Total Synthesis of 1,11- and 3,11-Diazasteroids

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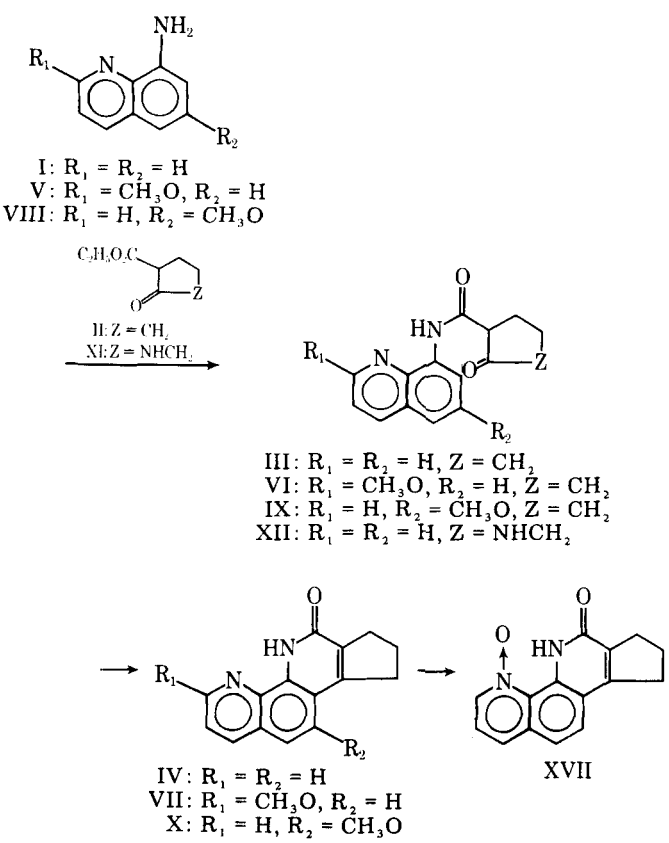
Abstract □ The 2- and 6-methoxy derivatives of 8-aminoquinoline, as well as 5-aminoisoquinoline, condensed with 2-ethoxycarbonylcyclopentanone to give tricyclic intermediates in 86–90% yield. These secosteroids were cyclized in 35–69% yield with polyphosphoric acid to 2-methoxy-1,11-diaza-, 7-methoxy-1,11-diaza-, and 3,11-diaza-1,3,5,7,9,13-gonahexaen-12-ones, respectively. The latter exhibits slight antileukemic activity.

Keyphrases □ Diazasteroids, various—synthesized, antitumor activity evaluated □ Steroids, various diaza—synthesized, antitumor activity evaluated □ Antitumor activity—evaluated in various diazasteroids □ Structure–activity relationships—various diazasteroids evaluated for antitumor activity

1,11-Diaza-8,14-seco-1,3,5,7,9-gonapentaene-12,14-dione (III, Scheme I) was cyclized (1) with polyphosphoric acid in 75% yield to 1,11-diaza-1,3,5,7,9,13-gonahexaen-12-one (IV), contrary to an earlier report that it would not cyclize (2). The synthesis has now been extended to the isomeric secosteroid (XIV) and to two methoxy derivatives of III. These diazasteroids were of interest for evaluation as antitumor agents in light of the reported activity of 2-azaestradiol 17-acetate 3-methyl ether (3). Consequently, the new diazasteroids, as well as *N*-oxides of two of them, were submitted to the National Institutes of Health for antitumor assay.



Scheme I

EXPERIMENTAL[1]

3,11-Diaza-8,14-seco-1,3,5,7,9-gonapentaene-12,14-dione (XIV)—An equimolar mixture of 5-aminoisoquinoline (XIII, 2.88 g, 0.02 mole) and 2-ethoxycarbonylcyclopentanone (II, 3.12 g) was dissolved in 45 ml of xylene, and the resulting orange solution was heated at reflux for 1 hr (Scheme II). Most of the xylene was distilled off, and the residue was solidified upon cooling. Filtration gave a light-orange cake, 4.62 g (0.018 mole), 90% yield of crude XIV, mp 112–115° [lit. (2) mp 120–122°]; IR: 1720 (keto C=O) and 1670 (amide C=O) cm^{-1}.

