Synthesis in the Diazasteroid Group. XII (1). Syntheses of the 10,17-Diazasteroid and 10-Aza-17-thiasteroid Systems

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Upon desulfurization with Raney Ni, the condensed heterocycles **2a,b** prepared by cyclization from β-ketosulfoxides **1a,b** gave β-ketones **3a,b**, which were condensed with 2-carbethoxymethylpiperidine **4** to afford the 10,17-diazasteroid **6** and the 10-aza-17-thiasteroid **7**, respectively.

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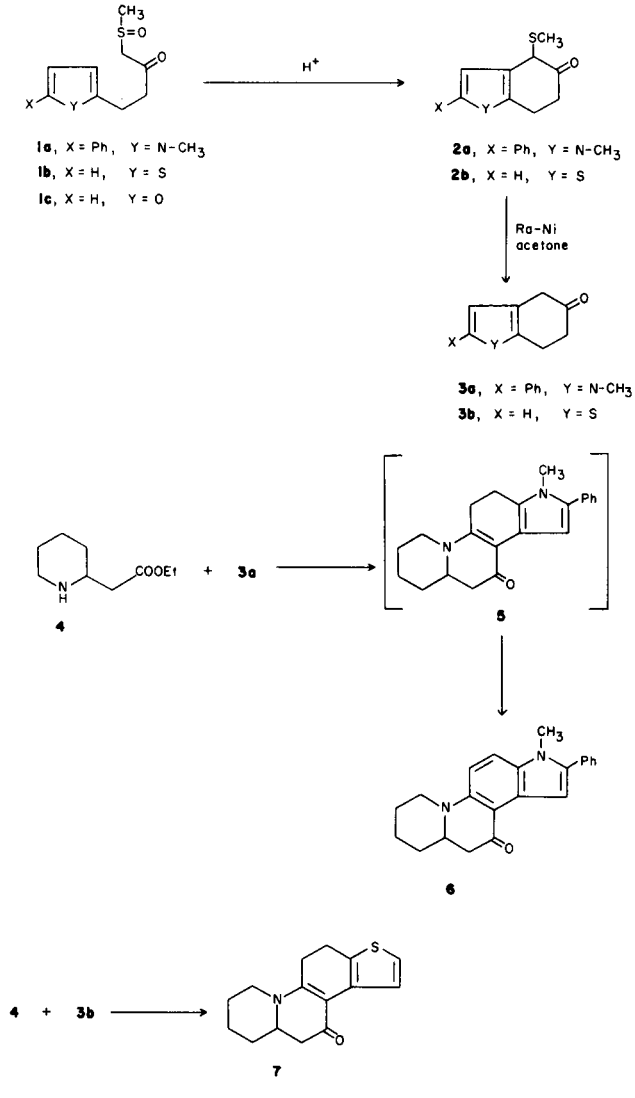
Much attention has been devoted to the synthesis of heterocyclic steroids (2) in view of their biological activities (3). Recently, several types of heterocycles, such as indole, benzothiophene, and carbazole derivatives have been synthesized by acid catalyzed cyclization of β-ketosulfoxides (4) through the Pummerer reaction (5). Following our preceding paper (1), we now report a facile synthesis of the 10,17-diazasteroid and 10-aza-17-thiasteroid ring systems, using **2a,b** as C-D ring segment synthons.

First, cyclization of β-ketosulfoxides **1a,b** afforded condensed heterocycles, **2a,b**, in moderate yields, whereas cyclization of **1c** resulted in decomposition under acidic conditions (6). Next, desulfurization of **2a,b** with Raney Ni in acetone produced β-ketones **3a,b** in 66% and 63% yields (**3a**, m.p. 95-99° and **3b**, m.p. 166-168° as its 2,4-dinitrophenylhydrazone), respectively. The ir spectra of **3a,b** showed characteristic absorptions of the carbonyl groups at 1700 and 1710 cm^{-1}, respectively. The nmr spectra of **3a,b** had singlets at δ 3.5 and 3.4, indicative of Ar-CH_2-CO- groups, respectively. 2-Carbethoxymethylpiperidine **4** as the A ring source was prepared from α-picoline by the modified method of Kofron, *et al.*, (7).

Condensation of **3a** with **4** in toluene in the presence of trifluoracetic acid using a Dean Stark apparatus gave the 10,17-diazasteroid system **6** (m.p. 199-200°) as orange plates in 65% yield. The mass spectrum of the above crude product exhibited both a parent ion peak at m/e 332 corresponding to **5** and a parent ion peak at m/e 330 attributed to **6**. Compound **5** was gradually oxidized on exposure to air to **6** and could not be purified. On the other hand, a similar reaction of **3b** with **4** gave the 10-aza-17-thiasteroid system **7** (8) (m.p. 113-116°) as pale yellow plates though in low yield, probably because of the lability of compound **3b**.

