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The Reaction of 1,8-Naphthosultam with Alkyl Phosphites and Chlorinated Phosphorus Reagents

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Trialkyl phosphites (**2a–c**) react with 1,8-naphthosultam (**6**) to give the respective N-alkylated products **7a–c**. Compounds **7a–c** were also prepared by the action of dialkyl phosphites on **6** in the presence of *p*-TsOH. Moreover, **7a** could be obtained by treating **6** with DMMP (**8**). On the other hand, chlorinated phosphorus reagents (**11**) condense with **6** to give products of type **12**. Structures of the new products were assigned according to consistent analytical and spectroscopic measurements.

Introduction

The behaviour of lactams (**1**) toward trialkyl (**2**) and dialkyl phosphites (**3**) has been thoroughly investigated [2] (Scheme 1). Similar attention,

however, has not been forwarded to sultams. Therefore, we have now studied the reaction of 1,8-naphthosultam (**6**) with these phosphorus reagents. This would shed light on the reactivity of **6** toward phosphorus nucleophiles in comparison to its known reactivity toward nitrogen nucleophiles [3].

Results and Discussion

We have found that the reaction of 1,8-naphthosultam (**6**) with trialkyl phosphites (**2a–c**) is completed after heating the reactants (*cf.* Experimental) in absence of solvent for 30–45 h (TLC). In each case, a light yellow crystalline substance – that did not contain phosphorus – was isolated in *ca.* 70% yield and proved to be the respective N-alkyl derivative **7** of the sultam. The identities of **7a, b** were established by comparing their mps and IR spectra with the appropriate authentic samples [4, 5]. N-Isopropyl-1,8-naphthosultam (**7c**) which is now prepared for the first time, gave compatible analytical and spectroscopic measurements (*cf.* Experimental).

In addition, N-alkyl derivatives **7a–c** could be obtained by other ways. Thus, for example, they were obtained in ~60% yield by reacting **6** with dialkyl phosphites (**3a–c**) in absence of solvent for 50–60 h. This reaction proceeded only when trace amount of *p*-toluenesulphonic acid (*p*-TsOH) was present in the medium. Compound **7a** was similarly obtained in ~45% yield by reacting **6** with dimethyl methylphosphonate (DMMP, **8**) in absence of solvent at 100 °C for 80 h.

A possible mechanism for the aforementioned N-alkylation processes is depicted in Scheme 2. This is based on direct attack by the anionic centre in **6** (*cf.* **6A**) on the alkoxy-alkyl group of the re-

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agent [6] (*e.g.* of TAP, **2a–c**) to give **7** in one process. On the other hand, alkylation of **6** with DAP (**3a–c**) which goes forward only in presence of a source of protons (*p*-TsOH), could be explained in terms of an initial protonation of the dialkyl phosphite reagent [6] by *p*-TsOH to afford the phosphonium species **9**. Nucleophilic attack by nitrogen in **6** on the protonated DAP (**9**) affords cation **10** which then releases a proton to afford **7**.

Since potential biological activities are recorded for many substrates incorporating nitrogen-to-phosphorus linkage [7, 8], we have now prepared compounds **12** to examine their biological activities. This was achieved by allowing the appropriate chlorinated phosphorus reagent (**11**) to react with the sodium salt of compound **6** (Scheme 3). The reaction products **12a–d** were obtained as colorless crystals insoluble in 10% NaOH aq. Sat-

isfactory elemental analyses and molecular weight determinations (MS) confirm the proposed structure **12**. The IR spectrum of **12b**, taken as example, in KBr showed no N–H absorption which is exhibited by compound **6** at 3220 cm^{-1} . Absorption bands shown by compound **12b** at 1370 and 1150 cm^{-1} are attributed to $(O_2S-N\curvearrowright)$ stretching vibrations [9]. Furthermore, **12b** revealed characteristic bands at 1220 and 970 cm^{-1} related to the P=O and P–N frequencies, respectively [9]. The 1H NMR spectrum of **12b** disclosed the presence of signals at: a) δ 1.28 (6H, $-CH_2-CH_3$, t, $J_{HP} = 10\text{ Hz}$), b) δ 4.3 (4H, CH_2-CH_3 , qt, $J_{HP} = 10\text{ Hz}$), c) δ 7.1–8.0 (6H, m, arom.). The ^{31}P NMR shift recorded for the product **12b** was δ -7.1 ppm . The value lies in the range of phosphoramidate shifts [10].

