New Heterocyclic Ring Systems from α-Hydroxymethyleneketones. VIII (1). Polyazasteroidal Analogues of Equilenin

A. Fravolini, A. Martani (2), G. Grandolini and C. Strappaghetti

Istituto di Chimica Farmaceutica e Tossicologica
Istituto di Chimica Farmaceutica Applicata, Università di Perugia, 06100 Perugia, Italy

Received September 13, 1976

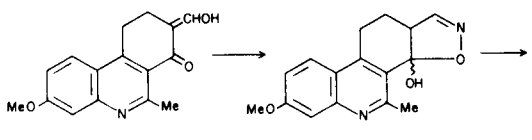
Some 6,15,16-triazasteroidal analogues of Equilenin carrying a 7-methyl substituent have been synthesized from 4-methyl-7-methoxy-10,11-dihydroisoxazolo[5,4-*i*]phenanthridine (III).

J. Heterocyclic Chem., 14, 43 (1977).

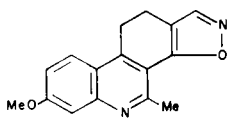
In an earlier communication (3) we described the synthesis of some 6-azasteroidal analogues carrying a 7-methyl substituent.

In order to study their biological properties, motivated by the significant observation that the 7-methyl substituent increased the estrogenic activity in estrone and estradiol (4,5), we have now extended the synthesis of this attractive class of steroids. This work is in connection with a general study on heterocyclic ring systems from α-hydroxymethyleneketones (6).

The synthesis of 4-methyl-7-methoxy-10,11-dihydroisoxazolo[5,4-*i*]phenanthridine (III) as a key intermediate for synthesis of pyrazolo-, pyrazolino- and isoxazolophenanthridine systems was achieved from 3-methoxy-6-methyl-7-oxo-8-hydroxymethylene-7,8,9,10-tetrahydrophenanthridine (I) (3):

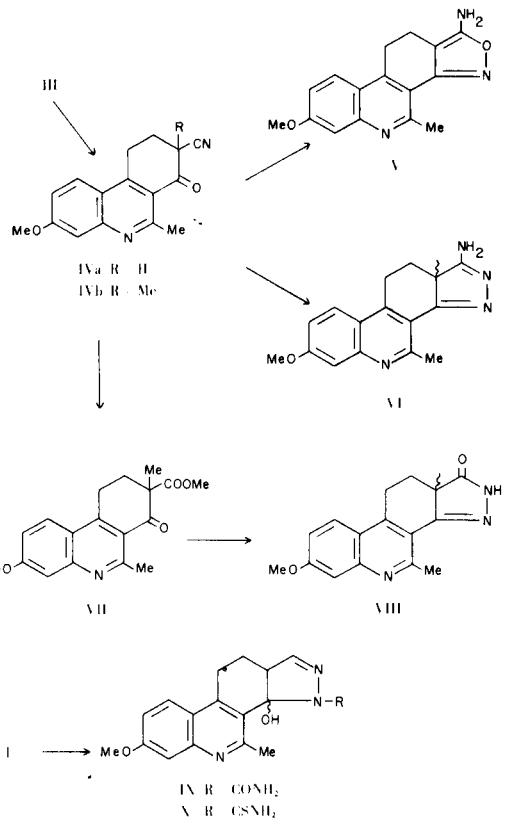


I II



III

The isoxazole derivative (III) was isomerized to 3-methoxy-6-methyl-7-oxo-8-cyano-7,8,9,10-tetrahydrophenanthridine (IVa) by action of sodium methoxide, confirming the isoxazole structure for compound (III). In accordance with its structure, the pmr spectrum (DMSO-d_6) of IVa showed a quadruplet centered at δ 4.42 for the C-8 proton, which disappeared when IVa reacted with methyl iodide to produce the α-cyanomethylketone (IVb) (70% yielded).



IVa R = H
IVb R = Me

V VI VII VIII

IX R = $CONH_2$
X R = $CSNH_2$

The α-cyanoketone (IVa) was easily converted to 1-amino-4-methyl-7-methoxy-10,11-dihydroisoxazolo[3,4-*i*]-phenanthridine (V) by treatment with hydroxylamine hydrochloride in ethanol/sodium hydroxide solution while the 6,15,16-triaza-14,15,16,17-dehydro-7-methyl-17-amino-17-deoxyequilenin methyl ether (racemic 3-methoxy-7-methyl-17-amino-6,15,16-triaza-1,3,5,6,8,14,16-estraheptaene) (VI) was obtained in 45% yield by treating IVb with an ethanolic solution of hydrazine hydrate in the presence of acetic acid.

