98. Reaction of Anthranilamide with Phosphorus Pentasulfide: Formation of 2-Mercapto-(1*H*)-1,3,2λ^5-benzodiazaphosphorine-2,4-dithione[1])

by **Kuppuswamy Nagarajan**[2]) and **Sharada J. Shenoy**
Hindustan *Ciba-Geigy Ltd.*, Research Centre, Bombay 400063, India

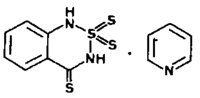
and **Hans Fritz, Othmar Hosang,** and **Wilhelm J. Richter***
Central Function Research, *Ciba-Geigy AG,* CH-4002 Basel

(19.III.85)

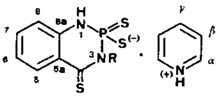
The reaction of anthranilamide with phosphorus pentasulfide in boiling pyridine leads to the benzodiazaphosphorine-pyridine salt **2**. The structure is established by elemental analysis, ^{1}H-, ^{13}C-, ^{15}N-, ^{31}P-NMR, and mass spectral data.

A recent report on the formation of a 2,1,3-benzothiadiazine derivative **1**, (pyridine complex, m.p. 189–190°) containing the novel dithiosulfone group [1] from the reaction of anthranilamide and phosphorus pentasulfide in pyridine, and our sustained involvement in developing antiparasitic compounds [2] prompted us to synthesise **1** for biological screening by the published procedure. In our hands, treatment of 2-aminobenzamide (30 mmol) with phosphorus pentasulfide (30 mmol) in refluxing pyridine (20 ml) for 1.5 h and dilution of the solution with H_2O afforded a yellow crystalline product, m.p. 220-2° (dec.) in 70% yield. Recrystallisation from EtOH/H_2O or DMF/H_2O raised the m.p. to 222-4° (dec.) (55%). Surprisingly, the product had elemental analysis correct for the pyridine adduct of $C_7H_7N_2S_3P$ rather than $C_7H_6N_2S_4$ required by **1** (found: C 44.34, H 3.77, N 12.91, P 9.48, S 28.70; $C_7H_7N_2S_3P \cdot C_5H_5N$ requires C 44.29, H 3.72, N 12.92, P 9.52, S 29.56. This would suggest that the product had structure **2** which would have been normally expected from such a reaction. This assumption was fully borne out by the results of mass spectral (*Varian MAT CH7* and *CEC 21-110 B* mass spectrometers) and NMR spectral (*Bruker WM-400* spectrometer) investigations.

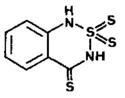
In agreement with structure **2**, the low-resolution MS of the product indicated the presence of only 3 S-atoms (M^+ of free acid **4** at m/z 246; second isotope peak at m/z 248, mainly due to ^{34}S, of only about 15% abundance as opposed to about 20% required for 4



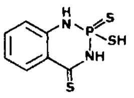
1



2 R = H
5 R = Ph
6 R = CH_2Ph



3



4

---

[1]) Contribution No. 744 from Research Centre, Bombay.

[2]) Present address: *Searle R & D Centre,* Thane Belapur Road, Thane 400601, India.

S). High-resolution measurements of M^+ definitely ruled out **3**, and consequently **1**, in that its accurate mass 245.9512 is well within the limits of error for **4** ($C_7H_7N_2S_3P$, calc. mass 245.9509) in contrast to those to be expected for **3** ($C_7H_6N_2S_4$, calc. mass 245.9414). This result was also found in agreement with a major ion at m/z 213 in the low-resolution mass spectrum of **2** that corresponds to the loss of a HS radical from M^+ ($C_7H_6N_2S_2P$: 212.9710 calc., 212.9711 obs.).

