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Syntheses of Angular Condensed Ring Systems Combining a Benzodiazepinic, or Benzothiazepinic, and a Coumarinic Moiety

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Summary. The title compounds were prepared via intermediates resulting from reactions of 3-formyl-4-hydroxycoumarin (**1**) with *o*-phenylenediamine, *o*-aminophenol, and *o*-aminothiophenol, respectively. Intramolecular ring closures were effected between the free hydroxy and amino or thiol groups.

Keywords. 3-Formyl-4-hydroxycoumarin; 8*H*-[1]-Benzopyrano[3,4-b]-1,5-benzodiazepin-8-one; 8*H*-[1]-Benzopyrano[3,4-b]-1,5-benzothiazepin-8-one.

Synthese von kondensierten Heterocyclen, die ein Benzodiazepin oder Benzothiazepin angular mit dem Coumarinsystem verknüpfen

Zusammenfassung. Die Titelsubstanzen werden über Zwischenverbindungen erhalten, die aus der Reaktion von 3-Formyl-4-hydroxycoumarin (**1**) mit *o*-Phenylendiamin, *o*-Aminophenol und *o*-Aminothiophenol enstehen. Der Ringschluß erfolgt über die freie Hydroxylgruppe und der Amino- bzw. Thiolgruppe.

Introduction

Hitherto described syntheses of benzodiazepines and benzothiazepines were based on reactions of *o*-substituted aniline derivatives with chalkones [1, 2], ethyl acetoacetate [3], various mono [4] and 1,3-diketones [5], malonic acid [6], derivatives of *o*-chlorobenzaldehyde [7], and thiophene carboxylic acid [8].

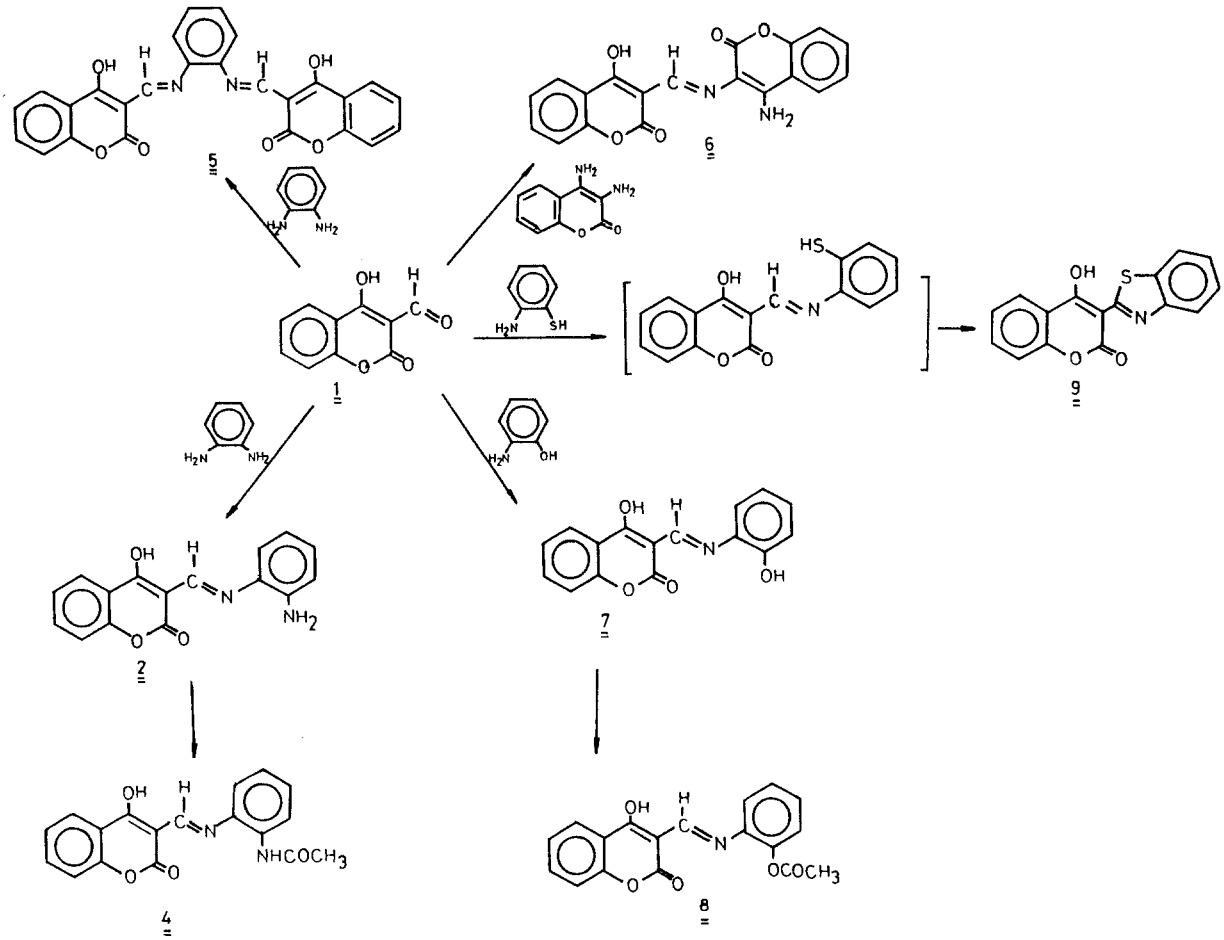
We now report syntheses of the title compounds recently carried out in our laboratory, which proceded along the pathways delineated in Schemes 1 and 2. The final products contained one benzopyrano moiety originating from the starting compound, 3-formyl-4-hydroxycoumarin (**1**), and one benzodiazepine or benzothiazepine moiety resulting from intramolecular cyclization of intermediately formed compounds.