The methanolysis of the 3-methoxy-6,8-dimethyl-7-oxo-cyano-7,8,9,10-tetrahydrophenanthridine (IVb) with methanol at -5° in the presence of dry hydrogen chloride furnished in excellent yield the β-ketoester (VII) which on heating with an ethanolic solution of hydrazine hydrate afforded the 6,15,16-triaza-14,15-dehydro-7-methyl-equilenin methyl ether (racemic 3-methoxy-7-methyl-6,15,16-triaza-1,3,5,6,8,14-estrahexaen-17-one) (VIII) in 75% yield.

Finally, 3-carbamoyl and 3-thiocarbamoyl-3a-hydroxy-4-methyl-7-methoxy-10,11-dihydro-Δ^1-pyrazolino[3,4-*i*]-phenanthridines (IX) and (X) were obtained by treatment of the hydroxymethylene derivative (I) with semicarbazide and thiosemicarbazide, respectively.

The pmr spectra of the reported compounds are in agreement with the assigned structures.

EXPERIMENTAL (7)

3-Methoxy-6-methyl-7-oxo-8-hydroxymethylene-7,8,9,10-tetrahydrophenanthridine (I).

The 3-methoxy-6-methyl-7-oxo-7,8,9,10-tetrahydrophenanthridine (3,8) was treated with sodium methoxide and ethyl formate in benzene solution under conditions similar to those reported by us in preceding papers (1,6,9). The resulting crude product was recrystallized from ethyl acetate to give I, white prisms, m.p. 173° (65% yield).

3a-Hydroxy-4-methyl-7-methoxy-10,11-dihydro-Δ^1-isoxazolino-[5,4-*i*]phenanthridine (II).

To a solution of 3-methoxy-6-methyl-7-oxo-8-hydroxymethylene-7,8,9,10-tetrahydrophenanthridine (I) (2.7 g., 0.01 mole) in ethanol (200 ml.) was added hydroxylamine hydrochloride (2.1 g., 0.03 mole) and then an aqueous solution (5 ml.) of sodium acetate (3 g.). Immediately a white precipitate was obtained. The reaction mixture was allowed to stand for 2 hours at room temperature. The crystalline precipitate was collected, washed with water, and recrystallized from dioxane to give prisms, m.p. 229° (80% yield).

Anal. Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.39; H, 5.70; N, 9.76.

4-Methyl-7-methoxy-10,11-dihydroisoxazolo[5,4-*i*]phenanthridine (III).

A solution of the isoxazoline derivative (II) (1 g.) in trifluoroacetic acid (30 ml.) was warmed for a few minutes and then poured into ice-water. The precipitated product was collected and washed with water. White prisms from ethanol, m.p. 178° (90% yield).

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.18; H, 5.26; N, 10.53. Found: C, 72.16; H, 5.35; N, 10.47.

3-Methoxy-6-methyl-7-oxo-8-cyano-7,8,9,10-tetrahydrophenanthridine (IVa).

A solution of sodium methoxide (0.6 g.) in dry methanol (20 ml.) was added dropwise to a suspension of III (2 g.) in dry methanol (200 ml.). The mixture was stirred for 2 hours at room temperature. The resulting solution, diluted with water and acidified with acetic acid, gave an orange precipitate which was collected and washed with 5% sodium bicarbonate and then with water, orange prisms from ethyl acetate, m.p. 202° (70% yield); pmr (DMSO-d_6): δ ~ 2.60 (broad m, 2H, C-9H_2), 2.84 (s, 3H, -N=C(I)-CH_3), ~ 3.40 (broad m, 2H, C-10H_2), 3.94 (s, 3H, -O-CH_3), 4.42 (quadruplet, 1H, J = 5 and 12 Hz, C-8H), 7.22 (dd, 1H, J = 2.5 and 9 Hz, C-2H), 7.30 (d, 1H, J = 2.5 Hz, C-4H) and 8.00 (d, 1H, J = 9 Hz, C-1H).

