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Steroid Xanthates and some Transformation Products thereof

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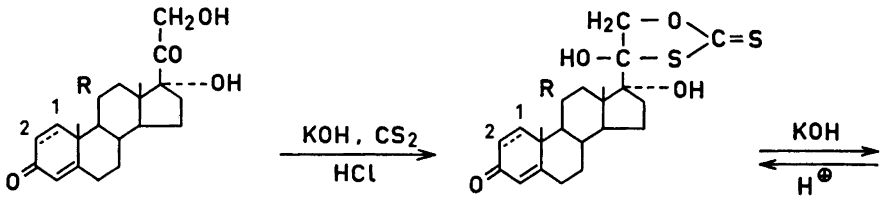
Treatment of steroids containing a ketol side chain such as hydrocortisone, prednisone, and prednisolone with carbon disulphide and potassium hydroxide affords the corresponding 21-potassium xanthates, which are transformed into derivatives of 1,3-oxathiolane-2-thione-4-ol upon acidification. The xanthates react with alkyl halides to yield S-alkyl xanthates.

Testosterone, upon treatment with carbon disulphide and potassium hydroxide, yields smoothly the 17-potassium xanthate, which with alkyl halides is converted to the corresponding S-alkyl xanthates. Oxidation of the potassium xanthate with iodine leads to the di-xanthate.

The need for water soluble derivatives of certain corticosteroids made the synthesis of 21-alkali xanthates of these compounds desirable. In the steroid series alkali xanthates and some S-alkyl derivatives have been prepared from cholesterol and cholestanol by action of carbon disulphide on the steroid alcoholates in benzene or toluene [1–5]. For various reasons, however, this method was not suitable for corticosteroids, and a method, in which the reaction was performed in a two phase system consisting of dioxan and aqueous potassium hydroxide was therefore worked out.

A chilled solution of hydrocortisone (Ia) in dioxan was stirred with aqueous potassium hydroxide while adding carbon disulphide. After acidification and extraction with ether a substance of the composition $C_{22}H_{30}O_5S_2 \cdot 3H_2O$ could be isolated from the organic phase. This substance, the structure of which, as shown below, may be represented by formula IIa, was in alcoholic potassium hydroxide solution transformed into a potassium salt, to which the structure IIIa has been assigned for the following reasons: The ultraviolet spectrum (in water) showed besides the Δ^4-3-keto band at 245 mμ a maximum at 304 mμ, which gradually disappeared upon storage of the solution, and which is characteristic of simple alkali xanthates [6,7]. The infrared spectrum (KBr) contained bands at 1 615 and 1 655 cm^{-1} (Δ^4-3-keto) and at 1 717 cm^{-1} (20-keto). Reaction of the potassium salt with methyl iodide in acetone yielded a compound

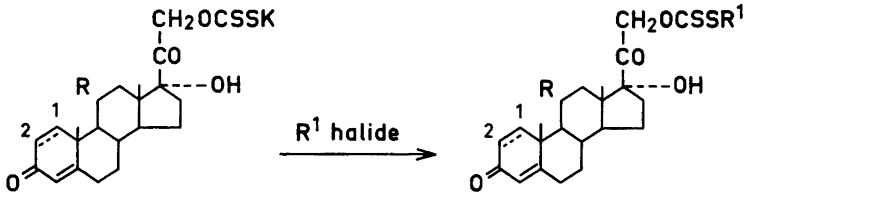


I a, b, c *II a, b, c*

a: R = H, OH(β)

b: Δ^1, R = O

c: Δ^1, R = H, OH(β)



III a, b, c

IV a, c: $R^1 = CH_3, CH_3(CH_2)_{11}$

IV b: $R^1 = CH_2{=}CHCH_2$, $CH_3(CH_2)_3$ *and* $CH_3(CH_2)_{11}$

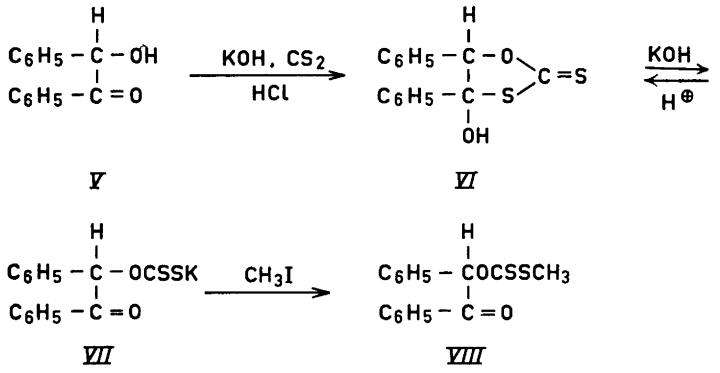
with an elementary analysis consistent with the 21-S-methyl xanthate formula (IVa, $R^1 = CH_3$) and an ultraviolet spectrum (ethanol) showing maxima at 239 mμ (Δ^4-3-keto) and 279 mμ. Simple S-alkyl xanthates are reported to absorb at the latter wave length [6,7]. The I.R. spectrum (KBr) contained bands at 1 617, 1 660 (Δ^4-3-keto), and 1 732 cm^{-1} (20-keto).

