\[ \alpha \] = \pm 127.8^\circ (c = 0.53, \text{CHCl}_3), \text{die keine Absorption bei } 232 \text{ m}\mu \text{ mehr zeigten. } \text{C}_{23}\text{H}_{30}\text{O}_{11} - \text{Ber.: C, 57.25; H, 6.27. Gef.: C, 57.44; H, 6.47.} \\
Diese Substanz erwies sich durch Mischprobe und IR-Spektren als identisch mit dem Bisdesoxyaucubin-tetraacetat vom Schmp. 134–136\(^\circ\), welches aus Aucubin durch Reduktion mittels Li in flüssigem \( \text{NH}_2 \) und darauffolgender Acetylierung erhalten wurde.

Decarboxylierung des Bisdesoxydihydromonotropin-tetraacetats (IV) — Zu einer Lösung von 310 mg (N) in 4 ml Chinolin wurden 20 mg basisches Kupfercarbonat gegeben und unter Rückfluß bei einer Badtemperatur von 190–200\(^\circ\) 2 Stunden lang erhitzt. Nach der Aufarbeitung genauso wie oben erhielt man etwa 140 mg rohe Kristalle vom Schmp. 120–126\(^\circ\), die durch mehrmalsige Umlösungen aus \( \text{EtOH-} \text{H}_2\text{O} \) farblose Nadeln vom Schmp. 129–131\(^\circ\) und \( \alpha \) = \pm 156.09^\circ (c = 0.40, \text{CHCl}_3) \) ergaben. Im UV-Spektrum zeigt dieser Stoff keine Absorption bei 232 m\( \mu \) mehr. \text{C}_{23}\text{H}_{30}\text{O}_{11} - \text{Ber.: C, 57.01; H, 6.56. Gef.: C, 57.04; H, 6.86.}

Zum Schluß sind wir Herrn Dr. K. Konobu und seinen Mitarbeiterinnen im Mikroanalysenlaboratorium unseres Instituts für die Durchführung der Mikroanalysen zum Dank verpflichtet. Ebenso sprechen wir Herrn T. Shingü von unserem Institut für die Aufnahme der NMR-Spektren unseren Dank aus.

Zusammenfassung


(Eingegangen am 3. Februar 1964)

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(Shionogi Research Laboratory, Shionogi & Co., Ltd.

As a part of the investigation of thiosteroids,\(^\text{a}\) the synthesis of steroids having a sulfur atom at C-16 was undertaken. There have been several reports on the preparation of such steroids; 16\(\alpha\)-acetyltiosteroids\(^\text{b}\) were prepared by addition of thiolacetic acid to 16-ene-20-ketosteroids, and 16\(\beta\)-mercaptopisteroids\(^\text{c}\) were obtained by the ring-opening reaction of 16,17-epoxides by thiocyanic acid. In this paper the synthesis of 16\(\beta\)-acetyltio- and 16\(\beta\)-alkylthio-estrone derivatives by substitution reaction of 16-bromo-17-ketosteroids with sulfur nucleophiles is reported.

When 16\(\alpha\)-bromoestrone methyl ether\(^\text{d}\) (I) was treated with s-potassium thioacetate in acetone, a compound (II), m.p. 186–187\(^\circ\), was obtained in 88% yield. This compound

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\(^\text{b}\) Fukushima-ku, Osaka, Japan (武田薬——米野太一郎, 徳竹伯夫, 松本佳子).

2) T. Komeno : This Bulletin, 8, 680 (1960).
shows the characteristic absorptions of thioacetate at 1702 and 1127 cm\(^{-1}\) in its infrared spectrum. It is of interest to note that the compound (II) was also prepared from 16β-bromoestrone methyl ether\(^{4}\) (III) by similar treatment.

Reduction of II with lithium aluminum hydride, followed by treatment with acetone and p-toluenesulfonic acid gave an acetonide (IV), m.p. 169~170\(^{\circ}\), in 60\% yield, which showed absorptions at 1386 and 1367 cm\(^{-1}\) due to a gem-dimethyl group in its infrared spectrum.