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 76.80; H, 5.60; N, 6.40. Found: C, 76.78; H, 5.63; N, 6.51.

3-Methoxy-6,8-dimethyl-7-oxo-8-cyano-7,8,9,10-tetrahydrophenanthridine (IVb).

To a suspension of III (3 g.) in dry methanol (200 ml.), a solution of sodium (0.9 g.) in dry methanol (30 ml.) was added dropwise with stirring. To the resulting solution, methyl iodide (5 ml.) was then added and the mixture was allowed to stand at room temperature overnight. After a further addition of methyl iodide (10 ml.), the mixture was refluxed for 3 hours, then evaporated to *ca.* 30 ml. and poured into water. The precipitated product was collected, washed with water, dried and then recrystallized from ethyl acetate to give IVb as white prisms, m.p. 165° (75% yield).

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.85; H, 5.71; N, 10.00. Found: C, 72.73; H, 5.70; N, 9.93.

1-Amino-4-methyl-7-methoxy-10,11-dihydroisoxazolo[3,4-*i*]phenanthridine (V).

A mixture of α-ketonitrile (IVa) (0.5 g.), hydroxylamine hydrochloride (1 g.), ethanol (15 ml.) and 2*N* sodium hydroxide (10 ml.) was refluxed for 2 hours and then cooled. The precipitated crystals were collected and recrystallized from ethanol to give V as yellow plates, m.p. 258° (45% yield); pmr (TFAA): δ 3.10 and 3.85 (multiplets, 4H, -CH_2-CH_2-), 3.24 (s, 3H, -N=C(I)-CH_3), 4.12 (s, 3H, -O-CH_3), 7.50 (d, 1H, J = 2.5 Hz, C-6H), 7.60 (dd, 1H, J = 2.5 and 9 Hz, C-8H) and 8.32 (d, 1H, J = 9 Hz, C-9H).

Anal. Calcd. for $C_{16}H_{15}N_3O_2$: C, 68.33; H, 5.34; N, 14.94. Found: C, 68.19; H, 5.31; N, 14.98.

6,15,16-Triaza-14,15,16,17-dehydro-7-methyl-17-amino-17-deoxy-equilenin Methyl Ether (VI).

A solution of α-ketonitrile (IVb) (1 g.) in ethanol (30 ml.) was treated with hydrazine hydrate (85%, 1.5 ml.) and acetic acid (0.5 ml.). The mixture was refluxed for 4 hours and then poured into ice-water. The resulting gummy precipitate was purified by chromatography on silica gel. Elution with 4% ethyl acetate in benzene afforded VI which was recrystallized from ligroin, white prisms, m.p. 160° (67% yield); pmr (deuteriochloroform): δ 1.68 (s, 3H, CH_3 at C-13), 2.93 (s, 3H, -N=C(I)-CH_3), 3.95 (s, 3H, -O-CH_3), 2.0-2.75 and 3.50 (complex multiplets, 4H, -CH_2-CH_2-), 7.18 (dd, 1H, J = 2.5 and 9 Hz, C-2H), 7.34 (d, 1H, J = 2.5 Hz, C-4H) and 7.85 (d, 1H, J = 9 Hz, C-1H).

Anal. Calcd. for $C_{17}H_{18}N_4O$: C, 69.38; H, 6.12; N, 19.05. Found: C, 69.50; H, 6.07; N, 19.11.

3-Methoxy-6,8-dimethyl-8-carboxymethyl-7,8,9,10-tetrahydrophenanthridine (VII).

Dry hydrogen chloride gas was passed through a solution of α-ketonitrile (IVb) (2 g.) in dry methanol (100 ml.) at 0° until saturation (2 hours). The reaction mixture was left overnight in a refrigerator, then poured into ice-water and made basic with solid sodium carbonate. The gummy precipitate was collected, washed with water, dried and then crystallized twice from hexane to give pure product as white prisms, m.p. 115° (85% yield).

Anal. Calcd. for $C_{18}H_{19}NO_4$: C, 69.00; H, 6.07; N, 4.47. Found: C, 69.12; H, 5.93; N, 4.39.

6,15,16-Triaza-14,15-dehydro-7-methylequilenin Methyl Ether (VIII).