Our motive in undertaking this work was the hope that molecular entities including two moieties which, as separate molecules, exhibit different biological activities might, in combination, show modified activities and even additional ones not shown by either part alone. Thus, several 1,5-benzodiazepines act fungicidally [9], and similar heterocyclic systems with an additional ring are well-known neuro-

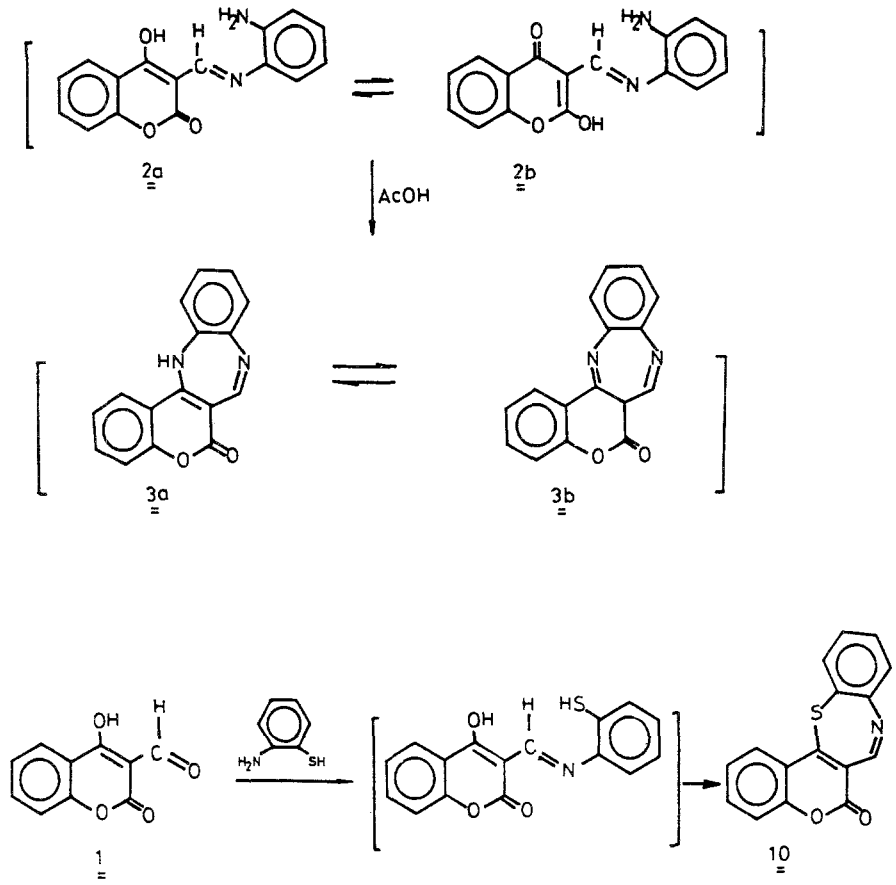
and psychotropic agents [10]. Coumarin derivatives, on the other hand, act in several ways [11]. If the title compounds would show just enhanced benzodiazepine activities, or possibly have the latters unwanted side effects weakened, they may become commercially valuable pharmaceutical agents in view of the still increasing demand for mood improving drugs, especially tranquilizers derived from seven-membered heterocycles.

