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STUDIES ON ORGANOPHOSPHORUS COMPOUNDS—VI[a]

DIMETHYLAMINO-HETEROCYCLIC COMPOUNDS FROM THE CORRESPONDING POTENTIAL HYDROXY-COMPOUNDS AND HMPA

E. B. PEDERSEN* and S.-O. LAWESSON
Department of Organic Chemistry, Chemical Institute,
University of Aarhus, DK-8000 Aarhus C, Denmark

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Abstract—Potential hydroxy heterocyclic compounds are heated in HMPA at 220–230° for 20 min–15 h. The OH Group is thereby replaced by a dimethylamino-group and the yields for the reactions are indicated for the following compounds: 2-Dimethylamino-quinoline (79%); 2-dimethylamino-lepidine (77%); 2-dimethylamino-benzo[b]furan (47%); 2-dimethylamino-1-methyl-indole (68%); 2-dimethylamino-thiophene (3%); 2-dimethylamino-5-methyl-thiophene (23%); 3-dimethylaminobenzoisothiazole-S-dioxide (80%). When the reaction was performed in the presence of pyrrolidine, the following compounds were obtained: 3-(1'-pyrrolidyl)-benzoisothiazole-S-dioxide (70%); 2-(1-pyrrolidyl)-lepidine (35%). Bis(dimethylamido)-aryl-phosphates, which could be postulated as intermediates in the above reactions, were easily ruled out as such.

We have recently reported that 2-dimethylamino-benzo[b]thiophene[1] is formed when benzo[b]thiophene-2(3H)-one is refluxed in hexamethylphosphoric triamide (HMPA). A recent report by Vorbrüggen[2] about the synthesis of dimethylaminopyridines from the corresponding pyridones and HMPA has prompted us to publish our results about the scope of this reaction for the synthesis of 2-dimethylamino-heterocyclic compounds. A variety of methods has been used for the synthesis of this class of compounds but no general method seems to have been used. Aminothiophenes[3] are prepared by treatment of the corresponding mercaptothiophene with an appropriate amine, aminobenzoisothiazole-S-dioxides[4] by treatment of pseudosaccharinchloride with an appropriate amine, and 2-dimethylamino-N-methyl-indole[5] by a multistep reaction procedure according to Scheme 1.

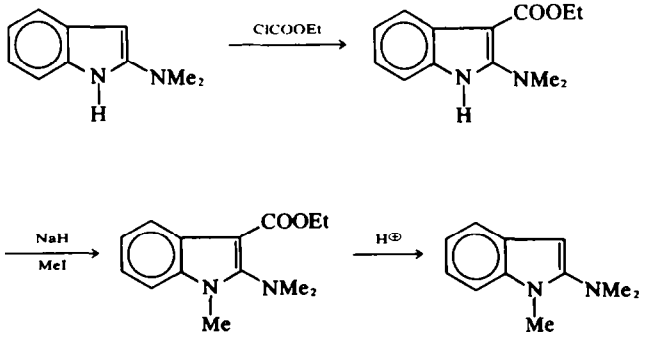
[a]Part V. T. Frejd, E. B. Pedersen and S.-O. Lawesson, *Tetrahedron* 643.

DISCUSSION

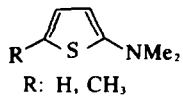
It has now been found that heating of a series of potential hydroxy heterocyclic compounds in all cases produced the corresponding dimethylamino-heterocyclic compounds.

The yields for the condensed heterocyclic compounds were generally above 50%, whereas the yields for 5-methylthiolene-2-ones were about 20%, and for 3-thiolene-2-one less than 5%. As 5-methyl-3-thiolene-2-one and 5-methyl-4-thiolene-2-one are known to form a base-catalyzed equilibrium mixture,[6] it is in accordance with our findings that these two compounds produced 2-dimethylamino-5-methylthiophene in almost the same yields.

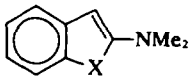
Recently it has been shown that *p*-nitro-phenol