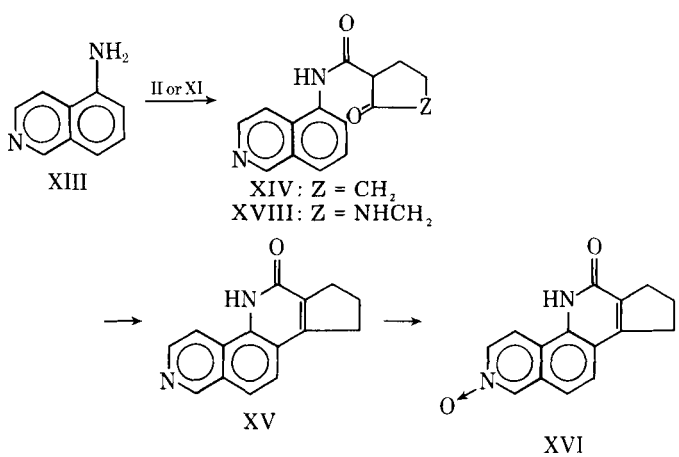
Since this intermediate was difficult to crystallize, a portion of it was converted to the corresponding methiodide salt for identification purposes. A solution of 0.5 g of crude XIV and 6 ml of methyl iodide in 10 ml of methanol was heated at reflux for 2 hr and then concentrated to a few milliliters. Orange plates were filtered and recrystallized from water, mp 217–219° [lit. (4) mp 206–207.5°].

Anal.—Calc. for $C_{16}H_{17}IN_2O_2$: C, 48.50; H, 4.32; I, 32.03; N, 7.07. Found: C, 48.10; H, 4.36; I, 32.27; N, 6.97.

3,11-Diaza-1,3,5,7,9,13-gonahexaen-12-one (XV)—The secosteroid XIV (3.44 g, 13.5 mmoles) was added to 35 g of polyphosphoric acid at 100–115° in 15 min. The reaction was exothermic with foaming. The mixture was kept at 100–115° for 1 hr with occasional stirring and then was poured onto crushed ice and brought to pH 6 with aqueous sodium hydroxide. Filtration gave 2.2 g of a yellow powder (XV) in 69% yield. The filtrate was made alkaline and extracted three times with chloroform to give 29% of recovered 5-aminoisoquinoline. Recrystallization of XV from methanol gave the analytical sample, mp >290°; IR: 1630 and 1610 cm^{-1}.

Anal.—Calc. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.06; H, 5.08; N, 11.75.

3,11-Diaza-1,3,5,7,9,13-gonahexaen-12-one 1-*N*-Oxide (XVI)—A solution of 3.54 g (15 mmoles) of XV in 20 ml of chloroform was added at room temperature to a stirred solution of 3.05 g of *m*-chloroperbenzoic acid in 100 ml of chloroform. The resulting suspension was stirred for 48 hr and then filtered to give 2.65 g of a yellow powder. This powder was treated with cold methanol, and filtering gave 2.19 g of crude XVI. The methanol solution contained unreacted XV. Recrystallization of crude XVI from aqueous methanol gave a powder, mp >290°. The IR spectrum



Scheme II

[1] Melting points were obtained on a Thomas-Hoover melting-point apparatus and are corrected. IR spectra were taken as smears or mineral oil mulls on a Perkin-Elmer 247 spectrophotometer. PMR spectra were obtained in deuterodimethyl sulfoxide on a Varian HA-100 spectrophotometer with tetramethylsilane as an internal standard. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. The 2-ethoxycarbonylcyclopentanone is actually a 1:1 mixture of methyl and ethyl esters.

Table I—Synthesis of 1,11-Diazasteroids

Number	Compound Name	Yield, %	Melting Point	Mass Spectrum, *m/e*	IR, cm^{-1}	Formula	Analysis, %	Calc.	Found
VI	2-Methoxy-1,11-diaza-8,14-seco-1,3,5,7,9-gonapentaene-12,14-dione[a]	86	143–144.5°[b]	—	1735, 1660	$C_{16}H_{16}N_2O_3$	C	67.59	67.55
							H	5.67	5.69
							N	9.85	9.71
VII	2-Methoxy-1,11-diaza-1,3,5,7,9,13-gonahexaen-12-one	35	275–276°	266	3360, 1660, 1600	$C_{16}H_{14}N_2O_2 \cdot CH_3OH$	C	68.44	68.45
							H	6.08	5.88
							N	9.37	9.88
IX	7-Methoxy-1,11-diaza-8,14-seco-1,3,5,7,9-gonapentaene-12,14-dione[a]	89	116–118°	—	1720, 1670	$C_{16}H_{16}N_2O_3$	C	67.59	67.40
							H	5.67	5.76
							N	9.85	9.95
X	7-Methoxy-1,11-diaza-1,3,5,7,9,13-gonahexaen-12-one[e]	39	247–249.5° dec.[c,d]	266	1620, 1610	$C_{16}H_{14}N_2O_2$	C	72.16	72.09
							H	5.30	5.35
							N	10.52	10.52
XII	1,11,15-Triaza-8,14-seco-D-homo-1,3,5,7,9-gonapentaene-12,14-dione	77	220–221.5°[d]	—	3320, 3160	$C_{15}H_{15}N_3O_2$	C	66.90	67.11
							H	5.61	5.45
							N	15.60	15.38
XVII	1,11-Diaza-1,3,5,7,9,13-gonahexaen-12-one 1-*N*-oxide	14	242.5–244° dec.[f]	252	3325, 1270, 850	$C_{15}H_{12}N_2O_2 \cdot H_2O$	C	66.66	66.89
							H	5.22	5.19
							N	10.36	10.42
XVIII	3,11,15-Triaza-8,14-seco-D-homo-1,3,5,7,9-gonapentaene-12,14-dione	83	186.5–188°[d]	—	1680, 1650, 1630	$C_{15}H_{15}N_3O_2$	C	66.90	66.81
							H	5.61	5.46
							N	15.60	15.56