Formation of the acetonide suggests that the aforementioned acetylthioketone (II) has 16β-configuration, since it is well known that lithium aluminum hydride reduction of steroidal 17-ketones almost exclusively affords 17β-ol derivatives.\(^5\)

When bromoketone (I) was treated with potassium ethylmercaptide in acetone, 16β-ethylthioestrone methyl ether (VA), m.p. 127.5–128.5⁰, was obtained in 72% yield. The configuration at C-16 of this compound was inferred by analogy with the formation of the 16β-acetylisothio derivative (II) from I. Lithium aluminum hydride reduction of this ethylthioacetone gave 16β-ethylthioestradiol 3-methyl ether (VAa), m.p. 120–120.5⁰, in good yield. VAa gave an acetate (VAb), m.p. 82.5–83.5⁰, by acetylation with acetic anhydride and pyridine. Similar treatment of bromoketone (I) with potassium butylmercaptide afforded 16β-butylthioestrone methyl ether (Vb), m.p. 107.5–108.5⁰, which gave 16β-butylthioestradiol 3-methyl ether (VCc), m.p. 74.5–75.5⁰, with lithium aluminum hydride reduction.

We next examined the transformation of these alkylthiosteroids to 19-norsteroid derivatives. Wilds and Nelson\(^6\) reported that estradiol 3-methyl ether was reduced with lithium and ethanol in liquid ammonia to 1,4-dihydroestradiol 3-methyl ether (X) in a good yield. According to this method, the anisole (VAa) in anhydrous ether was reduced in liquid ammonia with lithium metal. After addition of lithium metal, the mixture was allowed to stand at the same temperature for twenty minutes, then absolute ethanol was added and the reaction mixture was worked up in the usual manner. However, the reduction product no longer has a sulfur atom in its molecule and its physical constants were in good agreement with the values for 1,4-dihydroestradiol 3-methyl ether (X) reported by Wilds and Nelson. The structure of this product (X) was confirmed by the following procedures. The product (X) was converted to 17β-hydroxy-5(10)-estren-3-one by treatment with cold methanolic hydrochloric acid, and was further isomerized into 19-nortestosterone by warming in the same acid.\(^9\) It was now established that the anisole (VAa) suffered reductive cleavage of the bond between C₄-S with simultaneous reduction of ring-A.

Conditions of the reaction of anisole (VAa) with lithium metal and ethanol in liquid ammonia without reductive cleavage of the C-S bond was then examined. It was ultimately proved that reduction of the anisole ring was accomplished slightly faster than reductive cleavage of the C-S bond. Thus, when the reaction was interrupted by adding ethanol within eight minutes after the addition of the ether solution of anisole (VAa), 16β-ethylthio-1,4-dihydroestradiol 3-methyl ether (VII) was obtained in nearly 75% yield. The reduction product (VII), m.p. 130.5–131⁰, showed characteristic bands at 1696 and 1670 cm⁻¹ due to the dihydroanisole ring in its infrared spectrum and no absorption at 278 and 286 mμ due to the anisole ring in its ultraviolet spectrum.

The dihydroanisole (VII) thus obtained was hydrolyzed to the 5(10)-estrenolone derivative (VII) by treatment with acids such as 0.1M oxalic acid or 0.5% methanolic hydrochloric acid at room temperature in yields above 70%.

By treatment of the dihydroanisole derivative (VII) with a stronger acid such as 2% methanolic hydrochloric acid on a steam bath, 16β-ethylthio-19-nortestosterone (Ka), m.p. 113–114⁰, was obtained. Similar treatment of the nonconjugated ketone (VIII) also afforded the same compound, which gave 17-acetate (Kb), m.p. 152.5–153.5⁰, by acetylation.

On the other hand, the lithium-ammonia reduction of 16β-butythio analog (Vc) to 16β-butythio-1,4-dihydroestradiol 3-methyl ether under the same condition as described above gave 1,4-dihydroestradiol 3-methyl ether (X) as a sole product.

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Experimental

16β-Acetylthioestrone Methyl Ether (II)—a) From 16β-bromoestrostene methyl ether\(^1\) (I): To a solution of 142 mg. of I in 6 ml. of dried Me\(_2\)CO, 80 mg. of KS\(_{2}\)Ac was added, and the suspension was stirred for 3.5 hr. at room temperature. After dilution with H\(_2\)O, the precipitate was collected by filtration and recrystallized from Me\(_2\)CO–MeOH (5:1) to 124 mg. of scales (II), m.p. 186–187°, \([\alpha]_D^20+154.9 \pm 2^\circ (c=1.053)\). UV \(\lambda_{max} \text{m}_{\mu} (\lambda): 223.5 (11280), 278.3 (2190), 286.5 (2080)\). IR \(\nu_{\max} \text{cm}^{-1}: 1754 (\text{C}=\text{O}), 1702, 1127 (\text{S}=\text{Ac})\). Anal. Caled. for C\(_{19}\)H\(_{20}\)O\(_{2}\): C, 70.35; H, 7.31; S, 8.94. Found: C, 70.34; H, 7.40; S, 8.94.

b) From 16β-bromoestrostene methyl ether\(^1\) (III): A solution of 24 mg. of III in 3 ml. of Me\(_2\)CO was treated with 15 mg. of KS\(_{2}\)Ac as described above to give 8 mg. of a compound. This compound was shown to be identical with the above sample (II) by mixed melting point determination and by comparison of IR spectrum.

