Synthesis in the Diazasteroid Group XI. A Convenient Route to the 4,8-Diazasteroid System (1)

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The reaction of 1,6-naphthyridine **3** with acetic anhydride results in the formation of the 1:1 adduct **4**. Upon catalytic hydrogenation followed by acid hydrolysis and esterification, **4** affords **7** as an A-B steroid ring system synthon in moderate yield. Upon condensation with cyclopentanone and cyclohexanone, **7**, gives the 4,8-diazasteroid system **8** and the D-homo compound **9**, respectively.

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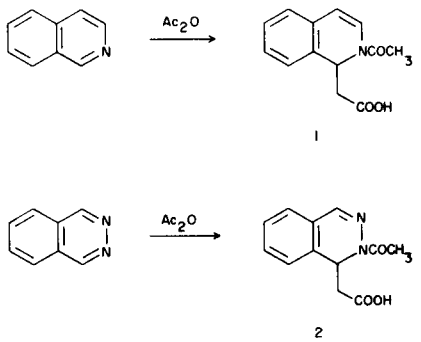
We have previously synthesized a number of diazasteroids in view of their potential biological activity (2). Recently, Yamanaka, *et al.*, (3), reported that upon reaction with acetic anhydride, isoquinoline and phthalazine afforded the interesting 1:1 adducts **1** and **2**. However, the same reaction with quinoline and quinoxaline was reported to result only in the recovery of the starting materials (Chart I). In a similar manner, upon the reaction of 1,6-naphthyridine **3** with acetic anhydride, we obtained the 1:1 adduct **4**.

Chart I



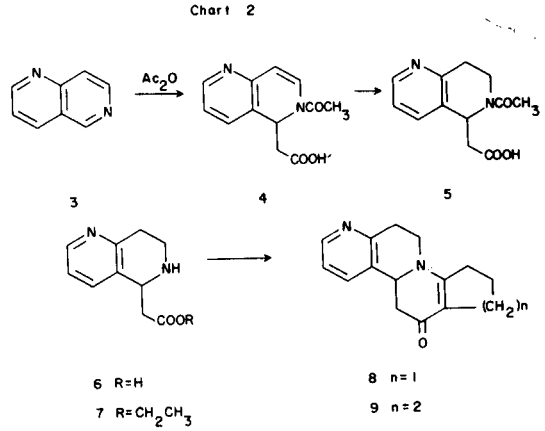
In this paper, we report a convenient synthesis of the 4,8-diazasteroid ring system using **4** as the starting material for the synthesis of the A-B ring segment synthon **7**. The reaction of the readily available naphthyridine **3** (4) with excess acetic anhydride at 145° for 40 hours afforded **4** (m.p. 155-156°) as pale yellow crystals in 20% yield. The nmr spectrum of **4** showed a singlet at δ 2.50, assigned to the acetyl methyl group, as well as a broad doublet at δ 3.12, assigned to the -CH_2COOH group. The ir spectrum showed characteristic carboxylic acid absorption (1680 and 2950-2500 cm^{-1}) together with a band at 1640 cm^{-1}, indicative of the amide carbonyl group.

Catalytic hydrogenation of **4** over palladium on carbon under atmospheric or medium pressures did not proceed smoothly to give **5**, presumably due to catalytic poisoning by the pyridine moiety. However, **5** was obtained from **4** in 62% yield upon catalytic hydrogenation over palladium on carbon in ethanol at 70° and 50 atmospheres pressure. The structure of **5** was confirmed by the disappearance of the vinyl protons in the nmr. Upon hydrolysis in acid followed by esterification, **5** afforded **7** in 69% yield.

The condensation of **7** with cyclopentanone in toluene in the presence of trifluoroacetic acid using a Dean Stark apparatus furnished the 4,8-diazasteroid system **8** (m.p. 196-198°) in 97% yield. Compound **8** exhibited analytical and spectroscopic data consistent with its assigned structure. In particular, the vinylogous amide group exhibited a strong maximum absorption at 330 nm in the uv along with a strong band at 1640 cm^{-1} in the ir. Similarly, the reaction of **7** with cyclohexanone gave the D-homo-4,8-diazasteroid system **9** (m.p. 225-227°) in 81% yield.

The biological activities of **8** and **9** are currently under investigation.

Chart 2



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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. Mass spectra were measured with a JEOL TMS-OISG (75 eV, direct inlet system) spectrometer. Uv spectra were obtained in ethanol using a Hitachi Model EPS-2T spectrometer.

Preparation of 6-Acetyl-5,6-dihydro-1,6-naphthyridine-5-acetic Acid (**4**).

A mixture of 1,6-naphthyridine (**3**) (13.3 g., 102 mmoles) and acetic anhydride (60 ml.) was heated at 145° for 40 hours. Condensation of the reaction mixture left a brown oil which was purified by column chromatography on silica gel using ethyl acetate as an eluent, affording **4** (4.75 g., 20%) as pale yellow needles, m.p. 155-156°; ir (potassium bromide): 2950-2500, 1680, 1640; nmr (trifluoroacetic acid): 2.50 (s, 3H, $-COCH_3$), 3.12 (b-d, J = 6, 2H, $-CH_2COOH$); ms: m/e 173 [M^+-59 ($-CH_2COOH$)].