[a] These condensations were carried out as in the preparation of XIV (see *Experimental*), except that the amine was added dropwise to a 10% excess of the keto ester over 40–60 min. [b] Crystallized from acetone–water. [c] After chromatography on Florisil. [d] Crystallized from acetone–chloroform. [e] NMR: δ 8.65 (1H, d, $J_{2,3}$ = 4 Hz, $J_{2,4}$ = 1.5 Hz, H_2), 7.99 (1H, d, $J_{3,4}$ = 8 Hz, $J_{2,4}$ = 1.5 Hz, H_4), 7.44 (1H, d, $J_{3,4}$ = 8 Hz, $J_{2,3}$ = 4 Hz, H_3), 6.71 (1H, s, H_6), 4.03 (3H, s, CH_3O), 3.00 (4H, m, $H_{15,17}$), and 2.30 (2H, m, H_{16}) ppm. [f] Crystallized from water.

exhibited *N*-oxide bands at 1240 and 850 cm^{-1}; the mass spectrum showed *m/e* 252 (also indicated the presence of water).

Anal.—Calc. for $C_{15}H_{12}N_2O_2 \cdot H_2O$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.27; H, 5.16; N, 10.26.

RESULTS AND DISCUSSION

8-Amino-2-methoxyquinoline, prepared by a minor modification of the method of Mislow and Koepeli (5), condensed with II to give an 86% yield of the secosteroid VI, which cyclized to 2-methoxy-1,11-diaza-1,3,5,7,9,13-gonahexaen-12-one in 35% yield (VII, Table I). Similarly, 8-amino-6-methoxyquinoline (VIII) and II reacted to produce IX (89%), which was cyclized to 7-methoxy-1,11-diaza-1,3,5,7,9,13-gonahexaen-12-one (X) (39%). 5-Aminoisoquinoline (XIII) and II gave XIV (90%), which was cyclized to the 3,11-diazasteroid XV (69%, see *Experimental*). Both I and XIII condensed with 3-ethoxycarbonyl-2-piperidone (XI) to give the secosteroids XII and XVIII, respectively, neither of which could be cyclized to steroids. *N*-Oxides of IV and XV were prepared by oxidation with *m*-chloroperbenzoic acid.

Diazasteroids IV, VII, X, XVI, and XVII were inactive in the National Cancer Institute screen against P-388 leukemia in mice. However, XV (NSC 265959) exhibited slight activity at 12.5–50 mg/kg; at higher dose levels, it was toxic[2].

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[2] *Note added in proof:* Dr. Chinan Fan, Department of Biochemistry, Scripps Clinic and Research Foundation, La Jolla, Calif., found that XV exhibits a modest inhibitory activity ($K_i = 1.3 \times 10^{-5}$ *M*) against the L-1210 dihydrofolate reductase; 1,2,3,4,13,14-hexahydro-IV (1) and 1-methyl-1,2,3,4-tetrahydro-XII (1) were inactive against P-388 and against dihydrofolate reductase.

Structures of Silver Sulfonamides

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Received June 7, 1976, from the *Laboratory for Pharmaceutical and Analytical Chemistry, State University of Groningen, Antonius Deusinglaan 2, Groningen 8004, The Netherlands.* Accepted for publication May 24, 1977.

Abstract □ The structures of silver sulfonamides were found to depend highly on the substituent at the amide nitrogen of the sulfonamide. Silver is coordinated to that nitrogen and the sulfonamide is in the amido form if no substituent is present or if the substituent is a phenyl, acetyl, or 2-pyrimidyl group. If the substituent is a 2-thiazolyl or 2-pyridinyl group, the sulfonamide is in the imido form and silver coordinates to the nitrogen of the substituent. Depending on the number of suitable donor atoms per sulfonamide, the silver compounds are charged or uncharged and the primary amino group may be involved in complexation.

Keyphrases □ Silver—coordinating properties with various sulfonamides, structures of complexes studied □ Sulfonamides, various—coordination with silver, structures of complexes studied □ Complexes—various silver sulfonamides, coordination properties and structures studied □ Anti-infectives, topical—various silver sulfonamides, coordination properties and structures studied

Interest in silver sulfadiazine as an antibacterial agent in the treatment of extensive burns has increased steadily. IR (1) and NMR (1) studies as well as X-ray analysis (2, 3) of the structure of silver sulfadiazine have been reported. The bactericidal action *in vivo* of silver sulfadiazine is superior to the related silver sulfonamides. Because the