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Received July 11, 1979

†Dedicated to the memory of Professor Alfio Martani

Some thiadiazasteroid analogues have been synthesized by the reaction of 3-hydroxymethylenebenzo[*h*]thiochroman-4-one with hydrazine and substituted hydrazines, semicarbazide and thiosemicarbazide. Pmr data supporting the structural assignments have been discussed.

J. Heterocyclic Chem., 17, 121 (1980).

In continuation of our studies on the chemistry of sulfur and/or nitrogen heterocyclic compounds (3-5) and because of the potential biological importance of heterocyclic steroids, the synthesis of a series of polyaza- (6) and thiadiazasteroid analogues (7) of Equilenin was reported.

Although the literature on the synthesis of heterocyclic steroids is extensive (8), it reveals only a few reports about the synthesis of thiadiazasteroid analogues (9). Therefore, it was considered of interest to extend our investigations in this field. In the present work the synthesis of some new pyrazolo- and pyrazolino-derivatives of naphtho[*b*]thiopyran was achieved in good yields, starting from the readily available 3-hydroxymethylenebenzo[*h*]thiochroman-4-one **1** (7).

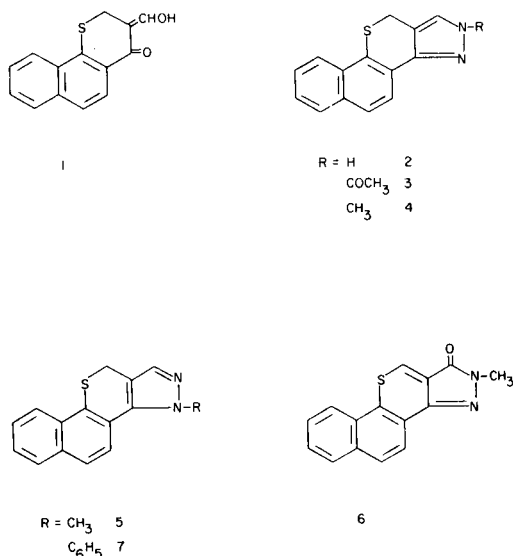
The reaction of **1** with hydrazine hydrate afforded 2,11-dihydronaphtho[2',1':5,6]thiopyrano[4,3-*c*]pyrazole **2** (10) whose pmr spectrum (pyridine-*d*₅) exhibited the pyrazole C₁ proton as a triplet-like signal at δ 7.58, split by the allylic C₁₁ methylene. Acetylation of **2** with acetic anhydride in the presence of sodium acetate gave only the

N₂-acetyl derivative **3**. The structure of this compound was substantiated by the following observations. In the pmr spectrum the pyrazole proton appeared as a well resolved triplet ($J = 1.1$ Hz) which was shifted downfield for about 0.6 ppm as compared to the parent molecule. Moreover, the chemical shift of the C₄ proton remained practically unchanged.

