with 2*N* HCl, concentrated *in vacuo* and water was added. The crystals which separated were collected and recrystallized from water with charcoal treatment giving 0.17 g. (38.4%) of colorless needles and 0.05 g. (total yield 50%) of a second crop, m.p. 246~247°. *Anal.* Calcd. for $C_5H_7ON_3 \cdot 2H_2O$: C, 33.90; H, 6.26; N, 23.72. Found : C, 34.28; H, 6.17; N, 24.07. The water of crystallization was eliminated after drying at 120~130° in vacuum and the anhydrous material melted at 252~253°. *Anal.* Calcd. for $C_5H_7ON_3$: C, 42.55; H, 5.00; N, 29.78. Found : C, 43.19; H, 5.32; N, 29.79.

ii) A solution of 2 g. of 1-methyl-3-methoxy-4-amino-6(1*H*)pyridazinone (V) and 3.6 g. of KOH (purity 85%) in 30 ml. of MeOH was heated in an autoclave at 155~160° for 10 hr. The solvent was removed by distillation, and the residue was taken up in small quantity of water and separated were collected and recrystallized repeatedly from water giving 1.51 g. (80%) of Ⅳ, m.p. 245~246°, and 0.13 g. (7%) of the second crop, m.p. 243.5~246°, both as colorless needles. Further recrystallization raised m.p. to 246~247°, undepressed when admixed with a sample prepared from Ⅲd. The IR spectra of the two samples were also identical.

The authors express their deep gratitude to Prof. Emeritus E. Ochiai of the University of Tokyo for his kind encouragements throughout the course of the present work. They are also indebted to Mr. M. Chikada and T. Kobayashi for their cooperation in this work, and to Mr. K. Iwai, Mr. N. Nishimura and Miss. M. Fujita for the elementary analysis.

Summary

4-Amino-3(2*H*)pyridazinone derivatives (Ia~Id) were methylated with dimethyl sulfate in aqueous sodium hydroxide solution, yielding 2-methyl compounds (Ⅱa~Ⅱd) and zwitterionic 1-methyl compounds (Ⅲa~Ⅲd). The position of the methyl group of these products (Ⅱ and Ⅲ) was unambiguously determined. The ratio of formation of both Ⅱ and Ⅲ in the methylation has been found to be markedly influenced by the substituent at adjacent 6-position.

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150. Ken'ichi Takeda, Taichiro Komeno, Shoichi Ishihara, and Hikaru Itani : Bile Acids and Steroids. XXXIV. Thiosteroids. (19).*1 6α- and 6β-Thiocyanato-progesterone and Related Compounds.

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A number of recently disclosed studies on steroidal 6-substituted 4-en-3-ones by means of NMR (nuclear magnetic resonance) spectroscopy and ORD (optical rotatory dispersion) measurements[1] prompted us to prepare 4-en-3-one substituted at C-6 with a pseudohalogen, especially a thiocyanato group, because the question has arisen whether or not the sign of the n-π^* Cotton effect of 6β-thiocyanato-4-en-3-one is

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*1 Thiosteroids. (18) : K. Kuriyama, T. Komeno, K. Takeda : Tetrahedron, **22**, 1039 (1966).

*2 Fukushima-ku, Osaka (武田健一, 米野太一郎, 石原照一, 井谷 光).

1) C. Djerassi, J. Osiecki, R. Riniker, B. Riniker : J. Am. Chem. Soc., **80**, 1216 (1958); C. Djerassi, O. Halpern, V. Halpern, B. Riniker : *Ibid.*, **80**, 4001 (1958); A. Bowers, M. B. Sánchez, H. J. Ringold : *Ibid.*, **81**, 3702 (1959); A. Bowers, E. Denot, R. Becerra : *Ibid.*, **82**, 4007 (1960); W. B. Whalley : Chem. & Ind. (London), **1962**, 1024; K. Tori, K. Kuriyama : *Ibid.*, **1963**, 1525; D. J. Collins, J. J. Hobbs, S. Sternhell : Tetrahedron Letters, **1963**, 197; T. S. Wittstruck, S. K. Malhotra, H. J. Ringold : J. Am. Chem. Soc., **85**, 1699 (1963); Y. Kondo, T. Takemoto, K. Yasuda : This Bulletin, **12**, 976 (1964); Y. Kondo, K. Kondo, T. Takemoto, K. Yasuda, G. Snatzke : Tetrahedron, **21**, 1191 (1965).

positive like that of 6β-acetylthio-4-en-3-one.[2] Therefore we attempted to synthesize 6α- and 6β-thiocyanatoprogesterone, and also to anticipate their physiological activities.