Results and Discussion

Condensation of **1** with *o*-phenylene diamine in absolute ethanol gave 2-(benzopyrano-3-formimino)aniline, **2a**. When glacial acetic acid was used as reaction medium, the type of product depended on the molar ratio of reactants and reaction time. Equimolarity of the former, together with a longer exposure to heat, led beyond the mere forming of **2**: the still free amino and hydroxy groups of this compound underwent intramolecular ring closure which gave 8*H*-[1]-benzopyrano[3,4-b]-1,5-benzodiazepin-8-one (**3b**); the same product was obtained when polyphosphoric acid was used instead of glacial acetic acid. [However, when *o*-phenylene diamine and **1** were reacted in the molar ratio 2:1, and for only one-



Scheme 1



Scheme 2

third the time specified for the reaction of equimolar amounts, the doubly substituted 1,2-bis(4′-hydroxycoumarin-3′-formimino)-2-acetylaminobenzene (**5**) was formed; however, a better yield for **5** resulted from reacting equimolar amounts of **1** and **2**.]

Since the ir spectrum of the product obtained by prolonged treatment of equimolar **1** with *o*-phenylenediamine in either glacial acetic or polyphosphoric acids lacked an NH band, we were tempted to conclude, at first, that **2** might have undergone ring closure in its keto form **2b**. But nmr data suggested an existence of the cyclization product in two tautomeric forms, **3a** and **3b**, thus **2** could have reacted both in its keto and enol forms.

Compound **1** was also successfully condensed with *o*-aminophenol, to give 1-(4′-hydroxycoumarin-3-forminino)-2-phenol (**7**), and with 3,4-diaminocoumarin to give 3-(4′-hydroxycoumarin-3′-formimino)-4-aminocoumarin (**6**). But an attempt at effecting an internal cyclization of **7** into 8*H*-[1]-benzopyrano[3,4-b]-1,5-benzoxazepin-8-one could not be confirmed, as this compound could not be isolated and characterized although nmr data suggested its presence in the reaction mixture. Likewise, the ring closure in **7** failed to occur in acetic acid anhydride. This attempt merely achieved acetylation to 1-(4′-hydroxycoumarin-3′-formimino)-2-acetoxybenzene (**8**). In a former report [12] we have described a pathway leading to

benzodiazepines, i.e. intramolecular cyclization of products obtained by condensing **1** with amino acids.

Compound **1**, furthermore, reacted readily with *o*-aminothiophenol. But even under mild conditions the primary product underwent intramolecular ring closure to 2-(4′-hydroxycoumarin-3′-yl)-benzothiazole (**9**). A detailed description of the procedure is omitted in the present paper as compound **9** was previously prepared in our laboratory and was reported in a former article [13].

