *Annalen*, 1956, **599**, 161, and earlier papers in that series.
[3] Bunyan and Cadogan, *J.*, 1962, 1304.
[4] Haszeldine and Jander, *J.*, 1954, 691.
[5] Clarke, " The Chemistry of Penicillin," Princeton University Press, Princeton, N.J., 1949, p. 177.

(VII) suggests that the reaction may be similar to that of the *N*-nitroso-amides (I) and (II) from which the ester arises by way of an initial migration of the acyl group to the oxygen of the nitroso-group.[1,2] This, however, cannot be the case, since, in methanolic solution, (IIIa) (similar behaviour is shown by the other compounds) gives methyl phenyl hydrogen phosphate as the sole phosphorus-containing compound, together with considerable amounts of benzyl methyl ether.

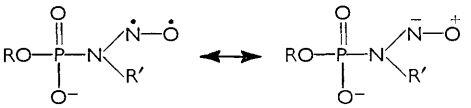
The above observations are most simply accounted for if it is assumed that the initial (and probably rate-determining) step in the reaction involves a nucleophilic attack by water or methanol [the ethereal solutions of (III) would certainly contain sufficient water to initiate the reaction]. This would give rise, as shown, to an ester (VI) or (VII) and an



N-nitroso-primary amine which, under the acidic conditions, would be transformed into the diazonium ion. Reaction of this diazonium ion with the various nucleophilic species present can account for the major products observed; alternatively, it can undergo an elimination reaction to give the olefin. The minor products observed almost certainly arise by way of the acid-catalysed denitrosation of the starting material. Additional support for such a mechanism is provided by the observation that nitrogen evolution from solutions of (IIIa) or (IIIb) in methanol or water is considerably more rapid than from ethereal solutions at the same temperature, although this may to some extent reflect the different polarities of the solvents. What does seem clear is that, unlike the thermal decomposition of (I) and (II), the initial migration of the acyl group to give a diazo-ester (more probably an ion-pair [1,2]) does not occur.

The salts of (III) are markedly unstable towards light, and this instability may, furthermore, be associated with the absorption band mentioned earlier. This band shows a small blue shift in less-polar solvents and may reasonably be attributed to a $n \longrightarrow \pi^*$ transition of the *N*-nitroso-group. The nature of the products of this photochemical decomposition depends on the structure of R′; thus, whereas a neutral aqueous solution of the sodium salt of (IIIa) gives, on irradiation, benzaldehyde and sodium phenyl phosphoramidate as the principal products (*ca.* 70%), the corresponding salt of (IIIc) gives sodium phenyl hydrogen phosphate and cyclohexene with no trace of cyclohexanone. The *N*-ethyl compound (IIIb) seemed to be intermediate between these two in its behaviour but it gave only small amounts (5—10%) of acetaldehyde and phenyl hydrogen phosphoramidate on irradiation in solution. It was observed also that the ammonium and cyclohexylammonium salts of (IIIa) developed, on exposure to light, a pale blue colour which was discharged immediately by dissolution in aqueous ethanol, with release of benzaldehyde.

Although there is, as yet, insufficient evidence for a mechanistic scheme for these photodecompositions, it is almost certain that the electronically excited state (VIII),



represented by the mesomeric structures shown,[6] is intimately involved. Recent work on the transformations of excited states of this general type [7] suggests that, in the case of the *N*-benzyl compound at least, abstraction of a benzylic hydrogen atom will occur to give an intermediate which, in solution, may reasonably be expected to break down

[6] McEwen, *J. Chem. Phys.*, 1961, **34**, 547.
[7] Zimmerman and Schuster, *J. Amer. Chem. Soc.*, 1962, **84**, 4527.

to the observed products. Two further observations on this reaction seem to be relevant. First, the blue compounds formed by irradiation of the solid amine salts of (IIIa) showed no electron spin resonance absorption even at liquid-nitrogen temperatures, and thus appear to be singlet states. Secondly, although the stoicheiometry of the decomposition of (IIIa) to give benzaldehyde and phenyl hydrogen phosphoramidate requires that the remaining nitrogen should be left at the oxidation level of nitrous oxide, only the merest traces of this were detected.

Experimental

Paper chromatograms were run on Whatman No. 1 paper, using the propan-2-ol–ammonia–water (7 : 1 : 2) system.