An intermediate, 5α-hydroxy-6β-thiocyanato-5α-pregnane-3,20-dione (Ⅲ), was synthesized through the following two routes. a) Treatment of 3β-hydroxy-5α-pregnan-20-one 5α-,6α-oxide (Ⅰ)[3] with thiocyanic acid,[4] followed by oxidation with chromic anhydride. b) Treatment of 3,3,20,20-bisethylenedioxy-5α-pregnane 5α,6α-oxide (Ⅳ)[5] with thiocyanic acid, followed by hydrolysis with aqueous acetic acid. In the latter case it is noteworthy that the bisketal oxide (Ⅳ) was converted to 3-monoketal (Ⅴ) with thiocyanic acid. The structure of the compound (Ⅴ) was confirmed from the NMR spectrum in which the signal of C-21 methyl group appears at a normal position, 7.87τ.

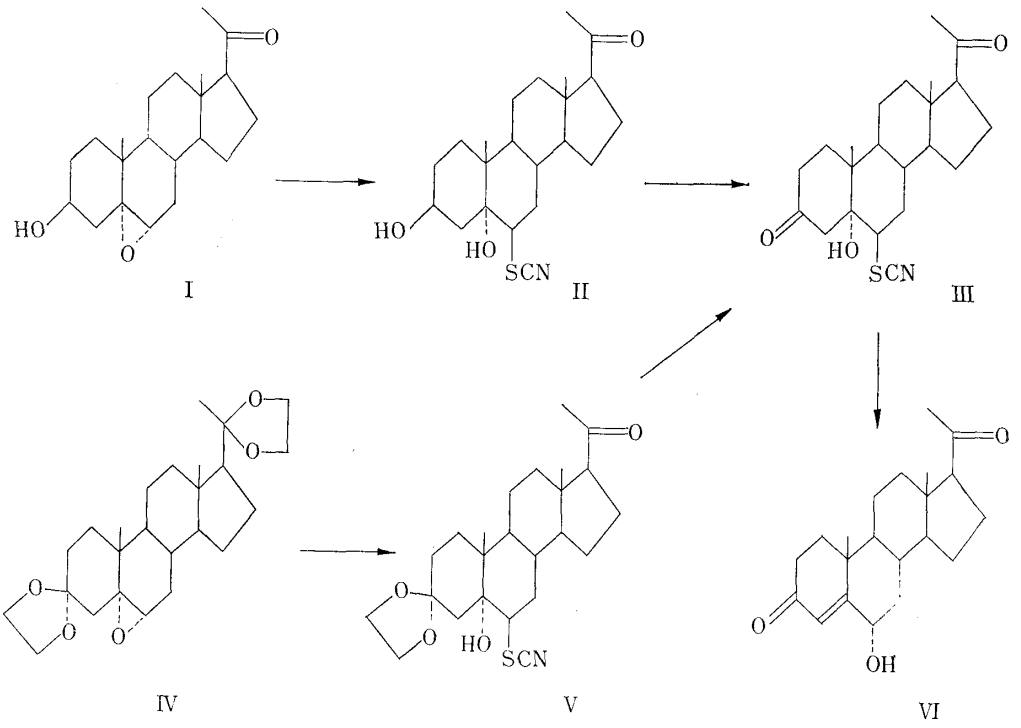

Chart 1.

We were interested in the behavior of the compound (Ⅲ) against base from the reason why it might be expected to give 3,20-dioxo-6-thione. When the compound was treated with sodium methoxide at room temperature in methanol, the product isolated in 74% yield was a hydroxyendione, 6α-hydroxyprogesterone (Ⅵ), which was established by mixed melting point and comparison of infrared spectrum with the authentic sample prepared by Ehrenstein's description.[6] It is assumed that this stereospecific reaction proceeds *via* an epoxydione by the following mechanism, although such an intermediate could not be isolated. However the similar result was available in the literature, in which Gardi and Pedrali[7] reported that 5α-hydroxy-6β-bromo-19-norandrostane-3,17-dione was converted to 6α-hydroxy-19-norandrost-4-ene-3,17-dione by treatment with potassium acetate in acetone.

2) K. Takeda, T. Komeno, S. Ishihara: This Bulletin, **11**, 500 (1963).
3) Y. Urushibata, M. Chuman, S. Wada: Bull. Chem. Soc. Japan, **24**, 83 (1951).
4) Ring-opening of 3β-hydroxycholestan-5α,6α-oxide with thiocyanic acid; T. Komeno: This Bulletin, **8**, 672 (1960).
5) G. Cooley, B. Ellis, D.N. Kirk, V. Petrow: J. Chem. Soc., **1957**, 4112.
6) C.P. Balant, M. Ehrenstein: J. Org. Chem., **17**, 1587 (1952).
7) R. Gardi, C. Pedrali: Steroids, **2**, 387 (1963).