Upon acidification of an aqueous solution of IIIa followed by extraction with ether the above mentioned substance of the formula $C_{22}H_{30}O_5S_2 \cdot 3H_2O$ was obtained from the ether phase. The ultraviolet spectrum (λ_{max}^{EtOH} 240 mμ and 281 mμ *) was very similar to that of IVa, but in the infrared spectrum the 20-keto band was absent.

To obtain further information about the structure of this substance a similar series for reactions was performed with the simple α-ketol benzoin (V), in which the keto group constitutes a part of the chromophoric system. (λ_{max}^{EtOH} 245 mμ).

Treatment of a dioxan solution of V at room temperature with aqueous potassium hydroxide and CS_2 followed by acidification and extraction with

* Upon storage of the solution the maximum at 281 mμ gradually disappears.



ether afforded a substance of the formula $C_{15}H_{12}O_2S_2$. The ultraviolet spectrum (ether) contained only one maximum at 282 mμ, which is characteristic of the chromophoric system RO · C(=S)—C— found in S-alkyl xanthates[6,7]. This finding in connection with the elementary analysis and the absence of a carbonyl band in the infrared suggested the structure VI.

A Zerewitinoff determination of active hydrogen was in accordance with this formulation. In alcoholic potassium hydroxide VI was converted into the potassium xanthate VII (U.V. $\lambda_{max}^{H_2O}$ 249 mμ and 304 mμ; I.R. (KBr) 1 690 cm^{-1}), which upon acidification was reconverted to VI. Alkylation of VII with methyl iodide yielded the S-methyl xanthate (VIII). (U.V. λ_{max}^{EtOH} 249 and 280 mμ; I.R. (KBr) 1 681 cm^{-1}).

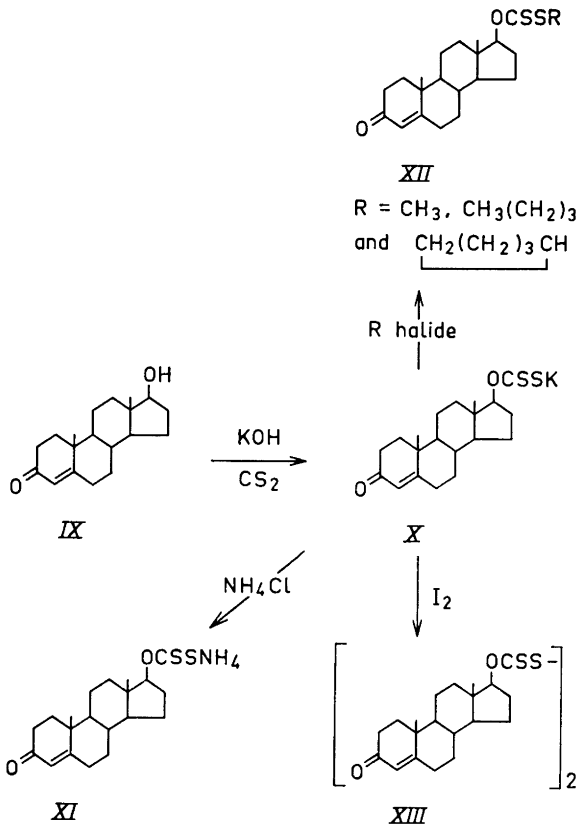
It will be seen, that the reactions of hydrocortisone and benzoin described above as well as the spectral data of the two series of reaction products are completely analogous and the assignment of the structure IIa to the product obtained by acidification of a solution of the 21-potassium xanthate of hydrocortisone seems therefore justified.

The same series of reactions were performed with two other steroids containing the α-ketol side chain, namely prednisone (Ib) and prednisolone (Ic).

A number of 21-S-alkyl xanthates of Ia, b and c, prepared by action of an appropriate alkyl halide on the corresponding 21-potassium xanthates, are listed in Table 1.

