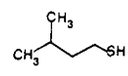
Table I. Volatile Constituents of Red Fox Urine

entry	compd	ca. concn, mg/L
1	4-heptanone	10
2	Δ^3-isopentenyl methyl sulfide (1)	50
3	6-methyl-5-hepten-2-one	2
4	benzaldehyde	1
5	acetophenone	50
6	2-phenylethyl methyl sulfide (2)	2
7	2-methylquinoline[a]	7
8	geranylacetone	7

[a] Male only.

3

4



5

also be of isoprenoid origin. These new terpenoid sulfur compounds suggest a broader significance of terpenes in mammalian olfaction.[17] We report herein the synthesis and spectral properties of compound **1**.

Experimental Section

Δ^3-Isopentenyl Methyl Sulfide (1). *p*-Toluenesulfonyl chloride (10.1 g, 53 mmol) and 4.23 g (47.7 mmol) 3-methyl-3-butenol (Aldrich) in pyridine/CH_2Cl_2 gave 11.13 g (97%) of tosylate which was used without further purification. Tosylate (4.8 g, 20 mmol) in 20 mL of HMPA was cooled to 0 °C and 2.4 g (44 mmol) of CH_3SLi[18] was added portionwise. After warming to 25 °C, the mixture was stirred overnight. The solution was then poured into 150 mL of water and extracted with 100 mL of petroleum ether. The petroleum ether was washed with 1 N NaOH, water, and brine. After drying over $MgSO_4$ the material was distilled to yield 1.77 g (76%) of compound **1**: bp 75 °C (85 mm); VPC (¼ in. × 10 ft Apiezon L at 110 °C; R_T = 5.5 min); IR (neat) 3.32, 6.03, 6.98, 7.30, 11.2 μm; NMR (220 mHz, $CDCl_3$) δ 1.74 (s, 3 H, C=CCH_3), 2.11 (s, 3 H, SCH_3), 2.27 (t, 2 H, J = 4.2 Hz, C=CCH_2), 2.57 (t, 2 H, J = 4.2 Hz, $-CH_2S-$), 4.73 (m, 2 H, CH_2=C); MS [*m/e* (% base)] 116 (26), 69 (4), 68 (17), 67 (17), 63 (5), 61 (100), 41 (20). Anal. Calcd for $C_6H_{12}S$: mol wt 116.0660. Found: mol wt 116.0662.

Registry No.—**1**, 5952-75-0; 3-methyl-3-butenol tosylate, 781-03-3; *p*-toluenesulfonyl chloride, 98-59-9; 3-methyl-3-butenol, 763-32-6; lithium methanethiolate, 35638-70-1.

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Alkyl Nitrate Nitration of Active Methylene Compounds. Nitration of Alkylphosphonate Esters[1]

Henry Feuer,* Wilber D. Van Buren II, and John B. Grutzner

Department of Chemistry, Purdue University, West Lafayette, Indiana 47907

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In continuation[2] of our studies of the alkyl nitrate nitration, we are now reporting on its application, with some success, to the preparation of 1-nitroalkylphosphonates **1** directly from the corresponding alkylphosphonate esters **2** (eq 1).

$$\underset{\mathbf{2}}{RCH_2P(O)(OR')_2} \xrightarrow[(2)\ H^+]{(1)\ (i\text{-}C_3H_7)_2NLi\text{–}THF\text{–}n\text{-}C_3H_7ONO_2} \underset{\mathbf{1}}{RCHP(O)(OR')_2}(NO_2) + RCH_2PNO_2 + n\text{-}C_3H_7OP(O)(OR')_2 \quad (1)$$

Recently, Petrov and co-workers[3] reported several methods for preparing compounds **1** which essentially involved the nitration of 2-oxoalkyl-, 2-alkoxyvinyl-, and 2-alkoxy-1-alkylvinylphosphonate esters with nitric acid in acetic anhydride. These methods suffer from the lack of readily available starting materials. Another procedure[4] which affords exclusively tertiary nitroalkylphosphonates consisted of oxidizing the corresponding 1-aminoalkylphosphonate esters.