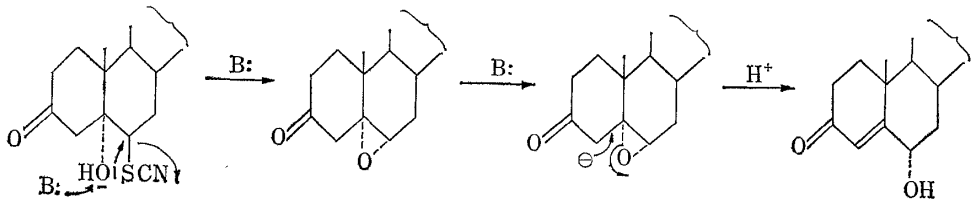

Chart 2.

Whilst dehydration of 5α-hydroxy-6β-acetylthio-3-one with thionyl chloride and pyridine at 0°[2] was performed in a few minutes, longer reaction time (about 30~60 minutes) was required for dehydration of the 5α-hydroxy-6β-thiocyanato-3-one (Ⅲ) under the same conditions and there was obtained 6β-thiocyanatoprogesterone (Ⅶ) in an appropriate yield. On the other hand, dehydration of the compound (Ⅲ) with hydrochloride in acetic acid gave a complicated mixture, from which 23.4% of a $C_{22}H_{30}O_2NSCl$ substance (Ⅷ) and 17.2% of 6α-thiocyanatoprogesterone (Ⅸ) were separated by column chromatography. The latter compound was further obtained in a higher yield from the conversion of 6β-thiocyanatoprogesterone (Ⅶ) to enolether (Ⅹ), followed by hydrolysis with aqueous acetic acid.[8] The physical properties of 6α- and 6β-thiocyanatoprogesterone were listed in Table I and support their assigned configuration.

Table I. The Physical Properties of 6α- and 6β-Thiocyanatoprogesterone

		6α-Thiocyanatoprogesterone (Ⅸ)	6β-Thiocyanatoprogesterone (Ⅶ)
m.p.		133~135°	165~167°
$[\alpha]_D$ in $CHCl_3$		+162°	+126°
UV λ_{max}^{EtOH} mμ (ε)		236.5 (13,470)	243 (13,540)
IR $\nu_{max}^{CHCl_3}$ cm^{-1}		2179, 1701, 1687, 1622	2166, 1700, 1680, 1612
NMR	18-H	9.32	9.28
(τ)	19-H	8.76	8.56
in $CDCl_3$	21-H	7.87	7.87
	6-H	5.93 octet ($J_{6\beta-H:4-H}\approx 1.8$ c.p.s., $J_{6\beta-H:7\beta-H}\approx 5.0$ c.p.s., $J_{6\beta-H:7\alpha-H}\approx 12.5$ c.p.s.)	5.55 multiplet ($W_H\approx 6.0$ c.p.s.)
	4-H	3.83 doublet	4.03 singlet
CD $[\theta]_{max}$ in dioxane		−4305 (339 mμ)	+3877 (355 mμ)

As is to be expected, CD curves of both compounds indicate the same relationship as observed in the acetylthio compounds. Furthermore UV maximum of 6β-thiocyanato compound is shifted by 6.5 mμ to longer waves than that of 6α-isomer, while only 2 mμ shift value was observed in the UV spectra of 6-acetylthio compounds.

The infrared spectrum of the former (Ⅷ) exhibited an absorption band caused by a saturated ketone at 1705 cm^{-1} and an intense band due to C=N bond at 1575 cm^{-1}. From the data it is assumed that the compound was 2-chloro-2-thiazoline derived from 6α-thiocyanatoprogesterone (Ⅸ) by additon of a chlorine anion to the thiocyanato group, followed by Michael-type addition of the newly-formed nitrogen anion to the α,β unsaturated ketone. Similar Michael-type addition of the nitrogen anion formed by attack of methoxyl anion to a thiocyanato group was reported by NIH group[9] in the

8) Collins, *et al.* reported that 6α-bromocholestenone could not be obtained purely from epimerization of 6β-bromocholestenone with acid but that the pure compound was prepared *via* enolether of the 6β-bromo compound. D. J. Collins, J. J. Hobbs: Australian J. Chem., **16**, 874 (1963).