3-Methoxy-16S, 17-O-isopropylidene-16β-mercapto-1,3,5(10)-estratrien-17α-ol (IV)—A solution of 2.0 g. of IV in 85 ml. of anhyd. tetrahydrofuran was added dropwise with stirring into a suspension of 1.0 g. of LiH\(_2\)O in 80 ml. of anhyd. Et\(_2\)O. After refluxing for 4 hr., the reaction mixture was treated as usual. The reduction product, 16β-mercaptoestradiol 3-methyl ether, 1.68 g. was dissolved in a mixture of 150 mg. of p-TsOH, 7 ml. of anhyd. Et\(_2\)O and 70 ml. of dried Me\(_2\)CO, and the mixture was heated under reflux for 4 hr. One hundred and sixty-one milligrams of a by-product, m.p. 284–285° (decomp.), separated and was filtered off, and the filtrate was diluted with H\(_2\)O. The precipitate was collected by filtration, dried and chromatographed over Al\(_2\)O\(_3\). From the eluate of petr. ether–benzene (1:1), 1.20 g. of IV was isolated as needles, m.p. 169–170°, as recrystallized from Me\(_2\)CO, \([\alpha]_D^20+18.4 \pm 2^\circ (c=0.748)\). UV \(\lambda_{max} \text{m}_{\mu} (\lambda): 278.5 (2150), 287 (1970)\). IR \(\nu_{\max} \text{cm}^{-1}: 1384, 1367 (\text{CM}=\text{S})\). Anal. Caled. for C\(_{23}\)H\(_{24}\)O\(_2\): C, 73.71; H, 8.44; S, 8.92. Found: C, 74.03; H, 8.57; S, 8.34.

16β-Ethylthioestrone Methyl Ether (Va)—To a solution of 728 mg. of I in 28 ml. of dried Me\(_2\)CO, 300 mg. of KSeI was added with stirring at room temperature. After 40 min., the reaction mixture was diluted with H\(_2\)O and extracted with Et\(_2\)O. The Et\(_2\)O solution was washed with 5%aq. NaOH and H\(_2\)O, dried over K\(_2\)CO\(_3\) and evaporated in vacuo. The oily residue was solidified by trituration with a small amount of Et\(_2\)O to 385 mg. of yellow powder, which was crystallized from Et\(_2\)O to 237 mg. of Va, m.p. 120°. The mother liquor was evaporated to dryness and chromatographed over Al\(_2\)O\(_3\). The eluate of petr. ether–benzene (1:1) gave further 219 mg. of Va, which was recrystallized from Me\(_2\)CO to colorless plates, m.p. 127.5–128.5°, \([\alpha]_D^20+109.2 \pm 2^\circ (c=1.029)\). UV \(\lambda_{max} \text{m}_{\mu} (\lambda): 221 (8590), 278.5 (1930), 287 (1810), 322 (170)\). IR \(\nu_{\max} \text{cm}^{-1}: 1726 (\text{C}=\text{O}), \text{Anal. Caled. for } \text{C}_{23}\text{H}_{23}\text{O}_2\text{S}: C, 75.21; H, 8.22; S, 9.31\). Found: C, 72.84; H, 8.19; S, 9.34.

16β-Butylthioestrone Methyl Ether (Vb)—To a solution of 2 g. of I in 135 ml. of dried Me\(_2\)CO was added 1.2 g. of KSBu with stirring at room temperature. After 2 hr., the reaction mixture was worked up as described above. The product was chromatographed over 120 g. of Al\(_2\)O\(_3\). From the eluate of petr. ether–benzene (1:1) was obtained 1.37 g. of Vb, which was crystallized from MeOH to colorless prisms, m.p. 107.5–108.5°, \([\alpha]_D^20+94.4 \pm 2^\circ (c=1.044)\). UV \(\lambda_{max} \text{m}_{\mu} (\lambda): 221.6 (9490), 278 (2190), 287 (2020), 321 (190)\). IR: \(\nu_{\max} \text{cm}^{-1}: 1729 (\text{C}=\text{O})\). Anal. Caled. for C\(_{23}\)H\(_{23}\)O\(_2\): C, 74.15; H, 8.66; S, 8.61. Found: C, 74.26; H, 8.62; S, 8.70.