In the ^{31}P-NMR spectrum of a 0.2 *m* solution in (D_6)DMSO at 25° a *d* at 70.2 ppm (ext. standard 85% H_3PO_4) with J(P,H) = 13.5 Hz was observed. The corresponding signal of *H*-N(3) appeared at 10.51 ppm in the ^{1}H-NMR spectrum. The signal for *H*-N(1) appeared as a broad peak at 8.6 ppm. The presence of the N-P-N structural fragment was indicated by 2 *d* at 185.6 ppm (^1J(P,N) = 21.7 Hz) and 113.6 ppm (^1J(P,N) = 11.5 Hz) for N(3) and N(1), respectively, in the ^{15}N-NMR spectrum of a 0.5 *m* solution in (D_6)DMSO at 25° (chemical shifts referenced to the liq. ammonia scale, the signal for the pyridinium-N-atom could not be observed). ^{1}H chemical shifts for the non-exchangeable protons as well as ^{13}C chemical shifts and P,C-coupling constants are given in the *Table* and are also fully consistent with structure **2**. In particular, ^{1}H and ^{13}C chemical shifts of the pyridine moiety are indicative of a protonated pyridine.

Table. *^{1}H- and ^{13}C-NMR Data*[a])[b])

C(H)	$\delta(^{13}C)$	J(P,C)	$\delta(^1H)$	C(H)	$\delta(^{13}C)$	J(P,C)	$\delta(^1H)$
4	190.93	9.1	–	8	117.62	8.4	6.85
5a	121.20	6.7	–	8a	141.56	4.6	–
5	133.02	0	8.29	α	142.57	–	8.93
6	118.07	0	6.76	β	126.92	–	8.06
7	133.02	0	7.28	γ	145.61	–	8.58

[a]) δ-Values at 100.6 and 400.1 MHz, respectively; 0.2 *m* soln. in (D_6)DMSO, internal standard TMS, T = 25°.
[b]) J-Values in Hz at 100.6 MHz.

Compound **2** is unknown to the best of our knowledge, although in the conversion of substituted anthranilamides to the respective thioamides [3] the ring system has been implicated. Compounds **5** and **6** have also been isolated, without the presence of phosphorus being demonstrated [4]. Two other related compounds, 2,3-dihydro-2-(*p*-methoxyphenyl)-1,3,2-benzodiazaphosphorine-2-sulphide carrying H or cyclohexyl group on N(3) have been reported more recently from the reaction of anthranilamides with the *Lawesson* reagent [5]. Compound **2** dissolves readily in aqueous NaOH; acidification surprisingly regenerates **2** without removing pyridine. Likewise upon addition of pyridine to **2**, initial dissolution occurs followed by separation of yellow crystals. Upon filtration, washing with Et_2O and drying in vacuum, only **2** is recovered. In contrast to **5** and **6**, **2** was recovered to the extent of 65% after heating under reflux min 1:1 mixture of toluene and H_2O for 16 h; 2-aminothiobenzamide was also formed as the Et_2O-soluble product to the extent of 30%; m.p. 116-7° (M^+ at m/z 152; correct C, H, N analysis). Perhaps the greater instability of **5** and **6** derives from an unfavourable interaction between the N(3) substitutent and the S-atoms on phosphorus.

We thank Dr. *S. Selvavinayakam* and Dr. *W. Padowetz* and their associates for analytical and some spectral data.

REFERENCES

[1] R. M. Acheson, M. R. Bryce, S. Das, Z. Dauter, A. J. Rees, C. D. Reynolds, *J. Chem. Soc., Chem. Commun.* **1983,** 1002.

[2] M. D. Nair, K. Nagarajan, in 'Progress in Drug Research', Ed. E. Jucker, Birkhäuser Verlag, Basel, 1983, Vol. 27, p. 163; K. Nagarajan, V. P. Arya, *J. Sci. Ind. Res.* **1982,** *41,* 232.

[3] R. F. Meyer, B. L. Cumings, P. Bass, H. O. J. Collier, *J. Med. Chem.* **1965,** *8,* 515.

[4] W. Walter, Th. Fleck, J. Voss, M. Gerwin, *Liebigs Ann. Chem.* **1975,** 275.

[5] A. A. El-Barbary, S. O. Lawesson, *Tetrahedron* **1981,** *37,* 2641.