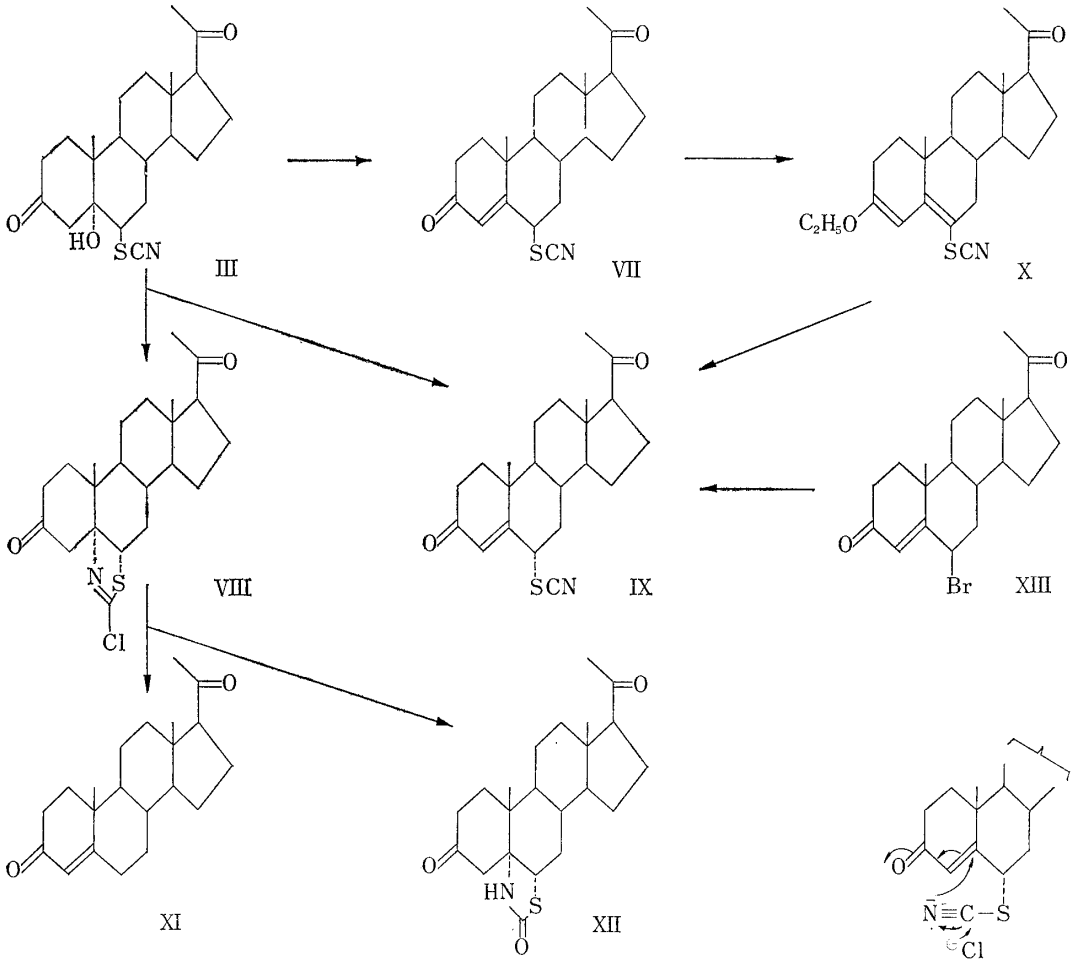

Chart 3.

case of 9α-thiocyanatoandrost-4-ene-3,11,17-trione. The configuration assigned as 5α,6α is further supported by the ORD curves of the compound (Ⅷ), in which a positive Cotton effect at 300 mμ and a negative one at 250 mμ were observed. The former is related with n-π^* transition of carbonyl groups and indicates that the sign of the Cotton effect due to 3-ketone is positive and that the octant diagram is in agreement with that having 5α,6α-configuration as shown Fig. 1. The second Cotton effect is presumably related with an azomethine group observed recently by Snatzke[10] and the chilarity of the thiazoline is in accord with those proposed by Snatzke.

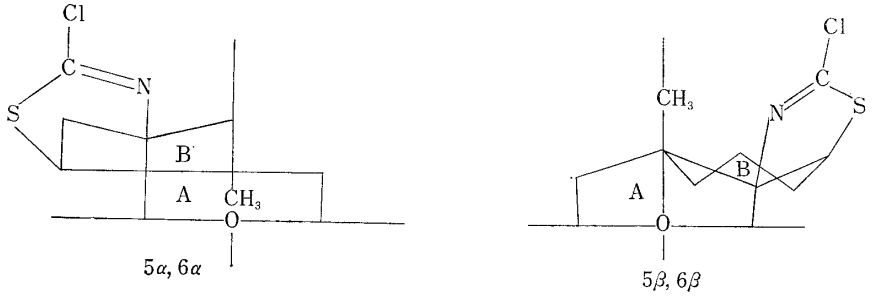

Fig. 1. Octand Diagram of the Compound (Ⅷ)

9) I. Kitagawa, Y. Ueda, T. Kawasaki, E. Mosettig : J. Org. Chem., **28**, 2228 (1963).
10) H. Ripperger, K. Schreiber, G. Snatzke : Tetrahedron, **21**, 1027 (1965).