In the present study, the alkyl nitration of esters **2** was investigated in such systems as potassium amide–liquid ammonia (A), butyllithium–THF (B), and lithium diisopropylamide–THF (C). Of these, system A was found to be unsuitable. For example, in a control test diethyl ethylphosphonate (**3**) was converted in a 60% yield to ethyl *P*-ethylphosphoramidate (eq 2). Moreover, treatment of dibutyl

$$\underset{\mathbf{3}}{C_2H_5P(O)(OC_2H_5)_2} \xrightarrow[(2)\ NH_4Cl]{(1)\ KNH_2\text{–liquid } NH_3} C_2H_5P(O)(NH_2)OC_2H_5 \quad (2)$$

butylphosphonate (**4**) with *n*-propyl nitrate in system A resulted in a 50% recovery of ester **4**. The remaining material constituted a mixture which could not be resolved.

Nitrations of **4** were successful in systems B and C, affording dibutyl 1-nitrobutylphosphonate (**5**) in yields of 27 and 41%, respectively. Similarly, dibutyl pentylphosphonate was converted in system C in 47% yield to dibutyl 1-nitropentylphosphonate (**6**). However, nitration of ester **3** in this system gave a mixture from which the nitro compound could not be separated.

As in the case of carboxylic esters,[5] the nitration reaction of **2** gave, in addition to **1**, cleavage products, namely, nitroalkanes and trialkyl phosphates (eq 1). It was ascertained that the cleavage occurred during the nitration and not in the acidification step as shown by the fact that trialkyl phosphates were isolated prior to acidification. Moreover, compound **6** was quantitatively regenerated from its sodium or lithium salt on acidification with acetic acid. It is very likely that the cleavage reaction occurs by the reaction pathway proposed for the nitration of carboxylic esters.[5]

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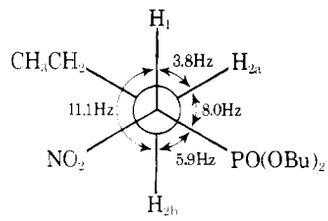
Chart I



In an effort to reduce the cleavage reaction, esters **2** with bulkier alkoxy groups were nitrated, in the hope of providing sufficient steric hindrance to nucleophilic attack on phosphorus. Nitration with propyl nitrate of **7** (R = *n*-C_3H_7, R′ = *i*-C_3H_7) in system B afforded only 21.2% of diisopropyl 1-nitrobutylphosphonate and 16.1% of diisopropyl *n*-propyl phosphate. Ester **7** was recovered in a 48.6% yield. No cleavage products were formed in the nitration of *tert*-butyl ester **8** (R = *n*-C_3H_7, R′ = *t*-C_4H_9). However, the *tert*-butyl nitro ester could not be purified because it decomposed on standing to a brown, water-soluble material.

The identity of the nitro esters **1** was established chiefly by their spectral data. Furthermore, structure **5** was also verified by its conversion to dibutyl 1-bromo-1-nitrobutylphosphonate (**9**). It was prepared by addition of bromine directly to the aqueous extract of the lithium salt of **5** obtained from the nitration of **4**. Several attempts to prepare **9** by alternate means were unsuccessful. These included reacting **5** with aqueous sodium hypobromite or sodium *n*-butoxide in butanol followed by addition of bromine in carbon tetrachloride.

The infrared spectra of **1** showed the characteristic NO_2 stretching absorptions at 1550–1560 (asymmetric) and 1330–1360 cm^{-1} (symmetric).[6] They are not appreciably affected by the presence of the phosphonate group. The characteristic broad P=O stretching absorptions of **1** appeared at 1260–1270 cm^{-1} and are in accord with the data reported in the literature.[3]

The NMR spectra of **5** exhibited[3] a characteristic seven-line pattern (overlapping quartets) at δ 4.93 for the unique methine proton (H_1). First-order analysis of 100 and 360 MHz proton spectra and 40.5 MHz ^{31}P spectra gave the coupling constants shown in Chart I. The couplings were confirmed by proton decoupling. As both three-bond H–H and P–H coupling constants follow a Karplus relationship,[7,8] the observed coupling constants can only be interpreted if **5** exists almost exclusively in the single conformer shown.