Data on the biological activity of the new compounds **12a–d** will be published later.

Conclusion

From the present study, it could be concluded that lactams (*e.g.*, **1**) and sultams (*e.g.*, **6**) behave differently toward nucleophilic phosphorus reagents. Thus, while alkyl phosphites cause lactam-ring cleavage of **1** to give phosphonate adducts (**4** and **5**, Scheme 1), the same reagents affect only N-alkylation of compound **6** to give N-alkyl-1,8-naphthosultam (**7**). This successful application of alkyl phosphites (**2** or **3**) and phosphonate (**8**) to induce N-alkylation, contributes to their potentialities as alkylating agents for acids [11], phenols [11–13], alcohols [6] and thiols [14]. Activity of the phosphorus compounds as alkylating agents for **6** increases in the succession:

These results certify that the activity of the reagent used is associated with the valency of the phosphorus atom. Trivalent phosphorus compounds appear to be more effective than the pentavalent derivatives. That dialkyl phosphites (DAP, **3**) lie in intermediate might find its explanation in terms of the presence of these compounds as tautomeric mixture [15] of the tri- and pentavalent states according to:

On the other hand, N-phosphorylation of **6** to give **12** could only be attained when its sodium salt was treated with chlorinated phosphorus reagents like **11**.

Mass spectrometry

The mass spectra of the N-alkyl-1,8-naphthosultam (**7a**, **c**) were also in accord with the assigned structures. The spectrum of **7a** showed the molecular ion peak (M^+) at m/z 219 ($C_{11}H_9NO_2S$, 65%). Loss of CH_2 radical from M^+ affords the base peak (cation **a**) at m/z 205 which loses a neutral SO_2 molecule in the usual manner [9] to afford cation **b** at m/z 141 (50%). Loss of SO_2 can also be suffered by the molecular ion peak to give ion **d** at m/z 154 ($C_{11}H_8N$, 45%) presumably, *via* loss of H-radical from a radical cation like **c** (m/z 155, < 5%). The mass spectrum of **7c** showed the molecular ion peak at m/z 247 ($C_{13}H_{13}NO_2S$, 31%). Its fragmentation pattern under electron impact was represented by the following ion peaks: cation **e** at m/z 232 ($M-\dot{C}H_3$, 6%), cation **a** ($M-\dot{C}_3H_6$, m/z 205, base peak) and cation **b** (base peak - SO_2 molecule, 40%). The spectrum showed no evidence for loss of a SO_2 molecule from the molecular ion peak.

Experimental

All melting points are uncorrected. The IR spectra were run on a Perkin-Elmer Infracord Spectrometer 157 (Grating) in KBr. The 1H NMR spectra were recorded on Bruker Model WH 90 Spectrometer. The chemical shifts are recorded in δ ppm relative to TMS. The ^{31}P NMR spectra were taken on Varian CFT-20 (*vs.* 85% H_3PO_4). The mass spectra were performed at 70 eV on MS-50 Kratos

(A.E.I) Spectrometer. All reactions were carried out under N_2 atmosphere.

Reagents and materials

Trialkyl phosphites (TAP) were purified by treatment with sodium ribbon followed by fractional distillation. Dialkyl phosphites (DAP) and chlorinated phosphorus reagents were freshly distilled. 1,8-Naphthosultam is commercially available from Aldrich Company.

Preparation of N-alkylated-1,8-naphthosultam (**7a-c**)

1) By the action of trialkyl phosphites (TAP, **2**) on 1,8-naphthosultam (**6**)

General procedure: A mixture of **6** (1 g, 0.005 mol) and TMP (**2a**, 2.5 ml, 0.02 mol) was heated in absence of solvent on a steam bath for 45 h (TLC). The excess of TMP was removed under vacuum, then the residue was washed several times with light petroleum and crystallized from

n-hexane to give 0.85 g (78%) of N-methyl-1,8-naphthosultam (**7a**), m.p. 125 °C, lit. 125 °C [4]. MS: *m/z* 219 (M^+).