Sodium Phenyl N-*Benzyl*-N-*nitrosophosphoramidate*.—Diphenyl *N*-benzylphosphoramidate [8] (6·8 g.), dissolved in hot ethanol (25 ml.), was added to a hot solution of sodium hydroxide (1·4 g.) in water (30 ml.). After 15 min. at 100°, the residual ethanol was removed, and the solution cooled and brought to pH 7 with acetic acid. The liberated phenol was extracted with ether (4 × 50 ml.), and the resulting aqueous solution of sodium phenyl *N*-benzylphosphoramidate concentrated to *ca.* 15 ml. (The pure sodium salt can be isolated by acidifying this solution at 0°, neutralising the liberated phenyl hydrogen phosphoramidate with sodium hydroxide solution, and, after removal of the water *in vacuo*, crystallising the residue from dioxan; this is, however, unnecessary.) The solution was cooled to 0°, and sodium nitrite (2·0 g.) in water (4 ml.) added, followed by glacial acetic acid (1·6 ml.). Crystallisation began within 5 min., and, after 1 hr. at 0°, the *product* was filtered off and washed with ether, to give crystals (5·1 g., 77%) which showed a single spot (R_F 0·8) on a chromatogram. For analysis a sample was recrystallised from a small volume of water (Found: C, 46·9; H, 4·5; N, 8·1. $C_{13}H_{12}N_2NaO_4P,H_2O$ requires C, 47·0; H, 4·2; N, 8·4%). The ammonium and cyclohexylammonium salts crystallised out when aqueous solutions of the sodium salt were mixed with the appropriate amine hydrochloride.

Sodium Phenyl N-*Ethyl*-N-*nitrosophosphoramidate*.—A similar procedure to the above was followed, starting from diphenyl *N*-ethylphosphoramidate,[9] to give the crude *product* as needles (72%). It is quite soluble in water in the absence of other sodium salts, and was purified by treating a cold saturated aqueous solution with an equal volume of saturated sodium perchlorate solution. The crystals were washed with 30% sodium perchlorate solution and acetone (Found: C, 37·4; H, 3·9; N, 11·5. $C_8H_{10}N_2NaO_4P$ requires C, 38·1; H, 4·0; N, 11·1%).

Cyclohexylammonium Phenyl N-*Cyclohexyl*-N-*nitrosophosphoramidate*.—From diphenyl *N*-cyclohexylphosphoramidate [8] was prepared the crude sodium salt (81%), using the above procedure. Since it is sparingly soluble in cold water and rather labile in solution, it was converted into the cyclohexylammonium salt by mixing a solution of the crude sodium salt in cold aqueous methanol with an aqueous solution of cyclohexylamine hydrochloride. The *product* formed needles, decomp. 110° (Found: C, 55·6; H, 8·1; N, 10·6. $C_{18}H_{30}N_3O_4P$ requires C, 56·1; H, 7·8; N, 11·0%).

2-*Benzyloxyethyl Phenyl* N-*Cyclohexylphosphoramidate*.—To a mixture of phenyl phosphorodichloridate (13·5 g.) and dry pyridine (4·8 ml.) in ether (150 ml.) was added, dropwise with stirring, 2-benzyloxyethanol (9 g.), the temperature being maintained at 0° during the addition. After 2 hr. at 10°, cyclohexylamine (18 g.) in ether (50 ml.) was added, with cooling. After 1 hr. at room temperature, the mixture was poured into water, and the ethereal layer washed with 2N-sulphuric acid and sodium hydrogen carbonate solution. After drying, the ether was removed, to give a viscous, slightly yellow, oil which crystallised from ether–light petroleum. The *product* (18·5 g.), recrystallised from the same solvent, had m. p. 78—79° (Found: C, 64·4; H, 7·2; N, 3·6. $C_{21}H_{28}NO_4P$ requires C, 64·8; H, 7·3; N, 3·5%).

Cyclohexylammonium 2-*Benzyloxyethyl* N-*Cyclohexyl*-N-*nitrosophosphoramidate*.—Following the earlier procedure, 2-benzyloxyethyl phenyl *N*-cyclohexylphosphoramidate was hydrolysed with sodium hydroxide, to give sodium 2-benzyloxyethyl *N*-cyclohexylphosphoramidate which crystallised as a hexahydrate on cooling the aqueous solution. To a cooled solution of sodium nitrite (0·5 g.) in water (5 ml.) was added this sodium salt (2 g.) followed by glacial acetic acid (0·4 ml.). After 2 hr. at 0°, all the starting material had dissolved, and the resulting solution was added to a solution of cyclohexylamine hydrochloride (1 g.) in water (10 ml.). The *product*

[8] Foster, Overend, and Stacey, *J.*, 1951, 980.
[9] Michaelis, *Annalen*, 1915, **407**, 290.

crystallised as colourless needles (1·4 g.), decomp. 114° (Found: C, 57·2; H, 8·4; N, 9·5. $C_{21}H_{36}N_3O_5P$ requires C, 57·1; H, 8·2; N, 9·5%).