Experimental Section

Apparatus. Nitrations were performed in a 300- or 500-mL three-neck flask equipped with a mechanical stirrer, dry ice condenser, thermometer, pressure-equalizing addition funnel, and rubber septum. The 100 MHz proton and 40.5 MHz ^{31}P NMR spectra were obtained on a Varian XL-100-15 in $CDCl_3$ solution with internal Me_4Si as reference. The 360 MHz spectra were obtained with a Nicolet Technology 360 spectrometer. Chemical shifts are reported on the δ scale, and coupling constants are accurate to ±0.2 Hz.

Dibutyl 1-Nitrobutylphosphonate (5). The following experiment is typical of the procedure employed in the nitration of alkylphosphonic esters **2**.

To diisopropylamine (6.05 g, 0.06 mol) dissolved in 100 mL of dry THF was added *n*-butyllithium (0.06 mmol) in *n*-hexane. The mixture was warmed to 30 °C for 15 min, and then it was cooled to −60 °C and dibutyl butylphosphonate[9] (**4**; 10 g, 0.04 mol) added. The mixture was stirred at −60 °C for 1 h and then kept at 30 °C for 30 min. After recooling at −60 °C, *n*-propyl nitrate (8.42 g, 0.08 mol) was added. (*Caution: cooling must be maintained during the addition of the nitrating agent, as long as the high exotherm persists.*) After 1 h when the temperature of the mixture was 15 °C, 100 mL of water was added and the mixture extracted with ether. The ether extract was dried (Na_2SO_4) and concentrated, and the residue was distilled at 101–105 °C (1 mm) to give a mixture composed of 0.8 g (8%) of ester **4** and 4.1 g (23%) of dibutyl propyl phosphate (as determined by GLC): n^{20}_D 1.4225; IR (neat) 1278 cm^{-1} (P=O); NMR ($CDCl_3$) δ 0.98 (m, 9, CH_3), 1.58 (m, 10, CH_2), and 4.05 (m, 6, OCH_2). Anal. Calcd for $C_{11}H_{25}O_4P$: C, 52.49; H, 10.01; P, 12.07. Found: C, 52.77; H, 10.24; P, 12.30.

The aqueous solution was acidified with acetic acid and extracted with ether, and the extract was dried (Na_2SO_4) and concentrated in vacuo. Distillation gave 4.9 g (41.4%) of dibutyl 1-nitrobutylphosphonate (**5**): bp 110–112 °C (0.2 mm); n^{20}_D 1.4421; IR (neat) 1555 and 1350 (NO_2) and 1260 (P=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.93 (H-1, ddd, J_{1-2a} = 3.8 Hz, J_{1-2b} = 11.1 Hz, J_{1-P} = 14.8 Hz), 4.16 (4, OCH_2, m, J_{H-P} = 8 Hz), 2.36 (H-2b, dddt, J_{2b-P} = 5.9 Hz, J_{2b-1} = 11.1 Hz, J_{2b-2a} = 14.7 Hz, J_{2b-3} = 8.6 Hz), 2.02 (H-2a, dddt, J_{1-2a} = 3.8 Hz, J_{2a-P} = 8.0 Hz, J_{2a-2b} = 14.8 Hz, J_{2a-3} = 7.6 Hz), 1.68 (2, m, H-3), 1.41 (8, "sextet", J = 6.5 Hz), 0.97 (3, triplet, J = 7 Hz), and 0.94 (6, triplet, J = 7 Hz); ^{31}P NMR ("septet", J = 7.5 Hz). Anal. Calcd for $C_{12}H_{26}NO_5P$: C, 48.80; H, 8.87; N, 4.74; P, 10.49. Found: C, 48.95; H, 9.10; N, 4.70; P, 10.34.