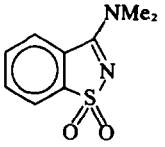
SCHEME 1

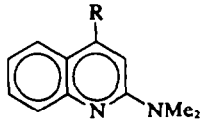


R: H, CH_3



X: O, NCH_3



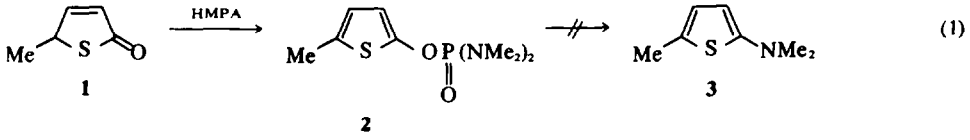


R: H, CH_3

when treated with HMPA at 230° produces N,N-dimethyl-*p*-nitroaniline.[7] In this reaction, bis(dimethylamido)-*p*-nitrophenylphosphate could be postulated as an reaction intermediate as this compound when heated at 220° produced the same product. A similar reaction sequence (exemplified in Eq 1 by 5-methyl-3-thiolene-2-one, **1**) should be expected for the treatment potential-heterocyclic compounds with HMPA at elevated temperature. However, by treatment of **2** under the same reaction conditions as for **1**, no trace of **3** could be detected. It could be suggested that dimethylamine formed in the reaction of **1** with HMPA could catalyze the thermal decomposition of **2** to **3** but if dimethylamine was bubbled through the solution of **2** in HMPA heated at 220° could **3** be detected. In fact, only a partial conversion of **2** to **3** could be found when **2** was heated to 310° for 25 min. It can therefore be concluded that **2** seems not to be an intermediate in the reaction of **1** with HMPA and similar phosphorodiamidates should neither be expected as intermediates in the reaction of the other heterocyclic compounds with HMPA.

Instead, as donor-properties of HMPA have been established in complexes between HMPA and metal ions,[8] the mechanism for the dimethylamination reaction is suggested as exemplified in Scheme 2 by the reaction of **1** with HMPA. It is assumed that one of the N atoms in HMPA attacks the carbonyl C atom. Rearrangement of the bis(N,N-dimethylamido)-phosphoro group of **4** from N to O is supposed to form **5**, and $HO\text{-}PO(NMe_2)_2$ is then easily split off and **3** is formed. Further reaction of $HO\text{-}PO(NMe_2)_2$ with HMPA produces octamethylpyrophosphoramide. This compound was actually found as a by-product in the reaction of saccharin with HMPA.

Saccharin was refluxed in HMPA in the presence of pyrrolidine and 3-(1′-pyrrolidyl)-benzoisothiazole-S-dioxide, **7**, was formed in a high yield (Scheme 3). It is reasonable to suggest **6** as an intermediate in this reaction as reflux of **6** in HMPA in the presence pyrrolidine also produced **7** in a high yield. The success of the second step of the reaction seems highly dependent on the nucleophilicity of the amine added as reflux of saccharin in HMPA in the presence of N-methylaniline only produced **6**. Similarly was 2(1)-lepidone refluxed in HMPA in the presence of pyrrolidine. Even 56 h reflux did not give complete conversion of the lepidone to the 2-(1′-pyrrolidyl)-lepidine as 2-dimethylaminolepidine was also found in the reaction mixture.

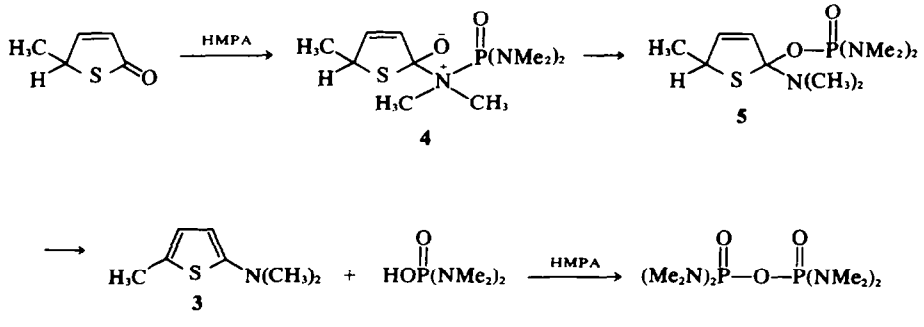


1 **2** **3** (1)

EXPERIMENTAL

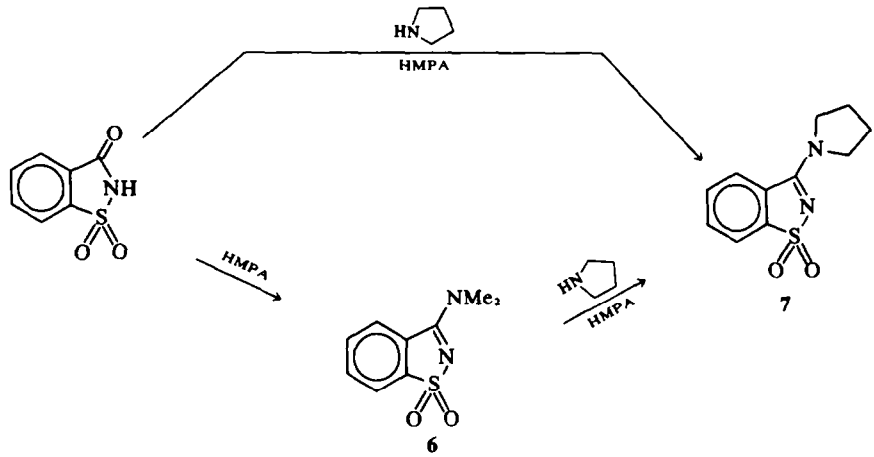
NMR spectra were recorded at 60 Mc/s on a Varian A-60 spectrometer (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet). The IR spectra were recorded on a Beckmann 18 IR spectrometer. UV spectra were measured on a Perkin-Elmer 402 spectrometer. M.ps and b.ps are uncorrected. The microanalyses were performed by Løvens kemiske Fabrik, Copenhagen. Commercial HMPA dried over molecular sieves (3A) was used in this investigation.