Decomposition of the Partly Esterified Acids.—To a solution of sodium phenyl *N*-benzyl-*N*-nitrosophosphoramidate (1·0 g.) in water (8 ml.) was added ether (15 ml.) followed, after cooling to 0°, by 2N-hydrochloric acid (2·5 ml.). The ethereal extract was dried for 15 min. at 0° ($MgSO_4$) and then warmed gently under reflux. Nitrogen evolution became rapid above 30°, and after 30 min. refluxing had ceased. Chromatography indicated that phenyl dihydrogen phosphate and benzyl phenyl hydrogen phosphate were the main phosphorus-containing products but traces of diphenyl dihydrogen pyrophosphate and phenyl hydrogen *N*-benzylphosphoramidate were also detected. The ether solution was extracted with water (3 × 5 ml.), cyclohexylamine (0·3 ml.) added, and the precipitated salt filtered off. After recrystallisation from ethanol–acetone, the cyclohexylammonium benzyl phenyl phosphate (310 mg.; the isolated yields were very variable) had m. p. 144—146° (lit.,[10] 147°).

A similar experiment was performed with sodium phenyl *N*-ethyl-*N*-nitrosophosphoramidate but in this case the ether extraction of the initial reactant is much less efficient. Almost all the phosphorus appeared as phenyl dihydrogen and ethyl phenyl hydrogen phosphate (identified by chromatographic and electrophoretic comparison with authentic samples [11]) which were present in approximately equal amounts.

Methanolysis of the Partly Esterified Acids.—The ethereal solution of phenyl hydrogen *N*-benzyl-*N*-nitrosophosphoramidate, prepared as above, was added to an equal volume of methanol. Nitrogen evolution was vigorous even at room temperature, and, on completion, chromatography showed that almost all the phosphorus was present as methyl phenyl hydrogen phosphate.[12] After removal of most of the solvent a considerable quantity of benzyl methyl ether was detected in the residue by gas chromatography.

A more convenient procedure, which gave the same result, consisted in treating a methanolic solution of a salt of (IIIa) with toluene-*p*-sulphonic acid (0·2 Equiv.). Using this modification it was found that (IIIb) and (IIIc) also gave methyl phenyl hydrogen phosphate as the sole phosphorus-containing product.

Photolysis of Salts of (III).—An aqueous solution of sodium phenyl *N*-benzyl-*N*-nitrosophosphoramidate (0·5 g. in 20 ml.) was allowed to stand in bright daylight in a Pyrex flask for 3 days. (Under these conditions no light of wavelength less than 310 mμ will reach the solution.) The solution darkens and benzaldehyde is liberated but there is no evolution of gas. Chromatography showed that most of the starting material had been converted into a slower-running species which was identified as phenyl hydrogen phosphoramidate by comparison with an authentic sample; [13] paper electrophoresis confirmed this. The solution was then heated to 95° and the evolved gas passed into acetone (5 ml.) at −30°. The infrared spectrum of the acetone solution showed bands at 4·5 and 7·8 μ, characteristic of nitrous oxide, but these (particularly the latter) were very weak whereas an acetone solution saturated at 10° with nitrous oxide gave quite strong bands at these wavelengths.

In a separate experiment, the liberated benzaldehyde was estimated by passing a stream of nitrogen through the solution during the irradiation and thence into a solution of dinitrophenylhydrazine in aqueous methanol containing a little sulphuric acid. From 500 mg. of the starting material there was obtained 340 mg. of the crude dinitrophenylhydrazone (m. p. 223—230°) which gave the pure product (292 mg., 65%), m. p. 235° (from ethanol).

In both experiments about 20% of the phosphorus appeared as slow-running compounds, two of which were identified as phosphoramidic acid and orthophosphate.

In similar experiments with sodium phenyl *N*-ethyl-*N*-nitrosophosphoramidate and the corresponding *N*-cyclohexyl compound considerable amounts of nitrogen were evolved (in contrast to the above). From the *N*-ethyl compound small amounts of acetaldehyde were detected (5% isolated as dinitrophenylhydrazone).

I should like to thank Dr. D. M. Brown for reading through the manuscript and making several helpful comments.

University Chemical Laboratory, Cambridge. [*Received, August 26th,* 1963.]

[10] Clark and Todd, *J.*, 1950, 2030.
[11] Brown, Flint, and Hamer, *J.*, 1964, 326.
[12] Mathieson and Russell, *J. Pharm. Pharmacol.*, 1957, **9**, 612.
[13] Stokes, *Amer. Chem. J.*, 1893, **15**, 198.