Dibutyl 1-Bromo-1-nitrobutylphosphonate (9). Proceeding as in the preparation of **5**, the aqueous solution obtained from the workup of the nitration mixture was cooled to 0 °C and bromine added until the bromine color persisted. The mixture was stirred overnight and extracted with ether. The extract was dried (Na_2SO_4) and concentrated in vacuo, and 10% aqueous sodium thiosulfate was added to the residue. The resulting mixture was extracted with ether and the extract dried (Na_2SO_4) and concentrated in vacuo. Distillation afforded dibutyl 1-bromo-1-nitrobutylphosphonate (3.99 g, 53.3%): bp 82 °C (10^{-3} mm); n^{20}_D 1.4644; IR (neat) 1560 and 1330 (NO_2) and 1270 (P=O) cm^{-1}; NMR ($CDCl_3$) δ 1.30 (m, 19, CH_2CH_3), 2.50 (m, 2, CH_2CBrNO_2), and 4.19 (m, 4, OCH_2). Anal. Calcd for $C_{12}H_{25}BrNO_5P$: C, 38.52; H, 6.73; Br, 21.35; N, 3.74; P, 8.28. Found: C, 38.68; H, 6.77; Br, 21.09; N, 3.86; P, 8.00.

Dibutyl 1-Nitropentylphosphonate (6). The experimental procedure was similar to that described for the nitration of **4** except that 21.12 g (0.08 mol) of dibutyl pentylphosphonate, 12.14 g (0.12 mol) of diisopropylamine, and 16.81 g (0.16 mol) of *n*-propyl nitrate were used. After 100 mL of water was added, the reaction mixture was concentrated in vacuo and the residue extracted with hexane to give a three-phase mixture.

The lowest (aqueous) phase was acidified with acetic acid and extracted with ether, and the extract was dried (Na_2SO_4) and concentrated in vacuo. Distillation gave 1-nitropentane (1.6 g, 1.7%): bp 65 °C (9 mm); n^{20}_D 1.4169 [lit.[10] bp 75–76 °C (23 mm), n^{25}_D 1.4161]. The residue contained some of the nitro ester as indicated by the NMR spectrum.

The middle phase, which contained both water and hexane, was acidified and then treated as the aqueous phase. Distillation gave dibutyl 1-nitrophenylphosphonate (**6**; 11.6 g, 47%): bp 115–116 °C (5 × 10^{-3} mm); n^{20}_D 1.4440; IR (neat) 1560 and 1355 (NO_2) and 1270 (P=O) cm^{-1}; NMR ($CDCl_3$) δ 0.93 (t, 9, CH_3), 1.68 (m, 14, CH_2), 4.15 (q, 4, OCH_2), and 4.92 (septet, 1, $CHNO_2$); mass spectrum (75 eV), *m/e* (relative intensity) 263 (7.8), 254 (6.6), 207 (10.5), 198 (60.5), 151 (100), 109 (25), 99 (23.7), 70 (36.8), 57 (32.9), and 41 (56.6). Anal. Calcd for $C_{13}H_{28}NO_5P$: C, 50.48; H, 9.12; N, 4.53; P, 10.01. Found: C, 50.72; H, 9.04; N, 4.41; P, 10.07.

The hexane phase was dried (Na_2SO_4) and concentrated in vacuo to give a liquid which by GLC consisted of 5.07 g (25%) of dibutyl propyl phosphate and 1.76 g (8.3%) of unreacted phosphonate ester.

Diisopropyl 1-Nitrobutylphosphonate. *n*-Butyllithium (22.1 mL, 0.1 mol) in hexane, diisopropyl butylphosphonate[11] (**7**, 11 g, 0.05 mol), and *n*-propyl nitrate (10.45 g, 0.10 mol) were used. The reaction mixture was extracted with water, and the aqueous solution was acidified with acetic acid and extracted with ether. The ether extract was dried (Na_2SO_4), concentrated in vacuo, and distilled[12] to give 2.81 g (21.2%) of diisopropyl 1-nitrobutylphosphonate: bp 73 °C (10^{-3} mm); n^{20}_D 1.4360; IR (neat) 1555 and 1360 (NO_2) and 1260 (P=O) cm^{-1}; NMR ($CDCl_3$) δ 0.95 (t, 3, CH_2CH_3), 1.35 (d, 12, $CHCH_3$), 1.65 (m, 4, CH_2), and 4.82 (m, 3, CH). Anal. Calcd for $C_{10}H_{22}NO_5P$: C, 44.94; H, 8.30; N, 5.24; P, 11.59. Found: C, 45.18; H, 8.53; N, 5.42; P, 11.41.

