Synthesis of an Acetyl-α-thio-β-carboline by Thermolysis of Dithio-2,2'-di(*N'*-acetyltryptamine)

Michel Barbier* and Michel Devys

Institut de Chimie des Substances Naturelles, CNRS,
91190 Gif sur Yvette, France

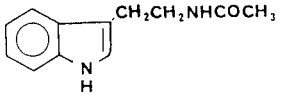
Received September 13, 1988

The first synthesis of an acetyl-α-thio-β-carboline [2-acetyl-2,9-dihydro-1,2-thiazino[6,5-*b*]indole (**4**) 28%] by the thermolysis of dithio-2,2'-di(*N'*-acetyltryptamine) **3** is reported. Deacetylation of **4** carried out in basic or acidic media does not lead to the free base but to a series of unidentified degradation products. This new substance **4** is therefore stabilized by the *N*-acetyl group. The results so far obtained are discussed and a mechanism is proposed for the cyclisation produced by the thermolysis.

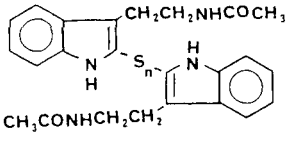
J. Heterocyclic Chem., **26**, 265 (1989).

The β carboline family [1] is of general interest, since many of these compounds possess important biological properties. For instance, certain β-carbolines display benzodiazepine receptor antagonism, psychoactive effects, and monoamine oxidase inhibition. Due to such properties, numerous syntheses were recently reported in this field [2,3] in order to generate models for the study of binding site competition. The indole-derived phytoalexins cyclobrassinin [4,5] and brassilexin [6] isolated from plants, can be considered to be sulfur containing analogues. To our knowledge, however, thio-β-carbolines are unknown as natural products and no reports have appeared concerning their synthesis.

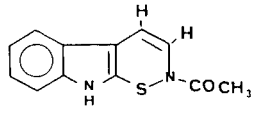
In the present publication, the synthesis of the 2-acetyl-α-thio-β-carboline **4** is reported. Thus this constitutes the synthesis of the novel 1,2-thiazino[6,5-*b*]indole ring system.



1



2 n = 1
3 n = 2



4

Tryptamine *N'*-monoacetate **1** was obtained by reaction of tryptamine with acetic anhydride at room temperature in presence of an excess of pyridine overnight. The monoacetate **1**, when treated by sulfuryl chloride in chloroform, gave the known disulfide **3** [7,8]. Examination of the reaction mixture by tlc and ms showed the existence of several other substances which were not pointed out in preceding publications. The disulfide **3** was isolated pure by preparative thin layer chromatography (30% yield). Among the products occurring from this reaction were the monosulfide **2** and a series of higher polysulfides resulting from disproportionation. The monosulfide **2** was also prepared by a reaction of tryptamine *N'*-monoacetate **1** with sulfur chloride.

The thermolysis of the acetyltryptamine disulfide **3** was carried out at 350° *in vacuo* leading to the 2-acetyl-α-thio-β-carboline **4**. As could be expected, the thermocyclisation proceeds through elimination of hydrogen sulfide as noticed from the residual smell of the resulting tar. The reaction mixture was extracted using ethyl acetate and the substance **4** was obtained by preparative tlc on silicagel (28%).

High resolution ms and elemental analysis are in agreement with the proposed structure **4**. The hyperconjugated indole system is demonstrated by the uv spectrum. The presence in the molecule of two olefinic protons, four aromatic H-atoms, and an *N*-acetyl group was determined from the ^{1}H nmr spectrum.

Experiments were carried out on the monothio derivative **2** but the presence of substance **4** among the numerous products recovered from the thermolysis could not be confirmed.

The olefinic double bond in **4** was probably generated by a sulfur-initiated deprotonation of **3** with elimination of hydrogen sulfide. As the monothio derivative of tryptamine acetate **2** did not lead to **4**, the S-S bond appears to be a necessary condition for cyclisation. Such a hypothesis is supported by the published syntheses of benzothiazoles [9] or of thiocoumarines [10] from precursors bearing monosulfide and unsaturated substitutions in 1,2-positions when treated by polyphosphoric acid. However, the α-thio-β-carboline **4** was not obtained on treatment of **3** with polyphosphoric acid, the starting material being recovered unchanged from this experiment.

Attempts to deacetylate the 2-acetyl-α-thio-β-carboline **4** with sodium hydroxide at different concentrations and temperatures gave mixtures in which (according to tlc and ms) the corresponding free base was absent. In contrast, substance **4** is stable at neutral or reasonably acidic *p*H at

room temperature but decomposes on warming to a mixture of unidentified products. These last results illustrate the stabilizing effect of the *N*-acetyl group in the thiazinoindole **4**.