Chemical evidence of this structure was obtained from the reaction with zinc dust and acetic acid, in which 31.9% of progesterone (XI) and 46.7% of a $C_{22}H_{31}O_3NS$ substance (XII) were isolated by alumina column chromatography of the products. It is profitable to consider that the formation of progesterone proceeds by the reverse Michael reaction.

The infrared spectrum of the $C_{22}H_{31}O_3NS$ compound shows two bands due to a NH group at 3403 and 3207 cm^{-1} and a band characteristic of a lactam group at 1674 cm^{-1} besides a carbonyl band at 1700 cm^{-1}. Furthermore the NMR spectrum exhibits a NH proton at 2.60 τ and 6β-proton as multiplets ($W_H \approx 24$ c.p.s.) at 6.64 τ. Hence, it is presumable that the compound is 2-oxo-thiazoline.

More facile preparation of 6α-thiocyanatoprogesterone was achieved by SN-2 substitution of 6β-bromoprogesterone with thiocyanate ion in dimethylformamide or in acetonitrile.

Experimental*3

6β-Thiocyanato-3β,5α-dihydroxy-5α-pregnan-20-one (II)——To a mixture of KSCN (30 g.) dissolved in a small volume iced water and ether (100 ml.), H_3PO_4 (45 g.) was added in small portions and shaken to move formed free HSCN to ether. The pink-colored HSCN solution was dried (Na_2SO_4) and added to a solution of pregnenolone 5α,6α-oxide (I) (9.50 g.) in CH_2Cl_2 (100 ml.). The reaction mixture was allowed to stand overnight at room temp. The solution was diluted with ether, washed with Na_2CO_3 solution and water, dried (Na_2SO_4), and evaporated to dryness *in vacuo*. Recrystallization of the resulting residue from acetone–hexane gave II (9.54 g.), m.p. 192~194°. $[\alpha]_D^{23.0}$ −43.9±2°(c=0.940). *Anal.* Calcd. for $C_{22}H_{33}O_3NS$: C, 67.48; H, 8.50; N, 3.58; S, 8.19. Found: C, 67.28; H, 8.47; N, 3.51; S, 8.64. IR ν_{max}^{Nujol} cm^{-1}: 3510, 3380, 2148, 1708, 1082, 1038, 1004.

5α-Hydroxy-6β-thiocyanato-5α-pregnane-3,20-dione (III)——a) From 6β-thiocyanato-3β,5α-dihydroxy-5α-pregnan-20-one (II): To a stirred solution of II (9.30 g.) in AcOH (200 ml.) a solution of CrO_3 (2.0 g.) in 50% AcOH (20 ml.) was added slowly during 1 hr. The reaction mixture was further stirred at room temp. for 4 hr. and poured into iced water. The precipitate was collected by filtration, washed with water, dried, and recrystallized from CH_2Cl_2–MeOH to yield III (7.92 g.) as prisms, m.p. 213~215°. $[\alpha]_D^{23.5}$ −58.5° (c=1.018). *Anal.* Calcd. for $C_{22}H_{31}O_3NS$: C, 67.83; H, 8.02; N, 3.60; S, 8.23. Found: C, 68.14; H, 8.11; N, 3.70; S, 8.02. IR ν_{max}^{Nujol} cm^{-1}: 3302, 2146, 1720, 1689.

b) From 5α-hydroxy-6β-thiocyanato-3,3-ethylenedioxypregnan-20-one (V): 3,3,20,20-Bisethylenedioxy-5α-pregnane 5α,6α-oxide (IV) (4.630 g.) was treated with HSCN-solution as described in preparation of II. The crude product was dissolved in 80% AcOH (100 ml.) and warmed on a steam bath for 30 min. To the mixture water was added after cooling. The precipitate was collected by filtration, dried, and recrystallized from CH_2Cl_2–MeOH to give III (3.927 g.) as prisms.

5α-Hydroxy-6β-thiocyanato-3,3-ethylenedioxy-5α-pregnan-20-one (V)——3,3,20,20-Bisethylenedioxy-5α-pregnane 5α,6α-oxide (IV) (1.400 g.) was treated with HSCN-solution as described in preparation of II. The product was recrystallized from acetone–hexane to give V (1.20 g.) as needles, m.p. 169~171°(decomp.), $[\alpha]_D^{23.5}$ −53.9±2°(c=1.037). *Anal.* Calcd. for $C_{24}H_{35}O_4NS$: C, 66.48; H, 8.14; N, 3.23; S, 7.40. Found: C, 66.88; H, 8.23; N, 3.25; S, 7.59. IR ν_{max}^{Nujol} cm^{-1}: 3474, 3322, 2164, 1700, 1102. NMR (τ): (18-H) 9.35, (19-H) 8.97, (21-H) 7.87, (ketal-H) 6.02.