The water-insoluble portion of the nitration mixture was extracted with ether, dried (Na_2SO_4), and concentrated in vacuo. GLC analysis indicated that the residue was composed of 5.34 g (48.6%) of unreacted **7** and 1.75 g (16.1%) of diisopropyl *n*-propyl phosphate: IR (neat) 1260 cm^{-1} (P=O); NMR ($CDCl_3$) δ 0.95 (t, 3, CH_2CH_3), 1.35 (d, 12, $CHCH_3$), 1.65 (pentet, 2, CH_3CH_2), 3.99 (q, 2, OCH_2), and 4.68 (sextet, 2, CH). Anal. Calcd for $C_9H_{21}O_4P$: C, 48.21; H, 9.44; P, 13.81. Found: C, 48.37; H, 9.23; P, 13.62.

Ethyl *P*-Ethylphosphoramidate. To potassium amide (prepared from 5.87 g of potassium) dissolved in 300 mL of anhydrous ammonia was added diethyl ethylphosphonate (16.62 g, 0.10 mol) at −38 °C. After 30 min, ammonium chloride (13 g, 0.19 mol) was added at −40 °C and the mixture stirred for 15 min. The filtrate was concentrated

in vacuo, and the remaining solid was recrystallized from a mixture (30:70 v/v) of ether and petroleum ether (bp 30–60 °C) to afford 8.25 g (60.2%) of ethyl *P*-ethylphosphoramidate: mp 62.5–63.5 °C; IR (KBr) 1180 (P=O), 1570 (P-NH_2), and 3230 (NH_2) cm^{-1}; NMR ($CDCl_3$) δ 1.35 (m, 8-PCH_2CH_3 and OCH_2CH_3), 3.45 (s, 2, NH_2), and 4.05 (m, 2, OCH_2). Anal. Calcd for $C_4H_{12}NO_2P$: C, 35.04; H, 8.82; N, 10.21; P, 22.59. Found: C, 35.13; H, 9.01; N, 10.06; P, 22.88.

Acknowledgment. We are indebted to the IMC Chemical Group Inc. for support of this investigation. The 360 MHz spectra were obtained at the Purdue University Biological Magnetic Resonance Laboratory supported by NIH Grant No. RR 01077.

Registry No.—**3**, 78-38-6; **4**, 78-46-6; **5**, 67774-24-7; **6**, 67774-25-8; **7**, 52468-61-8; **9**, 67774-26-9; dibutyl pentylphosphonate, 995-48-2; diisopropyl 1-nitrobutylphosphonate, 67774-27-0; diisopropyl *n*-propyl phosphate, 67774-28-1; ethyl *P*-ethylphosphoramidate, 62992-28-3; dibutyl propyl phosphate, 7242-63-9; propyl nitrate, 627-13-4.

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N-Methylpyruvanilide and 1,3-Dimethyl-3-hydroxyoxindole[1]

William Lopatin, Carol Sheppard, and Terence C. Owen*

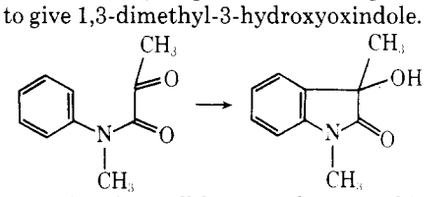
Department of Chemistry, University of South Florida, Tampa, Florida 33620

