Synthesis of an α-Amino-β-thiolactam (1)

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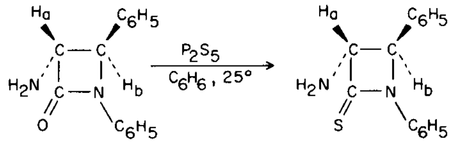
Sir:

Whereas great interest has been demonstrated in the synthesis, chemistry and biological activity of peptides and β-lactams, little information has been published on the synthesis of the corresponding thio derivatives. There appears to be no example in the chemical literature of a thiopeptide and only two reports on the synthesis of β-thiolactams (3). Phosphorus pentasulfide has long been utilized to exchange sulfur for oxygen in amides and reaction conditions are typically refluxing benzene or dioxane. Very few, if any, of these reactions have been effected at or below room temperature and we have investigated the use of mild conditions for the reaction of phosphorus pentasulfide with amides, peptides, β-lactams and penicillins (4). This communication reports the synthesis and characterization of an α-amino-β-thiolactam, 3-amino-1,4-diphenyl-2-azetidinethione (I), as well as an improved procedure for the preparation and isolation of thioamides.



II I

Treatment of 3-amino-1,4-diphenyl-2-azetidinone (II) (5) with phosphorus pentasulfide in benzene at ***room temperature*** followed by treatment with buffer afforded, after chromatography, the crystalline β-thiolactam I in a yield of 24-36%. The following procedure was used in a study of the effect of reaction conditions on the yield of compound I (Table I). The β-lactam II was stirred in a dry solvent (which had been passed through neutral alumina) with phosphorus pentasulfide in a system protected from

TABLE I

The reaction of Phosphorus Pentasulfide with 3-Amino-1,4-diphenyl-2-azetidinone (II)

β-Lactam II mmoles	P_2S_5 mmoles	Solvent (ml.)	Temp. °C	Time, hours	% Recovery of II	% Yield of I (a)
2.0	0.50	Benzene (10)	82	3	23	13
10.0	5.00	Benzene (30)	82	3	0	16
6.0	3.00	Benzene (15)	82	0.33	0	23
0.5	0.25	Benzene (5)	25	78	50	24-36
0.5	0.25	Dioxane (5)	25	74	60	5

(a) Based on unrecovered β-lactam II.

moisture. The reaction mixture was added to 0.5 *M* phosphate buffer (*p*H 8.0), the organic compounds extracted with ethyl acetate and the organic layer washed with saturated sodium chloride solution, dried and concentrated *in vacuo*. The oil was decolorized with carbon (in ethanol) and then chromatographed on silica gel G (0.08-0.20 mm.); the carbon tetrachloride-chloroform (1:3) fraction gave a crystalline compound with an R_f of 0.54 (6). The compound was rechromatographed to afford, after recrystallization from carbon tetrachloride, an analytical sample of I, m.p. 132-134°, λ max (potassium bromide), 6.25 (m), 6.30 (m), 6.70 (s), 7.05 (s) and 7.87 (s) μ; nmr (deuteriochloroform) δ 1.95 (s, 2, NH_2, on adding deuterium oxide this signal disappeared), 3.78 (d, 1, J=2 Hz, H_a or H_b), 5.17 (d, 1, J=2 Hz, H_a or H_b) and 7.12-7.90 ppm (m, 10, aromatic protons), the small coupling constant exhibited by protons H_a and H_b indicates that they have a *trans* relationship (7); mass spectrum (70 eV) *m/e* (rel intensity) parent ion 254(21), 183(18), 182(100), 135 (16) and 119 (22) (8).

Anal. Calcd. for $C_{15}H_{14}N_2S$: C, 70.85; H, 5.55; N, 11.02; S, 12.61. Found: C, 70.74; H, 5.80; N, 10.80; S, 12.58.

Compound I decomposed during 14 days storage in a vacuum desiccator to a crystalline compound, m.p. 110-120°, λ max (potassium bromide), 5.82, 6.00 and 6.55 μ.

A by-product of the reaction, R_f=0.80 (6), gave positive tests for sulfur and phosphorus. Thiophosphoric acid amides have been isolated from the reaction of phosphorus pentasulfide with amines (9). Thus by protecting the amino group in II, the yield of β-thiolactam should be increased.

The mild reaction conditions and work-up used in the synthesis of I were also very effective in increasing the yield of simple thioamides. Erlenmeyer and coworkers (10) obtained a 32% yield of thiopropionamide from the reaction of propionamide with phosphorus pentasulfide in refluxing dioxane (15 minutes). By using lower temperatures (25°), longer reaction times (74 hours), the same molar ratio (propionamide:phosphorus pentasulfide=5:1.1) and the same work-up (water), the yield of thiopropionamide was 48%; decomposition of the reaction mixture in 0.5 *M* phosphate buffer (*p*H 6.1) increased the yield to 59%.

REFERENCES

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(3a) A. Spasov, B. Panaiotova and E. Golovinsky, *Dokl. Akad. Nauk SSSR*, 158, 429 (1964); *Chem. Sec., English Transl.*, p. 924; (b) E. Testa and L. Fontanella, *Il Farmaco, Ed. Sci.*, in press.

(4) K. R. Henery-Logan and H. P. Knoepfel, to be published.

(5) K. R. Henery-Logan and J. V. Rodricks, *J. Am. Chem. Soc.*, 85, 3524 (1963).

(6) Thin layer chromatography determinations were carried out on silica gel using chloroform:ethyl acetate (19:1).

(7) J. L. Luche, H. B. Kagan, R. Parthasarathy, G. Tsoucaris, C. de Rango and C. Zelwer, *Tetrahedron*, 24, 1275 (1968). The nmr spectrum of compound II showed doublets at δ 4.00 (J=2 Hz) and 4.66 ppm (J=2 Hz) indicating that protons H_a and H_b also have the *trans* relationship.

(8) Compound II exhibited an analogous mass spectrum:parent ion 238 (16), 183 (15), 182 (100) and 119 (39).

(9) A. C. Buck, J. D. Bartleson and H. P. Lankelma, *J. Am. Chem. Soc.*, 70, 744 (1948).

(10) H. Erlenmeyer, O. Weber, P. Schmidt, G. Kueng, C. Zinsstag and B. Prijs, *Helv. Chim. Acta*, 31, 1153 (1948).

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