2-Dimethylamino-quinoline. 2(1)-Quinolone (5·0 g) and



4 **5** **3**

SCHEME 2



SCHEME 3

25 ml HMPA were heated at 230° for 4 h. The mixture was allowed to cool to room temp and was then poured into water (200 ml) and extracted 4 times with 100 ml ether. The combined ether phases were washed twice with 50 ml water, dried with $CaSO_4$, the ether was stripped off, and distillation gave 4·7 g (79%) of the title compound; $b.p._{0.4}$ 111–113°; m.p. 70–71° (light petroleum ether); lit.[9] m.p. 70–71°.

2-Dimethylamino-lepidine. 2(1)-Lepidone (5·0 g) and 30 ml HMPA were heated at 230° for 15 h and worked up as above. Distillation gave 4·5 g (77%) of the title compound; $b.p._{0.15}$ 116–122°; lit.[10] $b.p._{0.01}$ 100–105°; m.p. 50° (light petroleum ether); lit.[10] m.p. 47–50°.

2-Dimethylamino-benzo[b]furan. Benzo[b]furan-2-(3H)one (5·0 g) and 25 ml HMPA were heated at 225° for 20 min and worked up as above. Distillation gave 2·8 g (47%) of the title compound; $b.p._{12}$ 128–130°; $n_D^{25} = 1·5995$. (Found: C, 74·27; H, 6·95; N, 8·61. $C_{10}H_{11}NO$ requires: C, 74·51; H, 6·88; N, 8·69%); NMR ($CHCl_3$) δ 2·85 (s, 6H); 5·23 (s, 1H); 6·80–7·35 (m, 4H); IR (CCl_4) 1620 cm^{-1} (very strong; UV (C_6H_{12}) $\lambda_{max} = 273$ nm (log ε = 4·16), and 297 nm (log ε = 4·04).

2-Dimethylamino-1-methyl-indole. N-methyl-oxindole (5·0 g) and 25 ml HMPA were heated at 220° for 2 h. The cooled mixture was poured into 200 ml water, saturated with NaCl and worked up as above. Distillation gave 4·0 g (68%) of the title compound; $b.p._{0.1}$ 88°; NMR ($CDCl_3$) δ 2·70 (s, 6H), 3·52 (s, 3H), 5·85 (s, 1H), 6·9–7·2 (m, 3H), and 7·3–7·6 (m, 1H); lit;[5] NMR ($CDCl_3$) δ 2·77 (6H), 3·62 (3H), and 5·96 (1H); IR (film) 1550 cm^{-1} (very strong); UV (C_6H_{12}) $\lambda_{max} = 233$ nm (log ε = 4·33), 284 nm (log ε = 4·01), and 294 nm (shoulder).

2-Dimethylamino-thiophene. 3-Thiolene-2-one (10 g) and 50 ml HMPA were heated at 220° for 25 min. The cooled mixture was poured into 400 ml water, saturated with NaCl, and extracted 4 times with 200 ml ether. The combined ether phases were washed with 2 × 100 ml water, dried with $CaSO_4$. The ether was stripped off and distillation gave 0·43 g (3%) of the title compound; $b.p._9$ 66–69°; lit. $b.p._{24}$ 83°.

2-Dimethylamino-5-methyl-thiophene. 5-Methyl-3-thiolene-2-one (10 g) and 50 ml HMPA were heated at 220° for 25 min and worked up as above. Distillation gave 2·8 g (23%) of the title compound; $b.p._{10}$ 75°; $n_D^{24} = 1·5425$. (Found: C, 59·53; H, 7·96; N, 9·92; S, 22·37. $C_7H_{11}NS$ requires: C, 59·55; H, 7·85; N, 9·92; S, 22·67%); NMR ($CHCl_3$) δ 2·32 (d, 3H, $J = 1·3$ c/s), 2·80 (s, 6H), 5·69 (d, 1H, $J = 3·7$ c/s), and 6·35 (dq, 1H, $J = 3·7$ c/s, $J = 1·3$ c/s); UV (C_6H_{12}) $\lambda_{max} = 222$ nm (log ε = 3·55) and 280 nm (log ε = 3·85).