IR (KBr): 2920 ($\text{C}-\text{N}-\text{CH}_3$), 1370 and 1155 cm^{-1} ($\text{O}_2\text{S}-\text{N}$).

^1H NMR (CDCl_3): δ 3.33 (3H, $\text{N}-\text{CH}_3$, s), 7.25–8.1 ppm (6H, arom., m).

Compound **7b** was similarly obtained (0.8 g, 72%), by conducting triethyl phosphite (**2b**) and 1,8-naphthosultam (**6**) under the reflux temperature for 30 h. Compound **7b** was crystallized from light petroleum m.p. 85 °C, lit. [5] 85 °C. MS: *m/z* 233 (M^+).

IR (KBr): 2915 ($\text{C}-\text{N}-\text{C}_2\text{H}_5$), 1365 and 1155 cm^{-1} ($\text{C}-\text{N}-\text{SO}_2$).

^1H NMR (CDCl_3): δ 1.55 (3H, $\text{C}-\text{CH}_3$, t), 3.90 (2H, $-\text{CH}_2-\text{C}$, q), 7.0–8.1 ppm (6H, arom., m).

Under similar conditions, refluxing of **6** with TiPP for 40 h afforded N-isopropyl-1,8-naphthosultam (**7c**, 0.86 g, 70%). Compound **7c** was obtained as pale yellow crystals m.p. 105 °C from *n*-hexane.

Analysis for $\text{C}_{13}\text{H}_{13}\text{NO}_2\text{S}$ (247.318)

Calcd C 63.13 H 5.29 N 5.66 S 12.96,

Found C 63.24 H 5.26 N 5.63 S 12.82.

MS: *m/z* 247 (M^+).

IR (KBr): 2930 ($\text{C}-\text{N}-\text{C}_3\text{H}_7$), 1375 and 1150 cm^{-1} ($\text{O}_2\text{S}-\text{N}$).

^1H NMR (CDCl_3): δ 1.62 (6H, $-\text{C}-\text{CH}_3$ -i, d, $J_{\text{HH}} = 8$ Hz), 4.44 (1H, $-\text{CH}-$, sept., $J_{\text{HH}} = 8$ Hz), 7.2–8.11 ppm (6H, arom., m).

2) By the action of DAP (**3**) on 1,8-naphthosultam (**6**) in the presence of *p*-TsOH

General procedure: A mixture of **6** (1 g, 0.005 mol), DMP (4 ml, 0.04 mol) and *p*-TsOH (30 mg) was heated in absence of solvent on a steam bath for ~60 h. After removing the volatile materials *in vacuo*, the residual substance was washed with H_2O then extracted with CHCl_3 . After evaporation of CHCl_3 , the residual substance was crystallized from *n*-hexane and proved to be the corresponding N-methylsultam (**7a**, 0.7 g, 65%) (comparative IR and NMR spectra).

Under similar conditions, N-ethyl- (**7b**, 0.69 g, 60%) and N-isopropyl-1,8-naphthosultam (**7c**, 0.7 g, 57%) were obtained by the reaction of **6** with diethyl and/or diisopropyl phosphite, respectively.

3) By the action of dimethyl methylphosphonate (DMMP, **8**) on **6**

A mixture of DMMP (**8**, 2.5 ml, 0.02 mol) and **6** (1 g, 0.005 mol) was heated in absence of solvent

on a steam bath for 80 h. Working-up of the reaction mixture in the usual manner afforded the N-methyl-1,8-naphthosultam (**7a**). Identification of the product **7a** (0.4 g, 42%) was accomplished by m.p., mixed m.p. as well as by comparative IR and NMR spectra with a reference specimen.

