A New Synthesis of Benzothiopyrano[4,3,2-*de*]quinazolines

Richard A. Hollins and Maria T. L. Lima*

Instituto Militar de Engenharia, Praia Vermelha, Rio de Janeiro ZC-82, RJ, Brasil

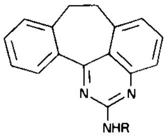
Received February 5, 1979

The synthesis of benzothiopyrano[4,3,2-*de*]quinazolines (**1a-c**) from 1-chloro-4-methylthioxanthone is described.

J. Heterocyclic Chem., **16**, 679 (1979).

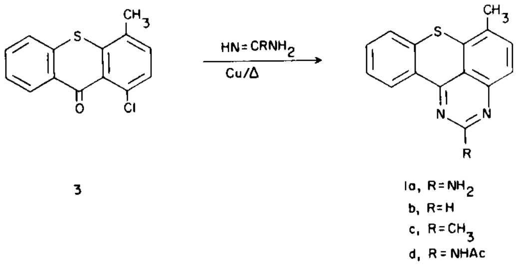
Dusemund has reported (1) the synthesis of benzothiopyrano[4,3,2-*de*]quinazolines (**1**) by the treatment of 1-aminothioxanthones with formamide in acid or with formamidine acetate. He also obtained the 2-phenyl derivative in very low yield (5%), and *via* a much longer route a 2-chloromethyl-6,6-dioxide derivative (1).

We recently reported (2) the synthesis of 7,8-dihydrobenzo[1,2]cyclohepta[3,4,5-*de*]quinazoline derivatives (**2**) *via* a route which we now report as being applicable to the synthesis of derivatives of **1**. Our method, which consists of treating 1-chlorothioxanthones (**3**) with guanidine or amidine derivatives, is simpler and potentially allows the introduction of a great variety of substituents in the 2-position of **1** (Scheme I).



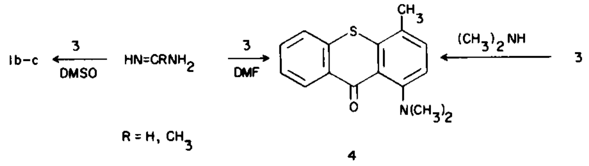
2

Scheme I



While the reaction of **3** with guanidine was readily affected in DMF, all attempts using the amidines in this solvent only led to the isolation of 1-dimethylamino-4-methylthioxanthone (**4**), also prepared by treating **3** with dimethylamine in pyridine (Scheme II). After trying various solvents and reaction conditions, we finally succeeded in obtaining **1b** and **1c** using DMSO.

Scheme 2



Although Dusemund also reported (1) the preparation of the 2-one and 2-thione derivatives of **1**, the spectral properties of **1a** are in accord with the amino-quinazoline structure presented. The acetylation of **1a** to **1d** provided us with a derivative for spectral comparison.

EXPERIMENTAL

The ir spectra were obtained on a Perkin-Elmer model PE 137 spectrophotometer and the mass spectra on a Varian MAT CH-5 mass spectrometer. The pmr spectra were recorded on a Hitachi Perkin-Elmer R-20B nuclear magnetic resonance spectrometer. All melting points are uncorrected.

2-Amino-6-methyl[1]benzothiopyrano[4,3,2-*de*]quinazoline (**1a**).

A mixture of 0.23 g. of **3** (3), 0.17 g. of guanidine nitrate, 59 mg. of copper powder and 0.125 g. of sodium hydroxide in 10 ml. of dimethylformamide was stirred and heated at reflux for 16 hours. After cooling, the reaction mixture was filtered and the filtrate diluted with 100 ml. of water and extracted with ether (2 x 100 ml.). The combined ether extracts were washed with water (4 x 100 ml.), dried over magnesium sulfate and evaporated at reduced pressure. The resulting solid was recrystallized from chloroform giving 113 mg. (46%) of orange crystals, m.p. 266-268°; ir (potassium bromide): 3340 cm^{-1} (NH) and 1650 cm^{-1} (C=N); pmr (acetic acid-d_4): δ 8.45-8.75 (m, 1, ArH), 7.10-7.75 (m, 5, ArH) and 2.25 (s, 3, CH_3); ms: m/e 265 (M^+).

Anal. Calcd. for $C_{15}H_{11}N_3S$: C, 67.90; H, 4.18; N, 15,84. Found: C, 67.71; H, 4.38; N, 15.64.

2-Acetamido-6-methyl[1]benzothiopyrano[4,3,2-*de*]quinazoline (**1d**).