EXPERIMENTAL

The melting points were determined with a Kofler apparatus under the microscope and are corrected. The uv spectra were obtained with a Perkin-Elmer Lambda-5 automatic recording spectrometer. The ms determinations were made with an AEI MS50 spectrograph and the ^1H nmr spectra were carried out on a Bruker 200 MHz apparatus in perdeuteriomethanol reported in ppm from TMS as an internal standard. Silicagel fluorescent films or plates (20 x 20 x 0.1 cm) Schleicher-Schüll were used for analytical and preparative purposes (uv observation with a Desaga lamp at 254 nm).

Tryptamine *N'*-Monoacetate (**1**).

To a solution of tryptamine (1.6 g, 0.01 mole) in dry pyridine (20 ml) was added acetic anhydride (16 ml) and the mixture was kept for 18 hours at room temperature. The reaction mixture was poured into an equal volume of crushed ice. Water was added (100 ml) and the acetate **1** was extracted from the aqueous phase with dichloromethane (2 x 80 ml). The combined organic layers were washed with water, dried over sodium sulfate and concentrated. The residual product was crystallised from ethyl acetate, 1.21 g (60%), mp 77-78°, Rf 0.60 on tlc in ethyl acetate. The previous method [11], mp 77°, required distillation of the final product.

Thio-2,2'-di(*N'*-acetyltryptamine) (**2**).

Tryptamine monoacetate **1** (202 mg, 1 mmole) was dissolved in chloroform (20 ml, distilled over calcium chloride) and the solution was kept in an ice bath. Sulfur dichloride (155 mg, 0.13 ml, 1.5 mmoles) was added dropwise with stirring. After standing for 2 hours at room temperature, supernatant liquid was decanted from the yellow precipitate. This precipitate was thoroughly triturated with a solution of sodium bicarbonate (saturated, 8 ml), then with warm chloroform (60°, 10 ml). This operation was repeated six times leading to an organic phase (collected, 60 ml) and to a residue. The chloroform solution was washed with water (10 ml), dried over sodium sulfate and concentrated (195 mg of a yellow mixture). The chloroform insoluble residue (40 mg) consisted of a gum of polymerized material which was discarded. Analytical tlc (ethyl acetate) of the chloroform extract, indicated 3 main products at Rf 0.50, 0.30 and 0. The corresponding substances were isolated by preparative tlc with the same solvent. The product found at Rf 0 (6 mg) was not further investigated. The substance at Rf 0.30 was identified as the disulfide **3** by direct comparison (46 mg, 10%, yellow foam, mp 83-88°; ms: (m/e) 466, M^+). The compound found at Rf 0.50 corresponded to the expected monosulfide **2** (180 mg, 40%, nearly colourless plates, mp 115-118°; ms: (m/e) 434, M^+).

Anal. Calcd. for $C_{24}H_{26}N_4O_2S$ (434.4): C, 66.29; H, 5.98; N, 12.89; S, 7.36. Found: C, 66.48; H, 6.01; N, 12.75; S, 7.08.

Dithio-2,2'-di(*N'*-acetyltryptamine) (**3**).

Compound **3** was prepared as for **2**, using sulfuryl chloride. To a solution of 202 mg (1 mmole) of tryptamine monoacetate **1** dissolved in 20 ml of anhydrous chloroform and kept at 0°, was added 0.12 ml of sulfuryl chloride (200 mg, 1.5 mmoles). After the reaction, examination of the chloroform extract (180 mg of a yellow mixture), revealed the presence of the same three compounds as obtained in the preparation of **2** (analytical tlc, ethyl acetate, Rf 0.50, 0.30 and 0). The substance at Rf 0.50 was identified as the monosulfide **2** (45 mg, 10%, mp 115-118°; ms: (m/e) 434, M^+, direct comparison with the previously obtained **2**). The product found at Rf 0.30 was the disulfide **3**, yellow foam, 140 mg, 30%, mp 83-88°; ms: (m/e) 466, M^+. This product could not be obtained crystalline.

Anal. Calcd. for $C_{24}H_{26}N_4O_2S_2$ (466.4): C, 61.79; H, 5.62; N, 12.01; S, 13.73. Found: C, 61.58; H, 5.59; N, 12.24; S, 13.76.

The fraction at Rf 0 (6 mg) showed in the ms a series of molecular ions differing by 32 mass units each, between m/e 498 (S_3 derivative and 690 (S_9 derivative) and thus corresponded to higher sulfides of tryptamine acetate.

2-Acetyl-2,9-dihydro-1,2-thiazino[6,5-*b*]indole (**4**). (2-Acetyl-α-thio-β-carboline) (**4**).