16β-Ethylthioestradiol 3-Methyl Ether (VIa)—A solution of 500 mg. of Va in 40 ml. of anhyd. tetrahydrofuran was added dropwise with stirring into a suspension of 250 mg. of LiAlH\(_4\) in 50 ml. of anhyd. Et\(_2\)O at room temperature. The mixture was heated under reflux for 2.5 hr., ice and 5%aq. Na\(_2\)CO\(_3\) were added, and extracted with Et\(_2\)O. After the Et\(_2\)O layer was treated in the usual manner, the product was recrystallized from MeOH to give 452 mg. of scales (VIa), m.p. 120–120.5°, \([\alpha]_D^20+35.3 \pm 2^\circ (c=0.961)\). UV \(\lambda_{max} \text{m}_{\mu} (\lambda): 279 (2110), 287 (1960)\). IR \(\nu_{\max} \text{cm}^{-1}: 3500–3460 (\text{OH})\). Anal. Caled. for C\(_{23}\)H\(_{22}\)O\(_2\): C, 72.78; H, 8.72; S, 9.25. Found: C, 73.02; H, 8.80; S, 9.19.

16β-Ethylthioestradiol 3-Methyl Ether 17-Acetate (VIIb)—A solution of 100 mg. of Va in 1 ml. of pyridine and 1 ml. of Ac\(_2\)O was heated under reflux for 2 hr., and worked up as usual. The product was recrystallized from Et\(_2\)O–MeOH to give 54 mg. of colorless prisms, m.p. 79–80.5°. By chromatography of the mother liquor and Al\(_2\)O\(_3\), a further 42 mg. of acetate, m.p. 77–80.5°, was obtained. Recrystallization from Me\(_2\)CO–hexane gave pure acetate (Vb) as colorless prisms, m.p. 82.5–83.5°, \([\alpha]_D^20+9.6 \pm 2^\circ (c=1.065)\). UV \(\lambda_{max} \text{m}_{\mu} (\lambda): 208 (24200), 279 (2120), 287.5 (1980)\). IR \(\nu_{\max} \text{cm}^{-1}: 1740 (\text{OAc})\). Anal. Caled. for C\(_{23}\)H\(_{23}\)O\(_3\): C, 71.10; H, 8.30; S, 8.33. Found: C, 71.10; H, 8.41; S, 8.28.

16β-Butylthioestradiol 3-Methyl Ether (Vlc)—A solution of 200 mg. of Vb in 20 ml. of anhyd. Et\(_2\)O was added with stirring into a suspension of 100 mg. of LiAlH\(_4\) in 10 ml. of anhyd. Et\(_2\)O, and

\(^*\) All melting points are uncorrected. IR spectra were measured with a Koken Infrared Spectrophotometer, Model DS-301, and UV spectra were taken in 95% EtOH with a Hitachi Recording Ultraviolet Spectrophotometer, EPS-2. Optical rotations were measured in CHCl\(_3\) solution with a Rudolf Photoelectric Polarimeter, Model-200.
refluxed for 3 hr. After treating the reaction mixture as described above, the product was recrystallized from Et$_2$O-hexane (1:3) to give 168 mg of scales, m.p. 74.5–75.5°C, [α]$_D^{28}$ +9.7±2° (c=1.024). UV $λ_{max}$ m$\mu$ (ε): 278.5 (2220), 287 (1070), 308 (38). IR: $ν_{max}$ cm$^{-1}$: 3440 (OH). Anal. Calcd. for C$_{37}$H$_{48}$O$_{5}$S: C, 73.75; H, 9.15; S, 8.56. Found: C, 73.56; H, 9.13; S, 8.56.