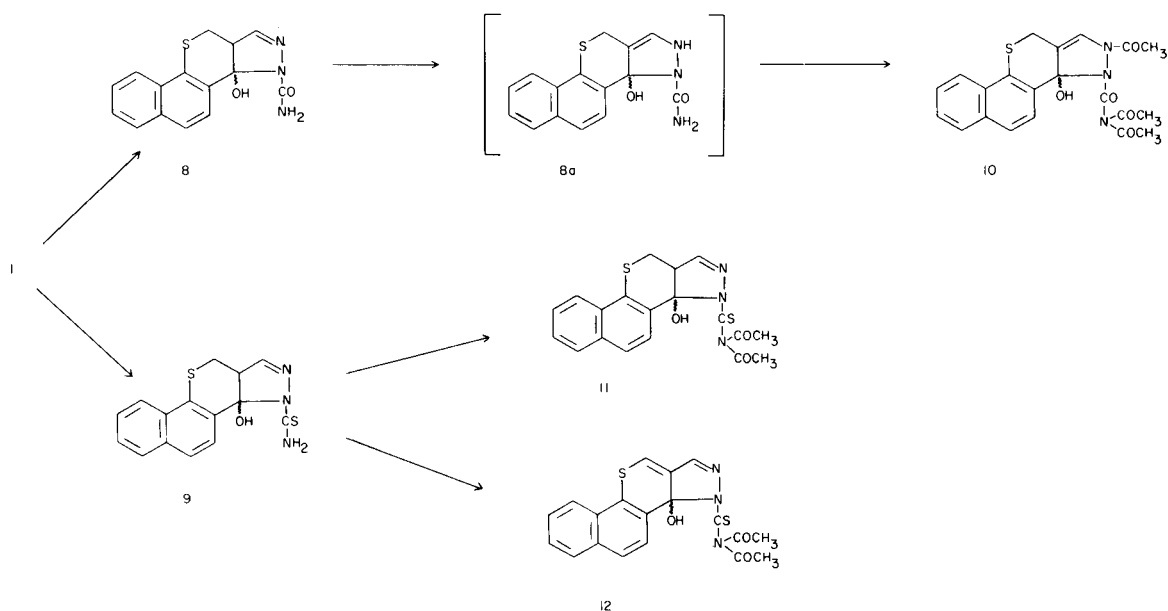
By reaction of **1** with methylhydrazine in methanol at room temperature, a mixture of the isomeric *N*-methylpyrazole derivatives **4** and **5** was obtained. As shown by the pmr spectrum, the major component of the mixture appeared to be compound **4**, which resulted from the attack of the most nucleophilic alkyl nitrogen at the potential aldehyde group of **1**. In accordance, the yields of compounds **4** and **5** were 84% and 16% respectively. The isolation of **4** was achieved by crystallization, while the isomer **5** was separated by chromatography on silica gel, although not in a pure state. Moreover, the chromatography gave a small amount of a new crystalline compound, m.p. 263°.

The structures of **4** and **5** were supported by their analytical and spectral data. Both isomers showed the parent ion peak at *m/e* 252. In the pmr spectrum of **4** the signal of the *N*-methyl group was observed at δ 3.79 and the pyrazole proton at δ 7.00, while the same signals in **5** appeared at δ 4.10 and 7.34 respectively (11). For the former compound such chemical shift values in deuteriochloroform and the difference between them ($\Delta\delta = 3.21$) are characteristic for the assigned structure **4** (12). In the case of the latter isomer the above method for structural assignment is inapplicable, owing to the anomalous δ -value of the *N*-methyl singlet, which was shifted to a lower field by the deshielding effect of the aromatic moiety. This effect is always present in angular compounds when the *N*-methyl group is situated on the same side of an electron withdrawing ring and can "see" it (4,13). Therefore, as also suggested by Elguero, *et al.* (14), the cited method of Albright and Goldman (12) for assigning structures to isomeric *N*-methylpyrazoles is not of general applicability. However, the structure of **5** was confirmed by the lower value of the pyrazole proton signal (δ 7.34)

Scheme 1



Scheme 2



and by the higher value of the C₄ proton (δ 7.67) with respect to the values found for the isomer 4 (δ 7.00 and δ 8.03 respectively). In addition the coupling of the pyrazole proton with the methylene group ($J = 0.8$ Hz) in compound 4 clearly confirmed the correctness of the assigned structures.

The above mentioned product m.p. 263°, isolated from the last fractions of the chromatography of the mixture of 4 and 5, could be formulated as 2-methylnaphtho[2',1':5,6]thiopyran[4,3-*c*]pyrazol-1(2*H*)one 6 on the basis of its analytical and spectral data. The elemental analysis and the parent ion peak (m/e 266) indicated molecular formula C₁₅H₁₀N₂OS. In the ir spectrum no band corresponding to an NH or to an OH group was observed, whereas a strong and broad absorption appeared at about 1665 cm⁻¹, attributed to the presence of both C=N and tertiary amide groups. Further support to structure 6 was provided by the pmr spectrum (DMSO-d₆) which did not show a signal for the S-CH₂ group, whereas a sharp singlet at δ 8.60 was observed, assignable to the vinylic proton at C₁₁, the downfield value being due to the deshielding effect by the "peri" carbonyl group. The same spectrum also showed a singlet at δ 4.12 for the *N*-methyl group and two doublets (AB system) at δ 8.34 and 7.88 for the C₄ and C₅ protons respectively. The remaining four aromatic protons appeared as multiplets between δ 7.55 and 8.15, the most downfield multiplet being due to the C₉ proton as it is deshielded by the sulfur atom of the thiopyran ring.