However, we now describe a procedure in which a ring closure to 8*H*-[1]-benzopyrano[3,4-b]-1,5-benzothiazepin-8-one [10] was achieved.

Experimental Part

All m.p.'s (Kofler stage, centrigrade scale) are uncorrected. Band positions on ir spectra (Perkin-Elmer M-377 infrared spectrophotometer, KBr pellets) are reported in cm^{-1}. Proton shifts for ^1H-nmr spectra (Perkin-Elmer R 12 A 60 MHz nmr spectrometer, solvent DMSO-d_6) are stated in ppm. Elemental analysis data relate to percentage composition.

2-(4′-Hydroxycoumarin-3′-formimino)-1-aminobenzene (**2**)

A absolute-ethanolic solution obtained by first dissolving 1 g (5.25 mmol) of 3-formyl-4-hydroxy-coumarin (**1**) and thereafter an equimolar amount (0.56 g) of *o*-phenylenediamine in 100 ml of solvent was refluxed for 1 h. Intensely yellow crystals started separating at once, and finally 1.40 g of the crystalline mass (86%) could be collected. Recrystallization from *Et*OH gave pure **2**: yellow needles, m.p. 220–2°; ir: 3 340–3 400 (OH, NH), 3 060 (CH), 2 810 (CH arom.), 1 715 (CO), 1 605 (C=C arom.); nmr: 8.70 (s, CH), 8.10–6.80 (m, 8 H arom., NH_2). Anal. calcd. for $C_{16}H_{12}N_2O_3$: C 68.57, H 4.32, N 9.99; found: C 68.48, H 4.31, N 9.73.

8 H-[1]-Benzopyrano[3,4-b]-1,5-benzodiazepin-8-one (**3**)

(a) Compd. **2** (0.5 g, 1.78 mmol) was refluxed with 50 ml of glacial acetic acid for 2 h. Recrystallization of the crude product from glacial acetic acid yielded 0.38 g (81%) of pure **3**, m.p. 317–20°; ir: 3 040, 2 910 (CH), 2 850 (CH, arom.), 1 700 (CO), 1 605 (C=C, arom.); ^1H-nmr: 8.67 (s, CH), 8.05–6.90 (m, 8 H arom., NH). Anal. calcd. for $C_{16}H_{10}N_2O_2$: C 73.28, H 3.84, N 10.68; found: C 72.67, H 3.93, N 10.24.

(b) The same amount of **2** was stirred with 20 ml of polyphosphoric acid at 150 °C for 5 h. During treatment the initially light yellow solution darkened considerably. The hot reaction mixture was poured into ice-water whereupon yellow crystals separated (yield 0.29 g, 88%). Recrystallization from glacial acetic acid gave pure **3**, m.p. 318–20°.

(c) Compd. **1** (0.5 g, 2.63 mmol) was dissolved in hot glacial acetic acid (30 ml) and an equimolar amount (0.28 g) of *o*-phenylene diamine was dissolved in the solution of **1**. The mixture was refluxed for 3 h. On cooling 0.41 g (88%) of yellow crystals of **3**, m.p. 317–20° could be collected.

2-(4′-Hydroxycoumarin-3′-formimino)-1-acetylaminobenzene (**4**)

Compd. **2** (0.5 g, 1.78 mmol) was dissolved in 30 ml of acetic anhydride and the solution refluxed for 3 h. After pouring onto ice the obtained crystals (0.36 g, 63%) were recrystalized from ethanol. Pure **4** (m.p. 235–6°) was obtained; ir: 3 400 (NH), 3 050 (CH_3), 2 910 (CH, arom.), 1 730, 1 700 (CO), 1 610 (C=C, arom.); nmr: 9.00 (s, NH), 8.10–7.15 (m, 8 H arom., CH). Anal. calcd. for $C_{18}H_{14}N_2O_4$: C 67.06, H 4.38, N 8.72, found: C, 66.78, H 4.09, N 8.97.