Dithio-2,2'-di(*N'*-acetyltryptamine) **3** (140 mg, 0.3 mmole) was deposited as a film (from a chloroform solution) on the wall of a pyrex ampoule (1.5 cm diameter). The ampoule was introduced into an air-bath pre-warmed at 350° for 3 minutes, resulting in an immediate charring. After cooling the ampoule, the brown tar was extracted twice with ethyl acetate (3 ml), then concentrated (80 mg). The presence of a new substancce on tlc was observed (dichloromethane-methanol 95:5, Rf 0.55, strong uv absorption). This product was isolated by preparative tlc in the same solvent mixture (13.8 mg, 28%, colourless amorphous substance, mp 266-269°); high resolution ms: Calcd. for $C_{12}H_{10}N_2OS$: 230.05138 (M^+). Found: (m/e) 230.0521 (98%); characteristic ions were analyzed at m/e 188.0419 (100%, M-42$^+$, ketene elimination from the acetyl group, Calcd. for $C_{10}H_8N_2S$ 188.0408); 187.0329 (70%, M-43$^+$, (-$COCH_3$). Calcd. for $C_{10}H_7N_2S$: 187.03299). The ion corresponding to $COCH_3^+$ at m/e 43 had a 50% relative intensity; P+2 isotopic ions found at M^+ and the main reported fragments, contain from 3.5 to 4% $^{34}S/^{32}S$, in agreement with the presence in the molecule of a single S-atom; uv: λ max in methanol, nm, ε, 202 (9100), 235 (15000), 286 (6600), 307 (shoulder, 5800); ^1H nmr: 1.88 (s, 3H, CH_3CO-), 7.28 (d, 1H, J = 15 Hz), 7.52 (d, 1H, J = 15 Hz, olefinic protons C-3, C-4), 6.95-7.10 (m, 4H, aromatic protons C-5 to C-8).

Anal. Calcd. for $C_{12}H_{10}N_2OS$ (230.05): C, 62.60; H, 4.34; N, 12.17; S, 13.91. Found: C, 62.32; H, 4.28; N, 12.37; S, 13.68.

Attempts to Deacetylate the 2-Acetyl-α-thio-β-carboline (**4**).

In Alkaline Media.

The product **4** was dissolved in methanol (2 mg, 0.5 ml) and an aqueous solution of sodium hydroxide was added (1*N* or 4*N* concentration) in equal volumes, in order to obtain a final concentration of 0.5 or 2*N*. After 1 hour at 20°, the solution was shaken with 1 ml of ethyl acetate, the organic supernatant liquid was pipetted off and dried over sodium sulfate and examined by tlc (analytical). The uv shows four substances in dichloromethane-methanol (95:5), Rf 0.1 to 0.4. The ethyl acetate mixture was directly submitted to ms and no ion could be detected for the free base (m/e 188).

In Acidic Media.

In this experiment, substance **4** was dissolved in methanol as above, and 1*N* or 4*N* hydrochloric acid solutions added to get a final concentration of 0.5 or 2*N*. After 2 hours at 20°, the careful neutralisation by 2*N* sodium hydroxide and extraction with ethyl acetate (equal volume), gave a product which from tlc was unchanged. The same reaction carried out at 80° (30 minutes) lead to the rapid destruction of the product. The free base was not present (tlc, ms) in the resulting mixture (extraction with ethyl acetate).

Acknowledgements.

Thanks are due to Drs. B. C. Das and C. Girard for mass spectrometry and to the NMR Department at Gif sur Yvette.

REFERENCES AND NOTES

[1] J. Torreilles, M. C. Guérin and A. Previero, *Biochimie*, **65**, 929 (1985).

[2] M. Beugelmans-Verrier and P. Potier, *Tetrahedron*, **43**, 3465 (1987).

[3] R. H. Dodd, C. Ouannes, M. C. Potier, L. Prado de Carvalho, J. Rossier and P. Potier, *J. Med. Chem.*, **30**, 1248 (1987).

[4] M. Takasugi, K. Monde, N. Katsui and A. Shirata, *Chem. Letters*, 1631 (1986).

[5] M. Takasugi, N. Katsui and A. Shirata, *J. Chem. Soc., Chem. Commun.*, 1077 (1986).

[6] M. Devys, M. Barbier, I. Loiselet, T. Rouxel, A. Sarniguet, A. Kollmann and J. F. Bousquet, *Tetrahedron Letters*, (1988) in press.

[7] H. Wieland and B. Witkop, *Ann. Chem.*, **543**, 171 (1940).

[8] A. Fontana, F. M. Veronese and E. Boccu, *Acta Vitaminol. Enzymol.*, **29**, 270 (1975).

[9] O. Meth-Cohn and B. Tarnovski, *Synthesis*, 58 (1978).

[10] O. Meth-Cohn and B. Tarnovski, *Synthesis*, 56 (1978).

[11] E. Späth and E. Lederer, *Chem. Ber.*, **63**, 120 (1930).