The 21-potassium xanthate of hydrocortisone as well as other salts, e.g. the diethanolamine salt, are soluble in water (5—7 %). In aqueous solution, however, the xanthates are rapidly decomposed with the formation of hydrocortisone, the halflife value at 37°C and pH 7.2 being about 15 min.

Treatment of testosterone (IX) in dimethylformamide with aqueous potassium hydroxide and CS_2 leads to the potassium xanthate (X), which is rather stable in aqueous solution, but is decomposed with the formation of testosterone upon acidification.



By action of alkyl halides on X the S-alkyl xanthates listed in Table 2 were obtained. Oxidation of X with iodine yielded the dixanthate XIII.

Biological properties. In adrenalectomized rats IIIa showed a glucocorticoid activity corresponding to that of hydrocortisone, when given intravenously *. The effect of intravenous administration of the corresponding diethanolamine salt in man has been investigated by Sprechler [8], and the topical use of these two salts in dermatology by Haxthausen [9,10]. X showed no androgenic activity in castrated male rats *.

EXPERIMENTAL

All melting points are uncorrected. Ultraviolet spectra were measured immediately after the preparation of the solutions.

17-(1,3-Oxathiolane-2-thione-4-ol-4-)androst-4-ene-3-one-11β,17α-diol (IIa). To a chilled solution of hydrocortisone (Ia) (3.0 g) in peroxide-free dioxan (90 ml) was added chilled 1.5 N aqueous potassium hydroxide (30 ml) with stirring. 5 min later a solution of carbon disulphide (3.0 g) in dioxan (5 ml) was added. After stirring of the chilled solution for 15 min ether (300 ml) followed by conc. hydrochloric acid (9 ml) were added

* These experiments were carried out in the endocrinological department of Leo Pharmaceutical Products.

with vigorous stirring. The two phases were separated, and the ether-phase washed with water. Hereby a precipitate separated, which was filtered off, washed with ether, and dried to yield 3.0 g of crude product. Recrystallization from aqueous acetone (10 % water) yielded the analytical specimen, which was decomposed at 118—120° (loss of CS_2) and melted at 215—17°C. Ultraviolet absorption spectrum: λ_{max}^{Ether} 233 mμ (ε 18 200) and 280 mμ (18 200). In 0.1 N aqueous NaOH: λ_{max} 245 mμ (ε 18 400) and 304 mμ (ε 18 800) *. (Found: C 53.63; H 7.42; S 12.84. Calc. for $C_{22}H_{30}O_5S_2,3H_2O$: C 53.63; H 7.37; S 13.02; H_2O 10.97). From acetone and methyl ethyl ketone solvated forms are obtained.

In the same way the following compounds were prepared:

17-(1,3-Oxathiolane-2-thione-4-ol-4-)androsta-1,4-diene-3,11-dione-17α-ol (IIb). The amount of ether was reduced to 60 ml. Yield: 58 %. From acetone a solvated product, which was decomposed at 134—135°C and melted at 232—233°C was obtained. Ultraviolet absorption spectrum: λ_{max}^{Ether} 229 mμ (ε 17 700) and 280 mμ (ε 18 000). In 0.1 N aqueous NaOH: λ_{max} 239 mμ (ε 21 000) and 304 mμ (ε 19 000). (Found: C 60.75; H 6.45; S 13.02. Calc. for $C_{22}H_{26}O_5S_2,C_3H_6O$: C 60.95; H 6.55; S 13.02).

17-(1,3-Oxathiolane-2-thione-4-ol-4-)androsta-1,4-diene-3-one-11β, 17α-diol (IIc). The amount of ether was reduced to 60 ml. Yield: 56 %. The substance crystallized from acetone in a solvated form, which was decomposed at 126—128°C and melted at 238—239°C. Ultraviolet absorption spectrum: λ_{max}^{Ether} 230 mμ (ε 18 100) and 280 mμ (ε 18 300). In 0.1 N aqueous NaOH: λ_{max} 241 mμ (ε 18 000) and 304 mμ (ε 18 200). (Found: C 60.64; H 6.97; S 12.89. Calc. for $C_{22}H_{28}O_5S_2$, C_3H_6O: C 60.70; H 6.93; S 12.96).