Treatment of 5α-Hydroxy-6β-thiocyanato-5α-pregnane-3,20-dione with Sodium Methoxide——To a suspension of 5α-hydroxy-6β-thiocyanato-5α-pregnane-3,20-dione (III) (488 mg.) in abs. MeOH (14 ml.) powdered NaOMe (212 mg.) was added and the mixture was stirred at room temp. for 4 hr. The resulting yellow solution was poured into water and extracted with CH_2Cl_2. The extract (461 mg.) was crystallized from ether to yield crystals, which were further recrystallized from acetone–hexane to yield 6α-hydroxyprogesterone (VI) (306 mg.) in 74% yield, m.p. 211~213°, $[\alpha]_D^{25.5}$ +179.6±2° (c=1.098). *Anal.* Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.33; H, 9.11. IR ν_{max}^{Nujol} cm^{-1}: 3605, 1707, 1660, 1612. UV λ_{max}^{EtOH} 241.5 mμ (ε 15,530). NMR (τ): (18-H) 9.33; (19-H) 8.81; (21-H) 7.88; (6β-H) 5.68 multiplet,*4 (4-H) 3.82 doublet (J=2.0 c.p.s.) (Reported[6] m.p. 192~193°, $[\alpha]_D$ +150°).

*3 All melting points were determined on a Kofler block and are uncorrected. Optical rotations were measured in $CHCl_3$ unless mentioned otherwise, using a Rudolf Photoelectronic Polarimeter, model 200, and ORD curves were taken with a Rudolf automatic recording spectropolarimeter. The UV absorption spectra were measured with a Hitachi Recording UV spectrophotometer, EPS-2, and the IR spectra were taken with a Koken IR spectrophotometer, Model DS-301. The NMR spectra were run in deuteriochloroform solution with a Varian A-60 spectrometer, tetramethylsilane serving as internal standard.

6β-Thiocyanatoprogesterone (VII)——To a stirred solution of 5α-hydroxy-6β-thiocyanato-5α-pregnane-3,20-dione (III) (1.125 g.) in anhydrous pyridine (15 ml.) $SOCl_2$ (800 mg.) was added dropwise at 0° for 5 min. The reaction mixture was further agitated for 30 min. and poured into iced water. The precipitate was collected by filtration, washed with water, dried, and recrystallized twice from acetone-hexane to yield VII (858 mg.) as plates, m.p. 165~167°, $[\alpha]_D^{23}$ +125.6±2°(c=1.013), *Anal.* Calcd. for $C_{22}H_{29}O_2NS$: C, 71.12; H, 7.87; N, 3.77; S, 8.63. Found: C, 71.29; H, 7.98; N, 3.76; S, 8.73. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2166, 1700, 1680, 1612. UV λ_{max}^{EtOH} 243 mμ (ε 13,540), infl. at 284 mμ (ε 2,080). CD (in dioxane) $[\theta]_{405}$ 0, $[\theta]_{355}^{max}$ +3877, $[\theta]_{328}^{min}$ +2053, $[\theta]_{299}^{max}$ +9692, $[\theta]_{280}$ 0. ORD (in dioxane) $[\phi]_{390}^{inf.}$ +3041, $[\phi]_{378}^{max}$ +3179, $[\phi]_{363}^{inf.}$ +1797, $[\phi]_{345}^{inf.}$ +346, $[\phi]_{337}^{min}$ +207, $[\phi]_{319}^{max}$ +2695, $[\phi]_{290}$ −7878.