Attempted synthesis of 6 from 3-cyano-4*H*-benzo[*h*]thiochromen-4-one (7) *via* hydrolysis to the corresponding

ketoacid and subsequent action of methylhydrazine was unsuccessful. Under a variety of conditions we were unable to effect the hydrolysis of the above unsaturated cyanoketone. The formation of 6 might reasonably arise by oxidation of 4 in the course of the chromatography. In fact, when a sample of pure 4 was chromatographed on silica gel with benzene as eluent, a spot corresponding to compound 6 also could be detected on tlc of the last fractions (15).

Treatment of 1 with phenylhydrazine in boiling ethanol led to the phenylpyrazole 7 as the sole product in excellent yield. The structure of 7 was confirmed by its pmr spectrum which showed the phenyl group as a singlet at δ 7.37 (16). Moreover, the proton at C₄ was found at δ 6.96 by the shielding effect due to the ring current of the phenyl group at position-3.

Finally, the reaction of 1 with semicarbazide and thiosemicarbazide yielded, in agreement with our preceding findings (4,6,17), the pyrazoline derivatives 8 and 9, respectively. The structures of these compounds were readily demonstrated by the close similarities of their spectral properties (mainly pmr and nmr experiments) with those of similar derivatives prepared from other α -hydroxymethyleneketones. Acetylation of 8 either with acetic anhydride in pyridine or with boiling acetic anhydride afforded the triacetyl derivative 10 while compound 9 under the same conditions gave different results. In fact in the former case the unstable diacetyl derivative 11 was obtained whereas in the latter case only product 12 resulted (Scheme 2). Structural assignments for com-

pounds **10-12** were based on their spectroscopic and analytical data. The formation of triacetate **10** should reasonably proceed through the intermediate **8a**, arising from **8** by a 1,3-prototropic shift. Evidently, this did not occur in the case of compound **9**; in fact the pmr spectrum

of **11** clearly showed the sequence $\text{-N=CH-}\overset{\text{I}}{\text{C}}\text{-CH}_2\text{-S-}$ confirmed by double resonance experiments. Moreover, diacetate **11** proved to be rather unstable, giving rise to a mixture of decomposition products, among which that one resulting from its dehydration, as shown by the pmr spectra of aged samples. Concerning structure **12**, proof that dehydrogenation occurred at C_{11} and C_{11a} positions was evidenced by the pmr spectrum which lacked the absorption of the $\text{S-CH}_2\text{-}$ group and showed instead signals for eight protons in the aromatic zone, two of these being due to those at positions C_1 and C_{11} . In any event, the formation of **12** was not unexpected since a similar oxidation of analogous structures has been previously reported (1,7).

EXPERIMENTAL

Melting points were measured with a Kofler hot-stage apparatus and are uncorrected. The ir spectra were obtained on a Perkin-Elmer 457 grating spectrophotometer. The uv spectra were recorded in 95% ethanol with a Hilger & Watts Ultrascan H999 instrument. The pmr spectra were determined in the indicated solvents on a Varian HA-100 spectrometer with tetramethylsilane as an internal standard; the chemical shifts are given in " δ " units (ppm), coupling constants in Hz. Mass spectra were run on a Varian MAT 311A spectrometer at 70 eV, by direct insertion into the ion source. The chromatographic separations have been carried out on silica gel Merck (Kieselgel 60, 70-230 mesh) columns. Thin-layer chromatography was performed on precoated silica gel plates F₂₅₄ Merck.

2,11-Dihydronaphtho[2',1':5,6]thiopyrano[4,3-c]pyrazole (2).

A solution of α -hydroxymethyleneketone (**1**) (2 g.) in methanol (20 ml.) was treated with hydrazine hydrate (98%, 2 ml.) and the mixture was refluxed for 6 hours. The product which precipitated on cooling was recrystallized from ethanol, white prisms, m.p. 280-282° (85% yield); ir (chloroform): ν 3450 (free NH) and \sim 3170 cm^{-1} (H bonded NH); uv λ max nm (log ϵ): 211 (4.44), 234 (4.42), 255 (4.43), 278 (4.57) and 326 (3.89); pmr (pyridine- d_5): δ 4.13 (2H, d, J = 0.6, S-CH₂), 7.30-7.85 (4H, complex m, aromatic protons), 7.58 (1H, t-like, pyrazole proton), 8.40 (2H, m, two overlapped aromatic protons: C₄-H and C₉-H) and \sim 14.2 (1H, very broad s, NH exchangeable with deuterium oxide).