Chart I



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EXPERIMENTAL

All melting points were taken with a Yanaco micro melting point apparatus and are uncorrected. Ir spectra were determined using a Hitachi Grating Infrared 215 spectrophotometer with absorptions given in cm^{-1}. Nmr spectra were recorded on a JEOL C-60H spectrometer using TMS as the internal standard. The chemical shifts and coupling constants are reported in δ and Hz, respectively. The mass spectra were measured with a JEOL TMS-OISG (75 eV, direct inlet system) spectrometer. The uv spectra were obtained in ethanol using a Hitachi Model EPS-2T spectrometer.

Preparation of 4-Methylthio-5-oxo-2-phenyl-1-methyl-4,5,6,7-tetrahydroindole (**2a**).

A solution of **1a** (1.08 g., 3.75 mmoles) and *p*-toluenesulfonic acid (0.285 g., 1.5 mmoles) in THF (75 ml.) was heated under reflux for 1 hour. Evaporation of the solvent gave an oil, which was neutralized with 10% sodium bicarbonate solution and extracted with dichloromethane. The extract was dried over anhydrous magnesium sulfate and evaporated *in vacuo* to leave an oil, which was purified by column chromatography on silica gel using benzene as an eluent, affording **2a** (0.67 g., 66%) as white plates, m.p. 117-119°; ir (nujol): 1690; nmr (deuteriochloroform): 2.2 (s, 3H), 3.5 (s, 3H), 4.1 (s, 1H), 6.2 (s, 1H), 7.4 (s, 5H).

Anal. Calcd. for $C_{16}H_{17}NOS$: C, 70.81; H, 6.31; N, 5.16. Found: C, 71.03; H, 6.14; N, 5.05.

Preparation of 5-Oxo-2-phenyl-1-methyl-4,5,6,7-tetrahydroindole (**3a**).

A solution of **2a** (0.684 g., 2.52 mmoles) in acetone (100 ml.) was heated under reflux in the presence of Raney-Ni (4 g.) for 1 hour. The mixture was filtered and the filtrate was evaporated *in vacuo* to leave an oil, which was purified by column chromatography on alumina using benzene as an eluent affording **3a** (0.63 g., 63%). Compound **3a** was recrystallized from hexane-dichloromethane to give white plates m.p. 95-99°; ir (nujol): 1700; nmr (deuteriochloroform): 2.8 (q, J = 5, 4H), 3.5 (s, 5H), 6.0 (s, 1H), 7.3 (s, 5H).

Anal. Calcd. for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.71; H, 6.91; N, 6.09.

Preparation of 5-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene (**3b**).

A solution of **2b** (5) (3.75 g., 19 mmoles) and Raney-Ni (6 g.) in acetone (300 ml.) was heated at 80° for 1 hour. The mixture was filtered and the filtrate was evaporated *in vacuo* to leave an oil, which was purified by column chromatography on silica gel using benzene as an eluent to give **3b** (1.66 g., 58%) as a pale yellow oil, m.p. 166-168° as the 2,4-dinitrophenylhydrazone of **3b**; ir (neat): 1710; nmr (deuteriochloroform): 2.45-3.3 (m, 4H), 3.4 (s, 2H), 6.67 (d, J = 5, 1H), 7.05 (d, J = 5, 1H).

Anal. Calcd. for $C_{14}H_{12}N_4O_4S$: C, 50.60; H, 3.84; N, 16.86. Found: C, 50.89; H, 3.55; N, 17.13.

Preparation of 2-Carbethoxymethylpiperidine (**4**).

To a solution of potassium (8 g., 0.2 g.-atom) in liquid ammonia (400 ml.) was added a solution of α-picoline (27.9 g., 0.3 mole) in ether (20 ml.) with stirring. The resulting orange solution of potassio-picoline was stirred for 30 minutes, and then cooled in a dry ice-acetone bath. As rapidly as possible, ethyl carbonate (11.8 g., 0.1 mole) was added, and the cooling bath was removed. After 5 minutes, the green colored reaction mixture was neutralized with ammonium chloride (10.7 g., 0.2 moles) to give a grey mixture, which was evaporated to leave a residue. The residue was extracted with ether and the extract was evaporated to give an oil, which was distilled *in vacuo* to give 2-carbethoxymethylpyridine (7.8 g., 47%), b.p. 85-87° (6 mm Hg) lit., (9) 135-137° (28 mm Hg). 2-Carbethoxymethylpyridine hydrochloride (9.85 g., 4.9 mmoles) was hydrogenated over platinum oxide (1 g., 4.4 mmoles) in glacial acetic acid (100 ml.) under 3 atmospheres pressure at room temperature overnight in a low-pressure apparatus. The mixture was filtered to remove the catalyst and the solvent was evaporated *in vacuo* giving a crude mass which was neutralized with saturated sodium bicarbonate solution. The solvent was extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and evaporated *in vacuo* leaving an oil **4** (4.2 g., 52%), b.p. 92-93° (9 mm Hg), lit., (10) b.p. 105° (14 mm Hg).