Corticosteroid-21-potassium xanthates (IIIa, b and c). These were prepared from IIa, b and c as follows: IIa (3.0 g) was dissolved in 2 % alcoholic potassium hydroxide (20 ml). Shortly afterwards crystals began to separate, which were collected and washed with ether to yield 2.7 g of IIIa. Ultraviolet absorption spectrum, $\lambda_{max}^{H_2O}$ 245 mμ (ε 17 500) and 304 mμ (ε 15 100).

Hydrocortisone-21-S-methyl xanthate (IVa, $R^1 = CH_3$). A mixture of IIIa (3.0 g), acetone (75 ml), and methyl iodide (6.0 ml) was stirred at room temperature for 1 h. Methyl *iso*butyl ketone (150 ml) was added, and the resulting solution was washed with water. After drying the solvent was removed *in vacuo*. The residue crystallized with ether to yield 1.7 g of crude product. After recrystallization from methanol the m.p. was 193—194°C. Ultraviolet absorption spectrum: λ_{max}^{EtOH} 239 mμ (ε 18 000) and 279 mμ (ε 12 300). (Found: C 61.07; H 7.00; S 14.08. Calc. for $C_{23}H_{32}O_5S_2$: C 61.03; H 7.13; S 14.17).

The 21-S-alkyl xanthates listed in Table 1 were prepared analogously.

4,5-Diphenyl-1,3-oxathiolane-2-thione-4-ol (VI). To a solution of benzoin (V) (10.0 g) in dioxan (300 ml) was added with stirring 1.5 N potassium hydroxide (100 ml) and carbon disulphide (10 ml). After stirring for 1 h ether (1 000 ml) and conc. hydrochloric acid (30 ml) were added. After separation the ether phase was washed three times with water. After drying and removal of the solvent *in vacuo* the residue was crystallized from chloroform-hexane to yield 9.4 g, which was decomposed at 111—113°C (loss of CS_2) and melted at 132—133°C. Ultraviolet absorption spectrum: λ_{max}^{Ether} 282 mμ (ε 16 400). (Found: C 62.52; H 4.10; S 22.32; "H" 0.37. Calc. for $C_{15}H_{12}O_2S_2$: C 62.47; H 4.20; S 22.23; "H" 0.35).

Potassium xanthate of benzoin (VII). To a solution of VI (5.0 g) in abs. ethanol (75 ml) was added 2 % alcoholic potassium hydroxide (50 ml). Upon scratching the potassium salt crystallized. After standing it was filtered off, washed with ethanol and ether, and dried. Yield: 4.5 g. Ultraviolet absorption spectrum: $\lambda_{max}^{H_2O}$ 249 mμ (ε 14 000) and 304 mμ (ε 11 400).

S-Methyl xanthate of benzoin (VIII). A mixture of VII (3.0 g), acetone (75 ml), and methyl iodide (6.0 ml) was stirred at room temperature for 1 h. Ether (200 ml) was added, and the solution was washed 2 times with water. After drying, the solvent was removed *in vacuo* and the residue recrystallized from ethanol to yield 2.1 g of a product with

* The bands at 233 mμ (ether) and 245 mμ (0.1 N NaOH) represent the sum of the Δ^4-3-keto band and a weaker band due to the xanthate group, which is reported to absorb near 226 mμ[6].

Table 1.

Compound	R [1]	Alkylhalide	Mole alkylhalide per mole K-salt	Yield %	M.p. °C	U.V. (ethanol) λ_{max} mμ	U.V. (ethanol) ε	Formula	C % Calc.	C % Found	H % Calc.	H % Found	S % Calc.	S % Found
IVa	$CH_3(CH_2)_{11}-$	Lauryl-bromide	2.4	42.4	135–36[c])	240 281	18 300 12 100	$C_{34}H_{54}O_5S_2$	67.28	67.22	8.97	9.12		
IVb[a])	$CH_2=CHCH_2-$	Allyl-bromide	3.3	60.0	188–89[b])	237 279	19 300 13 700	$C_{25}H_{30}O_5S_2$	63.26	63.23	6.37	6.24	13.51	13.20
	$CH_3(CH_2)_3-$	Butyl-bromide	5.4	67.3	118–20 and 173–75 [b])	237 281	18 700 13 700	$C_{26}H_{34}O_5S_2$	63.64	63.47	6.98	6.94	13.07	12.98
	$CH_3(CH_2)_{11}-$	Lauryl-bromide	2.4	31.3	124–26[b])	238 281	18 700 13 600	$C_{34}H_{50}O_5S_2$	67.73	67.62	8.36	8.55	10.64	10.62
IVc[a])	CH_3-	Methyl-iodide	10.7	52.6	220–21[c])	242 276	17 100 13 900	$C_{23}H_{30}O_5S_2$	61.30	61.38	6.71	6.79	14.23	13.58
	$CH_3(CH_2)_{11}-$	Lauryl-bromide	2.4	37.1	126–27[c])	240 279	16 900 13 500	$C_{34}H_{52}O_5S_2$	67.51	67.33	8.66	8.73	10.60	10.39

a) The reaction was performed in dimethylformamide and instead of methyl *iso*butyl ketone was used chloroform.
b) Recrystallized from ethanol.
c) Recrystallized from methanol.