Preparation of N-phosphorylated-1,8-naphthosultam (**12**)

a) Preparation of the sodium salt of 1,8-naphthosultam

The procedure was adopted from Dannerth's method [16] with a little modification. 1,8-Naphthosultam (10 g, 0.05 mol) was dissolved in boiling *tert*-butyl alcohol (~100 ml). Boiling was continued for 3 min and then filtered while hot. The cold solution was treated with NaOH (30 ml, 10%) where beautiful yellow crystals (quantitative yield) were immediately separated out, filtered, washed with hot ethanol (4 ml) and dried at 150 °C.

b) Preparation of compounds **12**

To a stirred solution of the sodium salt of 1,8-naphthosultam (1.2 g, 0.005 mol) in dry toluene, was added the appropriate chlorinated phosphorus reagent (**11**, 0.01 mol) and the mixture was refluxed for ~40–60 h (TLC). After removal of the inorganic material by filtration, the volatile materials were removed from the filtrate under reduced pressure. The residual material was collected and recrystallized from the appropriate solvent to give the phosphorylated products **12a–d**.

Compound **12a** was obtained as colorless crystals (0.9 g, 60%) m.p. 140 °C (cyclohexane).

Analysis for $\text{C}_{12}\text{H}_{12}\text{NO}_5\text{PS}$ (313.271)

Calcd C 46.01 H 3.86 N 4.47 P 9.88 S 10.23,

Found C 46.12 H 3.84 N 4.29 P 9.95 S 10.08.

IR (KBr): 1350 and 1130 ($\text{O}_2\text{S}-\text{N}$), 1200 ($\text{P}=\text{O}$), 1030 ($\text{P}-\text{O}-\text{C}$), 980 cm^{-1} ($\text{P}-\text{N}$).

^1H NMR (CDCl_3): δ 3.7 (6H, $-\text{CH}_3$, d, $J_{\text{HP}} = 12$ Hz), 7.1–8.1 ppm (6H, arom., m).

^{31}P NMR (CDCl_3): δ -8 ppm.

MS: *m/z* 313 (M^+).

Compound **12b**, colorless crystals (1.0 g, 65%) m.p. 114 °C (cyclohexane).

Analysis for $\text{C}_{14}\text{H}_{16}\text{NO}_5\text{PS}$ (341.327)

Calcd C 49.26 H 4.72 N 4.10 P 9.07 S 9.39,

Found C 49.08 H 4.69 N 4.07 P 9.04 S 9.39.

IR (KBr): 1355 and 1155 ($\text{O}_2\text{S}-\text{N}$), 1220 ($\text{P}=\text{O}$), 1025 ($\text{P}-\text{O}-\text{C}$), 980 cm^{-1} ($\text{P}-\text{N}$).

^1H NMR (CDCl_3): 1.28 (6H, $-\text{C}-\text{CH}_3$, dt, $J_{\text{HP}} = 10$ Hz), 4.3 (4H, $-\text{CH}_2-\text{C}$, qt, $J_{\text{HP}} = 10$ Hz), 7.1–8.0 ppm (6H, arom., m).

^{31}P NMR (CDCl_3): δ -7.1 ppm.

MS: m/z 341 (M^+).

Compound **12c**, colorless crystals (1.7 g, 90%) m.p. 200 °C (ethyl alcohol).

Analysis for $\text{C}_{22}\text{H}_{16}\text{NO}_2\text{PS}$ (389.413)

Calcd C 67.85 H 4.14 N 3.59 P 7.95 S 8.23,

Found C 67.78 H 4.07 N 3.39 P 7.97 S 8.20.

IR (KBr): 1355 and 1130 ($\text{O}_2\text{S}-\text{N}$), 1440 (P–Ph), 970 cm^{-1} (P–N).

^1H NMR (DMSO): Complex multiplet at 7.1–8.4 ppm.

^{31}P NMR (DMSO): δ 24.62 ppm.

MS: m/z 389 (M^+).

Compound **12d**, colorless crystals (1.3 g, 75%) m.p. 257 °C (ethyl alcohol).

Analysis for $\text{C}_{16}\text{H}_{11}\text{ClNO}_2\text{PS}$ (347.760)

Calcd C 55.26 H 3.18 Cl 10.19 N 4.02 P 8.90 S 9.22,

Found C 55.08 H 3.16 Cl 10.07 N 4.04 P 8.95 S 9.03.

IR (KBr): 1420 (P–Ph), 985 cm^{-1} (P–N).

MS: m/z 347 (M^+).

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