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.94; H, 5.49; N, 11.84.

Preparation of 6-Acetyl-5,6,7,8-tetrahydro-1,6-naphthyrid-5-ylacetic Acid (**5**).

Compound **4** (2 g., 8.6 mmoles) was hydrogenated over 10% palladium on carbon in ethanol at 70° under 50 atmospheres pressure in an autoclave overnight. The mixture was then filtered to remove the catalyst and the solvent was evaporated giving **5** as colorless needles (1.25 g., 62%), m.p. 220-221°; ir (potassium bromide): 3000-2500, 1700, 1630; nmr (deuteriochloroform): 2.05 (s, 3H, $-COCH_3$); ms: m/e 234 (M^+), 191, 133.

Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.52; H, 6.02; N, 11.96. Found: C, 61.35; H, 6.16; N, 11.82.

Preparation of 5-Carbethoxymethyl-5,6,7,8-tetrahydro-1,6-naphthyridine (**7**).

A solution of **5** (1.2 g., 5.1 mmoles) in 18% hydrochloric acid (10 ml.) was refluxed for 2 hours. Evaporation of the solvent *in vacuo* gave the crude **6**, which was dried over phosphorus pentoxide in a desiccator. Without further purification, the crude **6** (950 mg.) was refluxed in anhydrous ethanol (30 ml.) in the presence of concentrated sulfuric acid (0.5 ml.) for 4 hours. Evaporation of the solvent gave an oil which was neutralized with 10% sodium hydroxide solution and extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and evaporated *in vacuo* leaving an oil, which was purified by column chromatography on silica gel using chloroform as an eluent, affording **7** (780 mg., 69%) as an oil; ir (neat): 3370, 1740; nmr (deuteriochloroform): 1.17 (t, J = 7, 3H, $-COOCH_2CH_3$), 2.33 (S, -NH), 4.10 (q, J = 7, 2H, $-COOCH_2CH_3$). The picrolonate of **7** had m.p. 183-189°; ms: m/e 220 ($M^+-C_{10}H_8N_4O_5$).

Anal. Calcd. for $C_{22}H_{24}N_6O_7$: C, 54.77; H, 4.60; N, 17.42. Found: C, 54.52; H, 4.77; N, 17.62.

Preparation of 4b,5,6,7,8,9,11,12-Octahydrocyclopenta[5,6]pyrido[2,1-*f*][1,6]naphthyridin-6-one (**8**).

Compound **7** (414 mg., 1.88 mmoles), cyclopentanone (316 mg., 3.76 mmoles) and toluene (30 ml.) were placed in a flask fitted with a Dean Stark apparatus for water separation. Trifluoroacetic acid (321 mg., 2.82 mmoles) was then added and the reaction mixture was refluxed for 48 hours under argon. 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 recrystallization from ether to give **8** (438 mg., 97%) as colorless needles, m.p. 196-198°; ir (potassium bromide): 1640; nmr (deuteriochloroform): 4.80 (d-d, J = 10, J_2 = 14, 1H, (q-H)); ms: m/e 240 (M^+); uv: 330 nm (ϵ = 16,700).

Anal. Calcd. for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 75.21; H, 6.84; N, 11.51.

Preparation of 4b,5,7,8,9,10,12,13-Octahydro-6*H*-quino[2,1-*f*][1,6]naphthyridin-6-one (**9**).

In a similar manner to the method reported above, the condensation of **7** (215 mg., 0.97 mmole) with cyclohexanone (192 mg., 1.96 mmoles) was carried out in toluene (20 ml.) in the presence of trifluoroacetic acid (167 mg., 1.46 mmoles) under reflux for 48 hours, giving **9** (200 mg., 81%) as colorless needles. Compound **9** was recrystallized from ether-dichloromethane, m.p. 215-217°; ir (potassium bromide): 1620; nmr (deuteriochloroform): 4.58 (d-d, J = 10, J_2 = 14, 1H, (q-H)); ms: m/e 254 (M^+); uv: 330 nm (ϵ = 12,000).

Anal. Calcd. for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.02. Found: C, 75.32; H, 7.37; N, 10.80.

REFERENCES AND NOTES

(1) Part X: T. Yamazaki, H. Takahata, Y. Hama, Y. Takano, M. Nagata and R. N. Castle, *J. Heterocyclic Chem.*, submitted for publication. This work was presented at the 45th Meeting of the Horuriku Branch of the Pharmaceutical Society of Japan, Kanazawa, November, 1977.

(2a) For a review see: I. Ninomiya, *J. Org. Synth. (Japan)*, **30**, 318 (1972); (b) I. Y. Tao and R. T. Blickenstaff, *J. Pharm. Sci.*, **67**, 283 (1978).

(3) H. Yamanaka, T. Shiraishi and T. Sakamoto, *Heterocycles*, **3**, 1075 (1975).

(4) T. J. Kress and W. W. Paudler, *Chem. Commun.*, 3 (1967).