Reduction of Vla with Lithium in Liq. Ammonia — 16β-Ethylthio-1,4-dihydroestrodial 3-Methyl Ether (VII) — To a deep blue solution of 0.64 g. of Li in 80 ml of liq. NH$_3$, a solution of 0.4 g. of Vla in 92 ml of anhyd. Et$_2$O and 0.14 ml of abs. EtOH was added dropwise over a 5 min. period under cooling with dry ice-Me$_2$CO at −70°C. The reaction mixture was stirred for 5 min. and decolorized within 3 min. by addition of abs. EtOH. After evaporating most of the NH$_3$ and adding H$_2$O, the product was extracted with Et$_2$O, washed with 5% aq. KOH, H$_2$O, and dried over Na$_2$SO$_4$. The Et$_2$O solution was evaporated to dryness and the residue, m.p. 93–109°C, was recrystallized from Et$_2$O to give 0.30 g. of platelets (VI), m.p. 130.5–131°C, [α]$_D^{28}$ +46.9±2° (c=1.055). UV: no appreciable absorption was observed in the 230–290 m$\mu$ region. IR $ν_{max}$ cm$^{-1}$: 3530 (OH), 1696, 1670 (unconjugated dihydroisoandrosterone ring). Anal. Calcd. for C$_{37}$H$_{48}$O$_{5}$S: C, 72.36; H, 9.25; S, 9.18. Found: C, 72.30; H, 9.40; S, 8.76.

b) 1,4-Dihydroestrodial 3-Methyl Ether (X) — A solution of 0.8 g. of Vla in 180 ml of anhyd. Et$_2$O was added with stirring to 320 ml of liq. NH$_3$ under cooling with dry ice-Me$_2$CO at −70°C, and followed by the addition of 2.24 g. of Li in small pieces. The deep blue solution was stirred for 20 min. then, 75 ml of abs. EtOH was added to effect the excess of Li over a period of 20 min. The reaction mixture was treated as described above and the Et$_2$O solution was evaporated to dryness. The residue was recrystallized from Et$_2$O-EtOH to 0.43 g. of needles (X), m.p. 114–115°C, [α]$_D^{28}$ +110.2±2° (c=1.010). IR $ν_{max}$ cm$^{-1}$: 1695, 1664 (unconjugated dihydroisoandrosterone ring). Nitroprusside test for sulfur was negative.

Treatment of this compound with cold 0.5% HCl-MeOH gave 5(10)-estren-17β-ol-3-one, UV: $λ_{max}$ 282–287 m$\mu$ (ε 46). IR: $ν_{max}$ cm$^{-1}$: 1716 cm$^{-1}$, and further treatment with hot HCl-MeOH gave a compound, m.p. 125–125.5°C, underpressured by admixture with 19-nortestosterone, [α]$_D^{28}$ +55.7±2° (c=1.049). UV $λ_{max}$ m$\mu$ (ε): 241.3 (18400), 303–308 (380). IR $ν_{max}$ cm$^{-1}$: 1664, 1620 (J=4–3-ketone). Anal. Calcd. for C$_{19}$H$_{22}$O: C, 78.79; H, 9.55. Found: C, 78.73; H, 9.68.

Reduction of Vlc with Lithium in Liq. Ammonia — To a deep blue solution of 0.8 g. of Li in 80 ml of liq. NH$_3$, a solution of 0.54 g. of Vlc in 30 ml of anhyd. Et$_2$O and 0.1 ml of abs. EtOH was added dropwise over a period of 3 min. under cooling. After stirring the mixture for 2 min., the blue color of the solution was decolorized within 5 min. by addition of abs. EtOH. Treatment of the mixture as described above gave 0.49 g. of colorless oil (X), which showed absorptions at 1699 and 1666 cm$^{-1}$ due to the dihydroisoandrosterone ring in its IR spectrum, but had no sulfur atom in its molecule. By acid treatment, the product was converted to 19-nortestosterone, m.p. 124–125°C, underpressured by admixture with an authentic sample [α]$_D^{28}$ +54.6±2° (c=1.040). Anal. Calcd. for C$_{19}$H$_{22}$O: C, 78.79; H, 9.55. Found: C, 78.60; H, 9.43.

16β-Ethylthio-17β-hydroxy-5(10)-estren-3-one (VIII) — a) With 0.5% HCl-MeOH: To a solution of 800 mg. of Vlc in 207 ml of MeOH was added 23 ml of 5% HCl, and the mixture was allowed to stand at room temperature for 45 min. About 100 ml of the MeOH was removed below 35°C in vacuo, and H$_2$O was added. The precipitate was recrystallized from EtOAc to give 541 mg. of needles (VII), m.p. 112.5–113.5°C, [α]$_D^{23}$ +126.9±2° (c=1.069). UV $λ_{max}$ 282–284 m$\mu$ (ε 07). IR: $ν_{max}$ cm$^{-1}$: 1728 cm$^{-1}$. Anal. Calcd. for C$_{39}$H$_{48}$O$_{5}$S: C, 71.84; H, 9.04; S, 9.59. Found: C, 71.87; H, 8.97; S, 9.52.

b) With 0.1M oxalic acid: To a solution of 100 mg. of Vlc in 30 ml of MeOH, 460 mg. of (COO)$_3$H, 2H$_2$O in 6 ml of H$_2$O, and added the mixture was allowed to stand at room temperature for 1 hr. The product was extracted with Et$_2$O washed with aq. NaHCO$_3$, H$_2$O, and dried over Na$_2$SO$_4$. The Et$_2$O solution was evaporated to dryness in vacuo and 83 mg. of residue, m.p. 98–105°C, was recrystallized from EtOAc to give colorless needles (VII), m.p. 109–110°C.