Treatment of 5α-Hydroxy-6β-thiocyanato-5α-pregnane-3,20-dione (III) with Hydrochloric Acid——Into a suspension of 5α-hydroxy-6β-thiocyanato-5α-pregnane-3,20-dione (III) (2.566 g.) in AcOH (70 ml.) dry HCl gas was bubbled for 2.5 hr. under cooling. The clear solution was poured into iced water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with water, Na_2CO_3 solution, and again water, dried (Na_2SO_4), and evaporated *in vacuo* to dryness. Crystallization of the residue from acetone-ether afforded crystals (VIII) (360 mg.), m.p. 170~173°(decomp.). The mother liquor was evaporoted to dryness, dissolved in benzene, and chromatographed over Florisil (50 g.). The material eluted with benzene-CH_2Cl_2 (1:1) and only CH_2Cl_2 was collected and recrystallized from acetone-hexane to give the same crystals (VIII) (254 mg.). Combined yield of VIII, 614 mg., 23.4%, m.p. 172~174°(decomp.), $[\alpha]_D^{23.5}$ −120.8±2°. *Anal.* Calcd. for $C_{22}H_{30}O_2NSCl$: C, 64.84; H, 7.41; N, 3.43; S, 7.86; Cl, 8.69. Found: C, 65.09; H, 7.47; N, 3.57; S, 8.08; Cl, 8.42. IR ν_{max}^{Nujol} cm^{-1}: 1705, 1577, 964. $\nu_{max}^{CHCl_3}$ cm^{-1}: 1719 (sh.), 1701, 1575, 967. UV λ_{max}^{EtOH} mμ (ε): 206 (1,680), 237 (2,030), 253 (2,090). λ_{min}^{EtOH} mμ (ε): 216.5 (1,000), 244.5 (1,960). NMR (τ): (18-H) 9.36; (19-H) 8.83; (21-H) 7.88; (6β-H) 6.41 multiplet (W_H 24 c.p.s.). ORD (in MeOH): $[\phi]_{700}$ −347, $[\phi]_{360}$ −1175, $[\phi]_{310}^{max}$ +3070, $[\phi]_{267}^{min}$ −38700, $[\phi]_{241}^{max}$ +12700, $[\phi]_{235}$ +5300.

The material (679 mg.) eluated with CH_2Cl_2 and CH_2Cl_2-ether (9:1~1:1) was crystallized from ether to yield 6α-thiocyanatoprogesterone (IX) (410 mg., 17.2%), m.p. 133~135°. This substance was identified by mixed melting point and comparison of the infrared spectrum with the compound obtained *via* enol ether (X) described below.

3-Ethoxy-6-thiocyanatopregna-3,5-dien-20-one (X)——To a solution of 6β-thiocyanatoprogesterone (VII) (202 mg.) in anhydrous benzene (20 ml.), abs. EtOH (0.6 ml), ethyl orthoformate (0.6 ml.), and pyridine-HCl salt (30 mg.) were added. The resulting solution was heated under reflux for 1 hr., cooled, poured into iced Na_2CO_3 solution, and extracted with ether-CH_2Cl_2 (4:1). The extract was washed with water, dried (Na_2SO_4), and evaporated to dryness *in vacuo*. The residue was dissolved in petr. ether-benzene (1:1) and chromatographed over Al_2O_3 (5 g.). The material eluted with petr. ether-benzene (1:1~1:2) was recrystallized from MeOH to yield X (165 mg.), m.p. 146~147°, $[\alpha]_D^{23.5}$ −148.7±2°(c=1.066). *Anal.* Calcd. for $C_{24}H_{33}O_2NS$: C, 72.14; H, 8.33; N, 3.51; S, 8.03. Found: C, 72.40; H, 8.42; N, 3.67; S, 8.30. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2151, 1697, 1634. UV λ_{max}^{EtOH} 264.5 mμ (ε 20,500).

6α-Thiocyanatoprogesterone (IX)——a) From enol ether (X): i) A solution of enol ether (X) (50 mg.) and oxalic acid (51 mg.) in 90% acetone (5 ml.) was stirred at 25° for 2 hr. and treated to yield completely recovered enol ether (X). ii) A solution of enol ether (X) (1.085 g.) in 80% AcOH (12 ml.) was warmed on a steam bath for 30 min., poured into water, and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with water, Na_2CO_3 solution, and water, dried (Na_2SO_4), and evaporated to dryness. The residue (882 mg.) was crystallized from ether and recrystallized twice from acetone-hexane to yield 6α-thiocyanatoprogesterone (IX) (450 mg.), m.p. 133~135°. $[\alpha]_D^{23.5}$ +161.6±2°(c=1.074). *Anal.* Calcd. for $C_{22}H_{29}O_2NS$: C, 71.12; H, 7.87; N, 3.77; S, 8.63. Found: C, 71.31; H, 8.11; N, 3.81; S, 8.40. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2179, 1701, 1687, 1622. UV λ_{max}^{EtOH} 236.5 mμ (ε 13,470). CD (in dioxane): $[\theta]_{385}$ 0, $[\theta]_{364}^{inf.}$ −1107, $[\theta]_{350}^{inf.}$ −3075, $[\theta]_{339}^{min}$ −4305, $[\theta]_{330}^{inf.}$ −3690, $[\theta]_{314}^{inf.}$ +2337, $[\theta]_{295}^{max}$ +11193. ORD (in dioxane): $[\phi]_{392}^{max}$ +1752, $[\phi]_{376}^{min}$ +1491, $[\phi]_{367}^{max}$ +1714, $[\phi]_{361}^{min}$ +1677, $[\phi]_{347}^{inf.}$ +3802, $[\phi]_{336}$ +7156, $[\phi]_{305}^{max}$ +16321.

b) From 6β-bromoprogesterone (XIII): i) 6β-Bromoprogesterone (XIII) (423 mg.) and KSCN (500 mg.) were dissolved in dimethylformamide (10 ml.). The reaction mixture was stirred for 6 hr. at room temp., poured into water, and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with water, dried (Na_2SO_4), and evaporated to dryness. Crystallization of the residue from ether afforded 158 mg. of IX, m.p. 130~133°. ii) Bromo compound (XIII) (675 mg.) and KSCN (1.0 g.) were dissolved in acetonitrile (10 ml.). The mixture was agitated for 4 hr. at 45° and working up as above gave 365 mg. of IX, m.p. 130~133°. In each case, the product was identified by mixed melting point and comparison of the infrared spectrum with the authentic sample.