Anal. Calcd. for C₁₄H₁₀N₂S: C, 70.58; H, 4.23; N, 11.76; S, 13.44. Found: C, 70.20; H, 4.48; N, 11.97; S, 13.05.

2-Acetyl-2,11-dihydronaphtho[2',1':5,6]thiopyrano[4,3-c]pyrazole (3).

A solution of **2** (1 g.) in acetic anhydride (15 ml.) was refluxed for 30 minutes, then cooled and poured on ice. The precipitate was collected and recrystallized from ethanol, white prisms, m.p. 171-172°; uv λ max nm (log ϵ): 210 (4.19), 235 (4.22), 255 (4.28), 278 (4.36), 326 (3.86); pmr (pyridine- d_5): δ 2.70 (3H, s, COCH₃), 4.04 (2H, d, J = 1.1, S-CH₂), 8.12 (1H, t, J = 1.1, pyrazole proton), 8.22 (1H, d, J = 8.5, A part of an AB system, C₄-H), 8.37 (1H, m, C₉-H).

Anal. Calcd. for C₁₆H₁₂N₂OS: C, 68.56; H, 4.32; N, 10.00; S, 11.43. Found: C, 68.60; H, 4.35; N, 10.04; S, 11.39.

2-Methyl-2,11-dihydronaphtho[2',1':5,6]thiopyrano[4,3-c]pyrazole (4) and 3-Methyl-3,11-dihydronaphtho[2',1':5,6]thiopyrano[4,3-c]pyrazole (5).

To a cold solution of **1** (1.21 g., 0.005 mole) in methanol (40 ml.) was

added, with stirring, a solution of methylhydrazine (0.23 g., 0.005 mole) in methanol (5 ml.). After stirring at room temperature for 4 hours (the reaction was monitored by tlc), the solvent was removed *in vacuo* to give 1.36 g. of a pale yellow solid containing (pmr spectrum) the two isomers **4** and **5** (84% and 16%, respectively). This mixture was crystallized from ethyl acetate to give the isomer **4** which, after two further recrystallizations, afforded a pure sample as yellow prisms (0.4 g.), m.p. 135°. The product browned on standing; uv λ max nm (log ϵ): 213 (4.42), 236 (4.33), 256 (4.34), 273 (4.47), 282 (4.52), 327 (3.86); pmr (deuteriochloroform): δ 3.79 (3H, s, N-CH₃), 3.93 (2H, d, J = 0.8, S-CH₂), 7.00 (1H, t-like, pyrazole proton), 8.03 (1H, d, J = 8.5, A part of an AB system, C₄-H), 8.24 (1H, m, C₉-H); ms: m/e 252 (M⁺).

Anal. Calcd. for C₁₅H₁₂N₂S: C, 71.42; H, 4.76; N, 11.11; S, 12.70. Found: C, 71.44; H, 4.88; N, 11.23; S, 12.76.

The combined mother liquors of the first crystallizations of **4** were evaporated *in vacuo* and the residue was chromatographed on silica gel with benzene as the eluent. The first fractions gave an additional crop of **4** (90 mg.). The center fractions were combined to give the isomer **5** (95 mg. ca.) which seemed to be rather pure by pmr analysis, but could not be crystallized because of its instability. Therefore, the following spectral data were recorded without further purification; uv λ max nm (log ϵ): 213 (4.40), 234 (4.41), 275 (4.31); pmr (deuteriochloroform): δ 4.10 (3H, s, N-CH₃), 3.87 (2H, s, S-CH₂), 7.34 (1H, s, pyrazole proton), 7.67 (1H, d, J = 8.5, A part of an AB system, C₄-H), 8.30 (1H, m, C₉-H); ms: m/e 252 (M⁺).