16β-Ethylthio-19-nortestosterone (IXa) — a) From Vlc: To a solution of 108 mg. of Vlc in 16 ml of MeOH was added 4 ml of 10% HCl and the mixture was heated at 65°C for 10 min. The product was extracted with EtOAc washed with aq. NaHCO$_3$, H$_2$O, and dried over Na$_2$SO$_4$. The extract gave 78 mg. of oil, which was chromatographed over Al$_2$O$_3$. From the eluate of petr. ether–CHCl$_3$ (6:4), 68 mg. of crystal photographs were obtained. Recrystallization from Et$_2$O gave colorless plates (Ka), m.p. 113–114°C, [α]$_D^{25}$ −8.2±2° (c=1.017). UV $λ_{max}$ m$\mu$ (ε): 240 (17590), 310–312 (350). IR $ν_{max}$ cm$^{-1}$: 1663, 1618 (J=4–3-ketone). Anal. Calcd. for C$_{33}$H$_{38}$O$_{5}$S: C, 71.84; H, 9.04; S, 9.59. Found: C, 71.88; H, 9.12; S, 9.36.

b) From Vla: To a solution of 100 mg. of Vla in 12 ml of MeOH, 8 ml of 5% HCl was added and the mixture was treated as described above to give 65 mg of colorless plates (Ka), m.p. 112–113°C.

16β-Ethylthio-19-nortestosterone Acetate (IXb) — The above substance (Ka) was acetylated with pyridine-Ac$_2$O at room temperature overnight and the product was recrystallized from Me$_2$CO-hexane to give prisms (Kb), m.p. 152.5–153.5°C, [α]$_D^{25}$ +57.5±2° (c=1.04). UV: $λ_{max}$ 240.5 m$\mu$ (ε 19100). IR

$^{45}$ Wilds and Nelson$^6$ reported the following values for 1,4-dihydroestrodial 3-methyl ether (X): m.p. 118–119.5°C, [α]$_D^{25}$ +113.4±0.4° (c=1.13, CHCl$_3$), UV $λ_{max}$ 278 (2220), 320 (380), 358 (38). IR $ν_{max}$ cm$^{-1}$: 3380 (OH). Anal. Calcd. for C$_{37}$H$_{48}$O$_{5}$S: C, 73.75; H, 9.15; S, 8.56. Found: C, 73.56; H, 9.13; S, 8.56.

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Summary

Some 16β-acetylamthio and 16β-alkylthio estrones were prepared by substitution of 16-bromo-17-ketosteroids with sulfur nucleophiles. Both 16α- and 16β-bromoestrone methyl ether gave the same 16β-substituted product. Transformation of these alkylthio estrones into 19-norsteroid derivatives by lithium-ammonium reduction was studied.

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Diketene reacts easily with aromatic primary amine e.g. aniline, to give acetoacetanilide in a good yield.†‡ It has been also reported that aminoheterocycles such as 2-aminopyridine or 2-aminobenzothiazole react with diketene to yield their acetoacetates,§‖

On the other hand in the previous papers*§‖ of this series we reported that pyridine and quinoline reacted with diketene to give their diketene adducts, C_{12}H_{14}O_{2}N and C_{17}H_{15}O_{2}N, which were identified with so-called Wollenberg type compound*§‖ and that the reaction of quinoline 1-oxide with diketene was more complicated resulting in the formation of 2-methyl-6-[(2-quinolyl)methyl]-4H-pyran-4-one.

Interest in this laboratory has been focused on the reaction of aminopyridines and their N-oxides as to whether diketene reacts toward the amino function of pyridine according to the usual reaction reported as above*†‡ or toward C-N double bond in the pyridine ring as described in our previous papers.*§‖

* Kita-4, Sendai, Miyagi-ken (加藤鉄三, 山中宏, 新妻卓雄, 内田光吉, 大井雅子).
6 O. Wollenberg: Ber., 67, 1675 (1934).