Table 2.

R	Alkyl halide	Mole per 0.01 mole K-salt	Yield %	M.p., °C	U.V. (ethanol) λ_{max} mμ	U.V. (ethanol) ε	Formula	C % Calc.	C % Found	H % Calc.	H % Found	S % Calc.	S % Found
CH_3-	Methyl-iodide	0.13	63.8	121–22	236 278	22 600 10 700	$C_{21}H_{30}O_2S_2$	66.62	66.48	7.99	7.77	16.94	16.44
$CH_3(CH_2)_3-$	Butyl-bromide	0.013	35.9	77–78	237 282	23 300 11 000	$C_{24}H_{36}O_2S_2$	68.52	68.58	8.63	8.68	15.24	14.95
$CH_3(CH_2)_3CH-$ (cyclopentyl)	*Cyclo*pentyl-bromide	0.013	37.2	177–78	236 284	23 000 11 900	$C_{25}H_{36}O_2S_2$	69.39	69.20	8.39	8.48	14.82	14.73

m.p. 97–98°C. Ultraviolet absorption spectrum: λ_{max}^{EtOH} 249 mμ (ε 15 900) and 280 mμ (ε 14 000). (Found: C 63.45; H 4.70; S 21.15. Calc. for $C_{16}H_{14}O_2S_2$: C 63.55; H 4.67; S 21.20).

Potassium xanthate of testosterone (X). To a solution of testosterone (IX) (10.0 g) in dimethylformamide (50 ml) were added with stirring a solution of potassium hydroxide (10.0 g) in water (7.5 ml) and carbon disulphide (10 ml). After stirring for 1 h at room temperature the aqueous layer was removed by decantation and ether (800 ml) was added to the dimethylformamide phase. The oily precipitate, which formed, was crystallized from acetone-ether and thereafter recrystallized from ethanol-ether to yield 7.2 g of pure product. Ultraviolet absorption spectrum: λ_{max}^{EtOH} 235 mμ (ε 24 000) and 304 mμ (ε 15 200). (Found: S 15.78. Calc. for $C_{20}H_{27}KO_2S_2$: S 15.92).

Ammonium xanthate of testosterone (XI). To a solution of X (6.0 g) in water (225 ml) was added ammonium chloride (30.0 g) in water (100 ml). The precipitate was collected, washed with acetone followed by ether and dried to give 3.5 g of crude product. Recrystallization from methanol-ether yielded a product with m.p. 128–129°C (decomp.). (Found: C 62.87; H 8.16; N 3.73; S 16.43. Calc. for $C_{20}H_{31}NO_2S_2$: C 62.95; H 8.19; N 3.67; S 16.80).

S-Alkyl xanthates of testosterone XII (see Table 2). A mixture of 0.01 mole of the potassium xanthate (X), excess of the appropriate alkyl halide and acetone (200 ml) was stirred for 2–3 h. Ether (200 ml) was added, and the mixture was washed with water, dried, and evaporated to dryness *in vacuo*, whereafter the residue was recrystallized from abs. ethanol, combined, if necessary, with a treatment with decolorizing carbon.

Dixanthate of testosterone (XIII). The potassium xanthate (X) (5.0 g) was dissolved in water (300 ml). Iodine (1.58 g) in 10 % aqueous potassium iodide (50 ml) was added with stirring and the resulting suspension was extracted with methyl *iso*butyl ketone. The organic layer was separated, washed successively with water and aqueous sodium thiosulphate, and dried. After removal of the solvent *in vacuo* the residue crystallized with methanol. Yield of crude product: 3.5 g. Recrystallization from benzene-methanol yielded a product with m.p. 206–207°C (decomp.). Ultraviolet absorption spectrum: λ_{max}^{EtOH} 240 mμ (ε 55 000) and 286 mμ (ε 8 600). (Found: C 66.04; H 7.54; S 17.58. Calc. for $C_{40}H_{54}O_4S_4$: C 66.07; H 7.49; S 17.64).

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