A mixture of VII (1 g.), hydrazine hydrate (85%, 0.7 ml.) and ethanol (15 ml.) was heated at reflux temperature for 4 hours, cooled, and diluted with water, whereupon the product separated. Recrystallization from ethyl acetate gave VIII as pale yellow needles, m.p. 286° (55% yield); pmr (DMSO-d_6 + TFAA, 1:1): δ 1.22 (s, 3H, CH_3 at C-13), 3.13 (s, 3H, -N=C(-CH_3)-), 1.8-2.5 and 3.60 (complex multiplets, 4H, -CH_2-CH_2-), 4.02 (s, 3H, -O-CH_3), 7.48 (dd, 1H, J = 2.5 and 9 Hz, C-2H), 7.53 (d, 1H, J = 2.5 Hz, C-4H) and 8.23 (d, 1H, J = 9 Hz, C-1H).

Anal. Calcd. for $C_{17}H_{17}N_3O_2$: C, 69.15; H, 5.76; N, 14.24. Found: C, 69.09; H, 5.80; N, 14.25.

3-Carbamoyl-3a-hydroxy-4-methyl-7-methoxy-10,11-dihydro-Δ^1-pyrazolino[3,4-*i*]phenanthridine (IX).

A mixture of I (1 g.), semicarbazide hydrochloride (0.5 g.) and methanol (50 ml.) was refluxed for an half-hour. After cooling the reaction mixture, the precipitated solid was collected and washed with ethanol. Recrystallization from dimethylformamide gave pure IX as orange needles, m.p. 250° dec. (70% yield).

Anal. Calcd. for $C_{17}H_{18}N_4O_3$: C, 62.57; H, 5.52; N, 17.17. Found: C, 62.42; H, 5.78; N, 17.06.

3-Thiocarbamoyl-3a-hydroxy-4-methyl-7-methoxy-10,11-dihydro-Δ^1-pyrazolino[3,4-*i*]phenanthridine (X).

A mixture of I (0.5 g.), thiosemicarbazide (0.35 g.) and ethanol (100 ml.) was refluxed for 2 hours. The solution was then evaporated to about 50 ml. and diluted with water. The crude product was collected and crystallized from ethyl acetate, yellow prisms, m.p. 232° dec. (63% yield); pmr (DMSO-d_6): δ 2.80 (s, 3H, -N=C(-CH_3)-), 3.92 (s, 3H, -O-CH_3), 2.40 (broad m, 2H, C-11H_2), 3.2-3.8 (broad m, 3H, C-10H_2 and methine proton at C-11a), 7.73 (d, 1H, J = 5 Hz, C-1H), 7.24 (dd, 1H, J = 2.5 and 9 Hz, C-8H), 7.30 (d, 1H, J = 2.5 Hz, C-6H), 8.04 (d, 1H, J = 9 Hz, C-9H) and 11.15 (broad s, 1H, OH).

Anal. Calcd. for $C_{17}H_{18}N_4O_2S$: C, 59.65; H, 5.26; N, 16.37. Found: C, 59.77; H, 5.20; N, 16.40.

Acknowledgment.

This work has been supported by the National Research Council (CNR) of Italy.

(1) Part VII, G. Grandolini, A. Fravolini, A. Martani and F. Schiaffella, *Gazz. Chim. Ital.*, in press.

(2) Deceased March 6, 1976.

(3) A. Martani, A. Fravolini and G. Grandolini, *J. Heterocyclic Chem.*, **11**, 452 (1974).

(4) J. Kalvada, Ch. Krahenbuhe, P. A Desaulles and G. Anner, *Helv. Chim. Acta*, **50**, 281 (1967).

(5) G. C. Buzby, G. H. Douglas, C. R. Walk and H. Smith, "Proceedings of the Second International Congress on Hormonal Steroids," Milan, May, 1966.

(6) A. Fravolini, G. Grandolini and A. Martani, *Gazz. Chim. Ital.*, **103**, 1073 (1973).

(7) Melting points were measured with a Kofler hot-stage apparatus and are uncorrected. 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 reported in "δ" values (ppm).

(8) P. E. Cross and E. R. H. Jones, *J. Chem. Soc.*, 5916 (1964).

(9) A. Fravolini, G. Grandolini and A. Martani, *Gazz. Chim. Ital.*, **103**, 755 (1973).