Received April 13, 1978

The preparation of *N*-methylpyruvanilide seems to have been reported twice: by Wohl and Lips in 1907 and by Adams, Bramlet, and Tendick in 1920–1922. The reports do not agree with each other. Wohl and Lips[2] utilized the reaction of *N*-methylaniline with the pyridine "salt" of hydroxymaleic anhydride, a procedure which they used and which we also have used to prepare a variety of N-monosubstituted as well as N,N-disubstituted pyruvamides. They reported analytical data for C, H, and N, along with cryoscopic molecular weight determinations in two solvents. The melting point reported for the product, 152–153 °C, is some 50 °C *higher* than that of pyruvanilide, a finding which surprised us somewhat, and no carbonyl group reactions or derivatives are mentioned. Adams, Bramlet, and Tendick reacted methylmagnesium iodide with *N,N'*-dimethyloxanilide and obtained the product resulting from addition of the Grignard reagent to only one of the two carbonyl groups. They at first[3a] reported the *N*-methylpyruvanilide thus produced as being a solid melting at 83–84 °C, but in a correction[3b] two years later they reported it as being a liquid boiling at 148–150 °C (10 mm). The only characterization offered was an elemental analysis for nitrogen, an analysis which agrees neither with the calculated percentage of nitrogen reported nor the theoretical percentage required. The molecular formula is wrong in both the article and the correction, no identifying chemical or physical properties other than the boiling (melting) point are given, and the earlier work of Wohl and Lips is not cited.

N-Methylpyruvanilide is central to certain of our studies[4] of pyruvamides as model compounds which simulate both in structure and in reactivity the α-ketoamide prosthetic groups of a number of enzymes.[5] Accordingly, we deemed it necessary to repeat the preparation by both procedures in order to resolve the situation and to have the compound and a method for its preparation reliably in hand. We find that when solid pyridinium hydroxymaleic anhydride[6] is stirred into a solution of *N*-methylaniline in benzene at room temperature as described by Wohl and Lips, gas evolution (CO_2) commences smoothly and can be brought to completion by gentle heating. Removal of solvent and distillation of the product under reduced pressure affords *N*-methylpyruvanilide directly in 65% yield, but as a pale yellow liquid, bp 108–110 °C (0.5 torr), rather than as a solid. The same compound is obtained from the reaction of dimethyloxanilide with methylmagnesium iodide in ether (Adams' procedure) and also by the reaction of pyruvyl chloride, a reliable procedure for the preparation of which was reported[7] while this work was in progress, with *N*-methylaniline in pyridine–chloroform mixture. The product from the Grignard procedure contained a persistent impurity, probably unreacted dimethyloxanilide, recognizable by virtue of an enhancement of the intensity of the two downfield peaks in the NMR spectrum.

Wohl and Lips' crude product had been worked up with concentrated hydrochloric acid, a procedure of considerable value in the preparation of pyruvanilide itself and other pyruvyl derivatives of aromatic primary amines by the hydroxymaleic anhydride procedure since it effects a clean separation from otherwise troublesome byproducts. Accordingly, we warmed *N*-methylpyruvanilide with concentrated HCl, whereupon it did indeed yield a white solid, mp 152–153 °C, exactly as reported by the German workers. The spectroscopic properties of this substance suggested to us that cyclization might have occurred, hydrogen chloride being the Lewis acid catalyst, to give 1,3-dimethyl-3-hydroxyoxindole. This compound, it transpires, is a well-known substance which has been prepared by at least three different methods[8] but which has not previously been recognized as being identical with Wohl and Lips' product. A comparison with the very full range of properties most recently reported leaves no doubt as to the identity.



That *N*-methylpyruvanilide should undergo cyclization so smoothly, in sharp contrast to pyruvanilide which does not, a difference cogently corroborated by the fact that pyruvanilide can be nitrated[9] by sulfuric–nitric acid mixture to the *p*-nitroanilide while *N*-methylpyruvanilide is destroyed by this reagent, is curious. Nevertheless, given the ready availability of α-ketoacyl derivatives of aromatic secondary amines on the one hand and the known synthetic versatility of oxindoles on the other, the facile cyclization should afford a convenient route for the preparation of a variety of 1,3-disubstituted indoles and related compounds.

Experimental Section

NMR Varian EM 360 and A 60; IR, Beckman "Acculab"; Analyses, Galbraith Laboratories.

***N*-Methylpyruvanilide.** a. Solid pyridinium hydroxymaleic anhydride (20 g) was added to a stirred solution of *N*-methylaniline (10 g) in benzene (50 mL). Gas evolution (CO_2) commenced spontaneously and was brought to completion by gentle heating. The turbid

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