1,2-Bis(4'-hydroxycoumarin-3'-formimino)benzene (**5**)

Compd. **2** (0.5 g, 1.78 mmol) was dissolved in 12.0 ml of glacial acetic acid and an equimolar amount of **1** (0.34 g) was added to the stirred refluxing solution. Yellow crystals separate gradually. After 1 h refluxing, 0.62 g (77%) of crude product was collected. Recrystallization from glacial acetic acid gave pure **6**, m.p. 313–14°; ir: 3 040 (CH), 2 920 (CH, arom.), 1 710 (CO), 1 608 (C=C, arom.); mol. wt. by mass spectrometry (JEOL mass spectrometer): 452 (M^+). Anal. calcd. for $C_{26}H_{16}N_2O_6$: C 69.03, H 3.56, N 6.19; found: C 69.30, H 3.66, N 6.73.

1-(4'-Hydroxycoumarin-3'-forminino)-2-phenol (**7**)

Compd. **1** (1 g, 5.26 mmol) was dissolved in 40 ml of boiling glacial acetic acid and an equimolar amount of 2-aminophenol (0.57 g) was added in a single portion with stirring. Separation of yellow crystals started at once and seemed completed with 2 h of refluxing. Yield 1.20 g (81%). Recrystallization from acetic acid gave pure **7**, m.p. 282–5°; ir: 3 280–3 020 (CH, OH), 2 900 (CH, arom.), 1 705 (CO), 1 620 (C=C, arom.); nmr: 9.02 (s, OH), 8.78 (s, CH); 8.10–6.80 (m, 8 H, arom.): m.wt. by m.s.: 281 (M^+). Anal. calcd. for $C_{16}H_{11}NO_4$: C 68.33, H 3.94, N 4.98, found. C 67.91, H 3.92, N 4.64.

1-(4'-Hydroxycoumarin-3'-formimino)-2-acetoxybenzene (**8**)

Compd. **7** (0.5 g, 1.78 mmol) was dissolved in 30 ml of acetic acid anhydride and the solution refluxed for 3 h. On cooling, yellow crystals separated (yield: 0.47 g, 82%). Boiling with 30 ml of ethanol left a residue of **8**, m.p. 199–200°; ir: 3 030 (CH_3), 2 915 (CH, Arom.), 1 760, 1 723 (CO), 1 625 (C=C, arom.); nmr: 8.86 (s, CH), 8.05–7.10 (m, 8 H, arom.), 2.40 (t, CH_3). Anal. calcd. for $C_{18}H_{13}NO_5$: C 66.86, H 4.05, N 4.34; found. C 66.52, H 4.09, N 4.20.

2-(4'-Hydroxycoumarin-3'-yl)-1,3-benzothiazole (**9**)

Compd. **1** (1 g, 5.36 mmol) was dissolved in boiling ethanol and an equimolar amount of 2-aminothiophenol (0.66 g) was added in a single portion. The mixture was kept refluxing for 2 h, during which a small amount of needle-like crystals separated. Filtration of the hot mixture left 0.39 g of yellow needles, m.p. 279–282, later identified as **9** [13] (yield, 25%). After reducing the volume of the filtrate to ⅔ of the initial one (reduced pressure) and cooling, a crop of light yellow crystals separated. Recrystallization from ethanol gave 0.54 g (37%) of pure **10**, m.p. 199–203°; ir: 3 020 (CH), 2 880 (CH, arom.), 1 660 (CO), 1 605 (C=C, arom.); nmr: 7.85 (s, CH), 7.78–6.70 (m, 8 H, arom.). Anal. calcd. for $C_{16}H_9NO_3S$: C 68.79, H 3.24, N 5.03; found: C 68.51, H 3.53, N 4.59.

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