Finally, from the last fractions of the chromatography the unexpected compound described below was obtained.

2-Methylnaphtho[2',1':5,6]thiopyrano[4,3-c]pyrazol-1(2H)one (6).

This compound, obtained from the above chromatography, was crystallized twice from benzene-methanol (4:1) to give clusters of long, colorless needles (46 mg.), m.p. 263°; ir (nujol): ν \sim 1665 cm^{-1} (broad, =N-C=O and C=N); uv λ max nm (log ϵ): 240 (4.53), 261 (4.48), 305 (3.88); pmr (DMSO- d_6): δ 4.12 (3H, s, N-CH₃), 8.34 and 7.88 (2H, q, AB system, J = 9, C₄-H and C₅-H), 7.55-8.15 (4H, two m, aromatic protons) and 8.60 (1H, s, C₁₁-H); ms: m/e 266 (M⁺).

Anal. Calcd. for C₁₅H₁₀N₂OS: C, 67.67; H, 3.77; N, 10.51; S, 12.03. Found: C, 67.37; H, 3.84; N, 10.26; S, 12.30.

3-Phenyl-3,11-dihydronaphtho[2',1':5,6]thiopyrano[4,3-c]pyrazole (7).

To a solution of **1** (0.24 g., 0.001 mole) in ethanol (10 ml.) phenylhydrazine hydrochloride (0.15 g., 0.001 mole) was added and the mixture was then refluxed for about 2 hours. Concentration to one third of the original volume and addition of water (10 ml.) gave a pale yellow precipitate which was worked up with chloroform. The combined chloroform extracts were washed twice with 10% sodium carbonate and then with water. The extract was dried over anhydrous magnesium sulfate and evaporated *in vacuo* leaving **7** which was recrystallized from ethyl acetate to yield pale yellow prisms (232 mg.), m.p. 169°; uv λ max nm (log ϵ): 216 (4.51), 277 (4.32); pmr (deuteriochloroform): δ 3.92 (2H, s, S-CH₂), 6.96 (1H, d, J = 8.5, A part of an AB system, C₄-H), 7.37 (5H, s, N-C₆H₅), 7.56 (1H, s, pyrazole proton), 8.31 (1H, m, C₉-H).

Anal. Calcd. for C₂₀H₁₄N₂S: C, 76.43; H, 4.46; N, 8.91; S, 10.19. Found: C, 76.55; H, 4.51; N, 8.79; S, 10.23.

3-Carbamoyl-3a-hydroxy-11H-naphtho[2',1':5,6]thiopyrano[4,3-c]- Δ^1 -pyrazoline (8).

To a solution of **1** (2.42 g., 0.01 mole) in methanol (70 ml.) was added a solution of semicarbazide hydrochloride (1.2 g., 0.011 mole) and sodium acetate (1.5 g.) in water (5 ml.). A yellow-orange solid precipitated immediately. The mixture was allowed to stand overnight at room temperature. The precipitate was collected and recrystallized from acetic acid to afford yellow prisms of **8** (1.8 g.), m.p. 236° dec.; uv λ max nm (log ϵ): 225 (4.42), 273 (4.26); pmr (DMSO- d_6): δ 3.50-4.00 (3H, complex m, S-CH₂-CH), 6.15 (2H, broad s, CONH₂), 7.4-8.3 (7H, m, 6 aromatic protons and 1 pyrazole proton), 10.20 (1H, broad s, OH).

Anal. Calcd. for $C_{15}H_{13}N_3O_2S$: C, 60.19; H, 4.38; N, 14.04; S, 10.62. Found: C, 60.37; H, 4.30; N, 14.12; S, 10.51.

2-Acetyl-3-(carbamoyl-*N*-diacetyl)-3a-hydroxy-11*H*-naphtho[2',1':5,6]thiopyrano[4,3-*c*]- Δ^{11a} -pyrazoline (**10**).

Compound **8** (0.5 g.) in acetic anhydride (15 ml.) was refluxed for 30 minutes. After cooling the reaction mixture was poured into ice-water. The resulting precipitate was collected, washed with 5% sodium carbonate and then with water. Crystallization from ethanol gave **10** as canary yellow prisms, m.p. 148°; uv λ max nm (log ϵ): 227 (4.46), 264 (4.29), 294 (4.31); pmr (deuteriochloroform): δ 2.40 (9H, s, 3 COCH₃), 3.90 (2H, d, J \cong 0.8, S-CH₂), 7.67 (1H, t-like, CH=N); ms: m/e 382 (M-COCH₃).