Preparation of 10,17-Diazagona-16-phenyl-17-methyl-8,11,13,15-tetraen-7-one (**6**).

Compound **3a** (137 mg., 0.6 mmole), **4** (104 mg., 0.6 mmole) and toluene (20 ml.) were placed in a flask fitted with a Dean Stark apparatus for water separation. Trifluoroacetic acid (104 mg., 0.9 mmole) was then added and the reaction mixture was refluxed for 48 hours. Evaporation of the solvent *in vacuo* left an oil, which was neutralized with 10% sodium bicarbonate solution and extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and evaporated *in vacuo* giving a crude crystalline mass, which was purified by preparative chromatography on silica gel using chloroform-ethanol (20:1) as an eluent affording **6** (131 mg., 65%) as orange plates, m.p. 199-200°; ir (nujol): 1650; nmr (deuteriochloroform): 1.3-2.0 (m, 7H), 2.4-2.7 (m, 3H), 3.65 (s, 3H), 4.0 (m, 1H), 6.8 (bd, J = 10, 1H), 7.5 (bs, 7H); ms: m/e 330 (M^+); uv: 372 nm (ε = 15000), 229 (26000).

Anal. Calcd. for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.48. Found: C, 79.85; H, 6.73; N, 8.24.

Preparation of 10-Aza-17-thiagona-8,13,15-trien-7-one (**7**).

In a similar manner to the method reported above, the condensation of **3b** (0.71 g., 4.7 mmoles) with **4** (0.8 g., 4.7 mmoles) was carried out in toluene (50 ml.) in the presence of trifluoroacetic acid (0.8 g., 7.0 mmoles) under reflux for 48 hours, giving **7** (0.16 g., 13%) as pale yellow plates, m.p. 113-116°; ir (potassium bromide): 1660, 1580; nmr (deuteriochloroform): 1.2-2.0 (m, 6H), 2.3-2.7 (m, 3H), 3.2-3.8 (m, 6H), 6.7 (d, J = 9, 1H), 7.2 (d, J = 9, 1H); ms: m/e 259 (M^+); uv: 216 nm (ε = 12000), 248 (24000), 285 (12000).

Anal. Calcd. for $C_{15}H_{17}NOS$: C, 69.46; H, 6.61; N, 5.40. Found: C, 69.22; H, 6.38; N, 5.43.

REFERENCES AND NOTES

(1) Part XI. T. Yamazaki, H. Takahata, T. Matsuura and R. N. Castle, *J. Heterocyclic Chem.*, **16**, 525 (1979).

(2) For reviews see: (a) P. Morand and J. Lyall, *Chem. Rev.*, **68**, 85 (1968); (b) H. O. Huisman, *Angew. Chem., Int. Ed. Engl.*, **10**, 450 (1971). (c) I. Ninomiya, *J. Org. Synth. (Japan)*, **30**, 318 (1972).

(3a) L. F. Fieser and M. Fieser, "Steroids", Reinhold Publishing Corporation, New York, N.Y., 1959, Chapter 22; (b) I. Y. Tao and R. T. Blickenstaff, *J. Pharm. Sci.*, **67**, 283 (1978).

(4a) S. Kano, Y. Takahagi and S. Shibuya, *Synthesis*, 372 (1978); (b) T. Kurosawa, M. Tohma, Y. Oikawa and O. Yonemitsu, *Chem. Pharm. Bull.* **26**, 1533 (1978).

(5) Y. Oikawa and O. Yonemitsu, *J. Org. Chem.*, **41**, 1118 (1976).

(6) As acids trifluoroacetic acid (benzene) and *p*-toluenesulfonic acid (tetrahydrofuran) were used.

(7) *cf* W. G. Kofron and L. M. Baclawski, *Org. Synth.*, **52**, 75 (1972).

(8) Although there were few publications on thiasteroids, recently several have appeared: (a)T. Terasawa and T. Okada, *J. Chem. Soc., Perkin Trans. I*, 576 (1978); (b) *idem, ibid.*, 1252 (1978); (c) *idem, ibid.*, 1254 (1978; (d) M. S. Manhas, M. Sugiura and H. P. S. Chawla, *J. Heterocyclic Chem.*, **15**, 949 (1978); (e) S. Kano, K. Tanaka, S. Hibino and S. Shibuya, *J. Org. Chem.*, **44**, 1580 (1979).

(9) R. B. Woodward and E. L. Kornfeld, *Org. Synth., Coll. Vol.*, **3**, 413 (1955).

(10) G. R. Clemo, W. M. Morgan and R. Raper, *J. Chem. Soc.*, 1743 (1935).