A mixture of 90 mg. of **1a** and 3 ml. of acetic anhydride was stirred for 16 hours then evaporated at reduced pressure. The residue was dissolved in 50 ml. of chloroform and washed with 10 ml. of 10% aqueous sodium bicarbonate then 10 ml. of water. After drying over magnesium sulfate, the solvent was evaporated at reduced pressure. The resulting solid was recrystallized from chloroform giving 47 mg. (43%) of orange crystals, m.p. 210-214°; ir (potassium bromide): 3220 cm^{-1} (NH) and 1670 cm^{-1} (C=O); pmr (deuteriochloroform): δ 8.50-8.73 (m, 1, ArH), 8.15 (bs, 1, NH), 7.12-7.60 (m, 5, ArH), 2.65 (s, 3, CH_3) and 2.30 (s, 3, CH_3).

Anal. Calcd. for $C_{17}H_{13}N_3OS$: C, 66.43; H, 4.26; N, 13.67. Found: C, 66.63; H, 4.40; N, 13.47.

6-Methyl[1]benzothiopyrano[4,3,2-*de*]quinazoline (**1b**).

A mixture of 0.56 g. of **3** (3), 2 g. of formamidine acetate (4), 0.61 g. of sodium hydroxide and 60 mg. of copper powder in 50 ml. of dimethylsulfoxide was stirred and heated at reflux for 16 hours. The mixture was diluted with 100 ml. of water and extracted with chloroform (2 x 50 ml.). The combined chloroform extracts were washed with water (8 x 50 ml.), dried over magnesium sulfate and evaporated at reduced pressure. The residue was chromatographed (thick layer) over silica gel with chloroform-carbon tetrachloride (3:1) giving 99 mg. (17%) of a yellow solid, m.p. 158-161° (lit. (1) 164°); pmr (deuteriochloroform): δ 9.00 (s, 1, ArH), 8.70-8.90 (m, 1, ArH), 7.18-7.60 (m, 5, ArH) and 2.30 (s, 3, CH_3).

Anal. Calcd. for $C_{15}H_{10}N_2S$: C, 71.97; H, 4.03; N, 11.19. Found: C, 71.97; H, 4.03; N, 11.01.

2,6-Dimethyl[1]benzothiopyrano[4,3,2-*de*]quinazoline (**1c**).

A mixture of 0.52 g. of **3** (3), 2.0 g. of acetamidine acetate (4), 0.6 g. of sodium hydroxide and 60 mg. of copper powder in 50 ml. of dimethylsulfoxide was stirred and heated at reflux for 16 hours. The mixture was diluted with 100 ml. of water and extracted with chloroform (2 x 50 ml.). The combined extracts were washed with water (8 x 50 ml.), dried over magnesium sulfate and evaporated at reduced pressure. The resulting solid was chromatographed over silica gel with chloroform-carbon tetrachloride (4:1) giving 70 mg. (13%) of yellow crystals, m.p. 182-184°; pmr (deuteriochloroform): δ 8.75-8.95 (m, 1, ArH), 7.25-8.50 (m, 5, ArH), 2.80 (s, 3, CH_3) and 2.30 (s, 3, CH_3).

Anal. Calcd. for $C_{16}H_{12}N_2S$: C, 72.70; H, 4.58; N, 10.60. Found: C, 72.57; H, 4.63; N, 10.45.

1-Dimethylamino-4-methylthioxanthone (**4**).

A mixture of 0.42 g. of **3** (3), 0.186 g. of dimethylamine hydrochloride and 0.17 g. of sodium hydroxide in 10 ml. of pyridine was stirred and heated at reflux for 20 hours. The solvent was evaporated at reduced pressure and the residue dissolved in 50 ml. of chloroform, washed with water (2 x 50 ml.) and dried over magnesium sulfate. After evaporation of solvent the resulting solid was chromatographed (thick layer) over silica gel with chloroform giving 88 mg. (21%) of orange crystals, m.p. 88-92°; ir (potassium bromide): 1660 cm^{-1} (C=O); pmr (deuteriochloroform): δ 8.20-8.45 (m, 1, ArH), 6.72-7.55 (m, 5, ArH), 2.90 (s, 6, NCH_3) and 2.38 (s, 3, CH_3).

Anal. Calcd. for $C_{16}H_{15}NOS$: C, 71.34; H, 5.61; N, 5.20. Found: C, 71.51; H, 5.76; N, 5.12.

Acknowledgment.

We thank the Secretary of Planning (FINEP) and the National Council of Scientific and Technological development (CNPq) for their support of this work.

REFERENCES AND NOTES

(1) F. Eiden and J. Dusemund, *Arch. Pharm.*, **307**, 701 (1974).

(2) R. A. Hollins and P. R. C. Martins, *J. Heterocyclic Chem.*, **16**, 681 (1979).

(3) T. M. Sharp, *J. Chem. Soc.*, 2961 (1951).

(4) E. C. Taylor and W. A. Erhart, *J. Am. Chem. Soc.*, **82**, 3138 (1960).