Anal. Calcd. for $C_{21}H_{19}N_3O_5S$: C, 59.29; H, 4.47; N, 9.88; S, 7.53. Found: C, 59.42; H, 4.33; N, 10.12; S, 7.63.

When the acetylation was carried out at room temperature in pyridine solution the same compound **10** was obtained (pmr and mixed melting point).

3-(Thiocarbamoyl-3a-hydroxy-11*H*-naphtho[2',1':5,6]thiopyrano[4,3-*c*]- Δ^1 -pyrazoline (**9**).

To a solution of **1** (1.21 g., 0.005 mole) in methanol (60 ml.) was added a solution of thiosemicarbazide (0.46 g., 0.005 mole) in methanol (40 ml.) and the mixture was warmed on steam bath for 30 minutes. After a few minutes compound **9** started to precipitate. Crystallization from dioxane gave yellow prisms (0.85 g.), m.p. 250° dec.; uv λ max nm (log ϵ): 220 (4.44), 274 (4.46); pmr (pyridine-*d*₅): δ 3.50 (1H, m, C_{11a}-H), 3.98 (2H, broad s, S-CH₂), 7.4-8.4 (7H, m, 6 aromatic protons and 1 pyrazole proton), \cong 9.4 (2H, very broad signal, CSNH₂).

Anal. Calcd. for $C_{15}H_{13}N_3OS_2$: C, 57.14; H, 4.16; N, 13.33; S, 20.36. Found: C, 57.22; H, 4.08; N, 13.50; S, 20.54.

3-(Thiocarbamoyl-*N*-diacetyl)-3a-hydroxy-11*H*-naphtho[2',1':5,6]thiopyrano[4,3-*c*]- Δ^1 -pyrazoline (**11**).

To compound **9** (0.5 g.) in pyridine (20 ml.) was added acetic anhydride (15 ml.) and the mixture was allowed to stand at room temperature for a week. The diacetate **11** was crystallized from ethanol to give yellow prisms, m.p. 273°; pmr (pyridine-*d*₅): δ 2.20 and 2.25 (6H, 2s, 2COCH₃), 4.30 (1H, dt, C_{11a}-H), 3.55 (2H, o, S-CH₂), 6.96 (1H, d, J = 4, pyrazole proton); irradiation at 4.30 ppm caused the doublet at 6.96 ppm to collapse and, simultaneously, the octet pattern centered at 3.55 became a quartet (J = 13); the multiplet at 4.30 ppm collapsed into a quadruplet by irradiation at 6.96 ppm; ms: m/e 399 (M⁺).

Anal. Calcd. for $C_{19}H_{17}N_3O_5S_2$: C, 57.14; H, 4.26; N, 10.53; S, 16.04. Found: C, 57.34; H, 4.35; N, 10.72; S, 15.87.

3-(Thiocarbamoyl-*N*-diacetyl)-3a-hydroxy-3,3a-dihydronaphtho[2',1':5,6]thiopyrano[4,3-*c*]pyrazole (**12**).

Compound **9** (0.3 g.) in acetic anhydride (10 ml.) was refluxed for 2 hours. After cooling the reaction mixture was poured into ice-water. The solid was crystallized from pyridine to give gray-tinged crystals, m.p. >

300° dec.; pmr (pyridine-*d*₅ at 80°): δ 2.14 and 2.36 (6H, 2s, 2COCH₃), 7.4-8.4 (8H, m, 6 aromatic protons, C₁₁-H and pyrazole proton); ms: m/e 397 (M⁺).

Anal. Calcd. for $C_{19}H_{15}N_3O_3S_2$: C, 57.43; H, 3.78; N, 10.58; S, 16.12. Found: C, 57.55; H, 3.81; N, 10.44; S, 16.19.

Acknowledgment.

This work has been supported by the National Research Council (CNR) of Italy. The authors are grateful to Mr. A. Marani for technical assistance.

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