Similarly were 3·0 g (24%) of 2-dimethylamino-5-methyl-thiophene prepared from 10 g of 5-methyl-4-thiolene-2-one.

3-Dimethylamino-benzoisothiazole-S-dioxide, **6**. Saccharin (10 g) and 50 ml HMPA were heated at 225° for 2 h. The mixture was allowed to cool to room temp. The ppt was filtered off, washed with boiling $CHCl_3$ and yielded 9·2 g (80%) of the title compound; m.p. 297° (subl.); lit.[4] m.p. 301°. Distillation of the filtered reaction mixture gave 6 g of octamethylpyrophosphoramide; $b.p._{0.4}$ 130–132°; lit.[11] $b.p._{0.5}$ 120–122°.

3-(1'-Pyrrolidyl)-benzoisothiazole-S-dioxide, **7**. Saccharin (5·0 g), 4 g pyrrolidine, and 25 ml HMPA were refluxed for 5 h. The reaction temperature increased from 180° to 225°. There was work-up as above and 4·5 g (70%) of the title compound were obtained; m.p. 268° (subl). (Found: C, 55·65; H, 5·05; N, 11·80; S, 13·62. $C_{11}H_{12}N_2O_2S$ requires: C, 55·99; H, 5·12; N, 11·86; S, 13·55%); NMR (CF_3COOH) δ 2·0–2·7 (m, 4H), 3·9–4·7 (m, 4H, restricted rotation, separation of signals: 18 c/s), 7·8–8·5 (m, 4H); UV (EtOH) $\lambda_{max} = 245$ (log ε = 4·02), 280–290 (log ε = 3·64).

Treatment of **6** *with pyrrolidine and HMPA.* Compound **6** (5 g), pyrrolidine (3·3 g) and 25 ml HMPA were refluxed. During ½ h the reflux temp increased from 160° to 210° and further 1 g of pyrrolidine was added to the mixture which was then allowed to reflux for 6 h at 180–190°. On working up as above there was obtained 3·8 g (68%) of **7**.

2-(1'-Pyrrolidyl)-lepidine. 2(1)-Lepidone (5 g), pyrrolidine (4·5 g) and 25 ml HMPA were refluxed. After 56 h, the reflux temp had increased to 245° and there was work-up as for 2-dimethylamino-quinoline. Distillation 110–115°/0·1 mm gave 0·4 of 2-dimethylamino-lepidine and distillation 138–140°/0·1 mm gave 2·3 g (35%) of the title compound; $n_D^{26} = 1·6557$. (Found: C, 78·29; H, 7·67; N, 13·63. $C_{14}H_{16}N_2$ requires: C, 79·21; H, 7·60; N, 13·20%); NMR ($CDCl_3$) δ 1·7–2·1 (m, 4H), 2·48 (d, 3H, $J = 0·9$ c/s), 3·3–4·8 (m, 4H), 6·45 (q, 1H, $J = 0·9$ c/s),

6·9–7·9 (m, 4H); IR (CCl_4) 1615 cm^{-1} (very strong); UV (EtOH) λ_{max} = 252, (log ϵ = 4·52), 279 (shoulder), 354, (log ϵ = 3·75), 370 nm (shoulder).

Bis(dimethylamido)-(5-methyl-2-thienyl)phosphate, 2. To 5-Methyl-3-thiolene-2-one (11·4 g) in 200 ml anhyd C_6H_6 were added 26 g TlOEt.[12] The Tl salt was filtered off and washed with C_6H_6. To the Tl salt in 50 ml anhyd C_6H_6 was added dropwise 12 g tetramethyl phosphorodiamidic chloride by which the temp increased to 55°, the mixture was then allowed to stand for 1 h. The TlCl was filtered off, the benzene stripped off and distillation gave 11 g (63%) of the title compound; b.p.$_{0.5}$ 128–132°; n_D^{25} = 1·5110. (Found: H, 6·89; N, 11·28. $C_9H_{17}N_2PS$ requires: H, 6·90; N, 11·28%); NMR ($CDCl_3$) δ 2·33 (m, 3H), 2·72 (d, 12H, J = 10 c/s), 6·25–6·51 (m, 2H); UV (C_6H_{12}) λ_{max} = 242 nm (log ϵ = 3·78).

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