Reduction of 2-Chloro-2-thiazolino Compound (VIII) with Zinc Dust and Acetic Acid——A solution of 2-chloro-2-thiazoline compound (VIII) (614 mg.) in acetic acid (30 ml.) zinc dust (7.0 g.) was added. The stirred suspension was heated under reflux for 4 hr. After cooling, the mixture was poured into water and

*4 This unresolved multiplet was due to coupling with proton of the hydroxyl group. Addition of D_2O gave a clear spectrum, in which 6β-proton appeared as clear-cut eight lines. (apparent $J_{6\beta\text{-H}:7\beta\text{-H}}$=5.0 c.p.s., $J_{6\beta\text{-H}:7\alpha\text{-H}}$=12.0, $J_{6\beta\text{-H}:4\text{-H}}$=2.0).

extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water, Na_2CO_3 solution, and water, dried (Na_2SO_4), and evaporated to dryness. Crystallization of the residue from ether gave 259 mg. of crystals, which were recrystallized from CH_2Cl_2-MeOH to yield 2-oxo thiazolino compound (XII), m.p. 291~293° (decomp.). $[\alpha]_D^{27}$ −6.6±2°(c=0.950). *Anal.* Calcd. for $C_{22}H_{31}O_3NS$: C, 67.83; H, 8.02; N, 3.60; S, 8.23. Found: C, 67.75; H, 8.11; N, 3.57; S, 8.23. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3403, 3207, 1700, 1674. UV λ_{max}^{EtOH} 280 mμ (ε 120). ORD (in dioxane): $[\alpha]_{700}$ +50, $[\alpha]_{375}$ +150, $[\alpha]_{316}^{peak}$ +1506, $[\alpha]_{270}^{inf.}$ −3500, $[\alpha]_{250}$ −5200. NMR (τ): (18-H) 9.36, (19-H) 8.85, (21-H) 7.88, (6β-H) 6.64 multiplet (W_H≈24 c.p.s.), (4-CH_2) AB type quartet at 6.65, 6.92, 7.38, and 7.65. $|J_{AB}|$≈16 c.p.s., (NH) 2.60.

The mother liquor was evaporated to dryness. The residue (273 mg.) was dissolved in benzene and chromatographed over Al_2O_3 (7 g.). The material eluated with benzene was crystallized from ether-petr. ether to give 151 mg. (31.9%) of progesterone, m.p. 120~122°. The eluate with benzene-ether (9:1) was crystallized from ether to yield 14 mg. of XII. Combined yield of XII, 273 mg., 46.7%.

We are indebted to Dr. Kuriyama for the measurements and discussion of ORD and CD curves and to Dr. Tori for the measurements of NMR spectra.

Summary

Dehydration of 5α-hydroxy-6β-thiocyanato-5α-pregnane-3,20-dione with hydrochloric acid and with sodium methoxide, respectively, was studied. The former reagent gave 6α-thiocyanatoprogesterone and 2-chloro-2-thiazolino compound, whilst sodium methoxide yields 6α-hydroxyprogesterone.

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151. Masayuki Ishikawa, Sachiko Yamada, Hiromichi Hotta, and Chikara Kaneko: Photochemistry of the N-Oxides of Azanaphthalene and Their Substituted Derivatives.*1

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As has been reported in our communication,[1] ultraviolet irradiation of quinaldine 1-oxide in methanolic solution gave rise to N-methylcarbostyril (I), 3-methylcarbostyril (II), and N-acetylindole (III), in respective yields of 16, 22, and 10% together with a small amount (less than 5%) of quinaldine. Considering this observation, together with our[1] and other experimental results[2] on the photochemical alteration of aromatic N-oxides to the corresponding amide-type compounds, we have postulated the mechanism shown in Chart 1 for the formation of these rearrangement products. Plausibility of the formation of three-membered ring intermediates such as IV in the photochemical alteration of aromatic N-oxides to the corresponding amide-type

*1 This work was presented at International Conference of Photochemistry, Tokyo (August, 1965). cf. p. 179 of its abstracts.

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