Attempted oxidation of glycol IV. The glycol (IV, 0.25 g.) was dissolved in pyridine (11 ml.) and treated with a solution of sodium bisulfite (0.3 g.) in water (5 ml.). After 45 min. the solution was diluted with water and filtered. The colorless solid weighed 0.25 g. and melted at 228°. A mixture of the product and glycol IV melted at 228–230°.

Department of Chemistry
University of Maine
Orono, Me.

Optical Rotatory Dispersion Studies. LVI.[1] Thiones[2]

Carl Djerassi and David Herbst

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The success of our initial studies[3] on the optical rotatory dispersion behavior of carbonyl-containing substances encouraged us to examine other chromophores[4] which may exhibit anomalous optical rotatory dispersion. From a theoretical standpoint,[5] a comparison of the rotatory dispersion curves of ketones and thiones would be most instructive. The anomalous rotatory dispersion of a variety of C=S containing chromophores—such as dithiocarbamates,[6] xanthates,[6,7] thionocarbalkoxy derivatives,[8] thiohydantoins[8] and trithiones[9]—have already been recorded and in a number of instances valuable correlations could be made between these Cotton effect curves and certain stereochemical features.

Simple thio ketones, however, are essentially unavailable,[10] largely because of their instability in the monomeric state. Recently, Dodson and Sollman[11] have reported that certain steroidal dibenzylmercaptals upon reduction with sodium in liquid ammonia produce relatively stable monomeric thiones and through their cooperation, a sample of Δ^4-pregnen-3-one-20-thione (I) was obtained. Its rotatory dispersion curve is reproduced in Fig. 1 and it will be noted that the two individual chromophores produce completely separate Cotton effects. The fine structure in the 350-400 mμ region is typical[12] of the Δ^4-3-keto moiety, while the positive Cotton effect in the visible is clearly associated with the low-intensity absorption maximum at 493 mμ of the 20-thione function. The rotatory dispersion curve of this 20-thiono analog I of progesterone (II) is thus completely different from that [13] of progesterone (II), since the latter's 20-keto function exhibits a strongly positive Cotton effect with a peak near 320 mμ, which already makes itself felt in the rotatory dispersion of the Δ^4-keto grouping, whose multiple Cotton effect now appears at a much more positive rotation value as compared to an ordinary Δ^4-3-ketone.

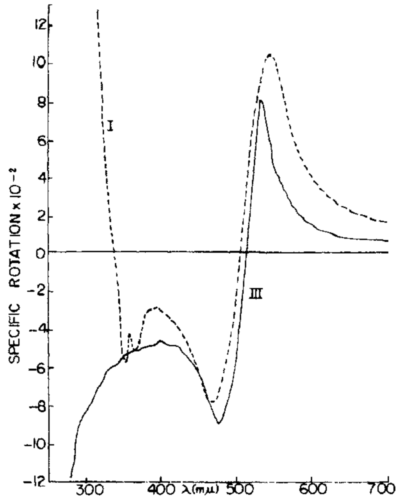

Fig. 1.—Optical rotatory dispersion curves (dioxane solution) of Δ^4-pregnen-3-one-20-thione (I) and Δ^5-androsten-3β-ol-17-thione (III).

In order to secure a thione containing no other chromophoric substituent, the dibenzylmercaptal[14] of Δ^5-androsten-3β-ol-17-one was reduced with sodium in liquid ammonia to yield Δ^5-androsten-3β-ol-17-thione (III), whose physical constants were in reasonable agreement with those reported in the patent literature.[11] This thio ketone exhibits a high intensity absorption maximum at 237.5 mμ (log ε 4.06) and a low intensity one (dioxane solution) at 492.5 mμ (log ε 1.15). As shown in Fig. 1, it is this latter absorption band which gives rise to the positive Cotton effect in the 500-mμ region. The corresponding rotatory dispersion figures in

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[1] Paper LV, C. Djerassi, *Pure and Appl. Chem.*, 2, 475 (1961).

[2] Supported by grant No. CRTY-5061 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

[3] For pertinent references see C. Djerassi, *Optical Rotatory Dispersion: Applications to Organic Chemistry*, McGraw-Hill Book Co., New York, 1960.

[4] Our most recent papers in this area are summarized in ref. 1, as well as in C. Djerassi, *Endeavour*, 20, 138 (1961). See also C. Djerassi, E. Lund, E. Bunnenberg, and B. Sjöberg, *J. Am. Chem. Soc.*, **83**, 2307 (1961) and C. Djerassi, E. Lund, E. Bunnenberg, and J. C. Sheehan, *J. Org. Chem.*, **26**, 4509 (1961).

[5] See J. W. Sidman, *Chem. Revs.*, **58**, 702 (1958).

[6] B. Sjöberg, A. Fredga, and C. Djerassi, *J. Am. Chem. Soc.*, **81**, 5002 (1959).

[7] T. M. Lowry and H. Hudson, *Phil. Trans. Roy. Soc. London*, **232A**, 117 (1933).

[8] C. Djerassi, K. Undheim, R. C. Sheppard, W. G. Terry, and B. Sjöberg, *Acta Chem. Scand.*, **16**, July (1961).

[9] C. Djerassi and A. Lüttringhaus, *Ber.*, **94**, 2305 (1961).

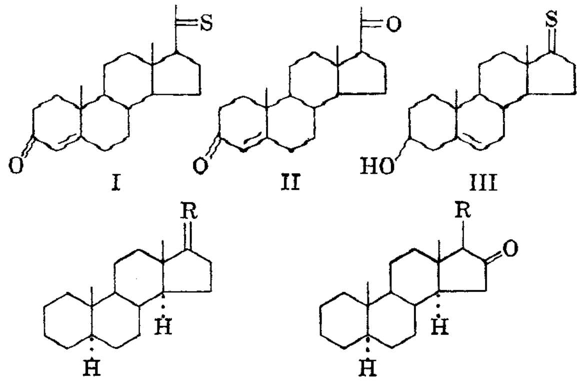
[10] For leading references see N. Lozac'h, *Rec. Chem. Progress*, **20**, 23 (1959); A. Schönberg in E. Müller (ed.) *Methoden der Organischen Chemie*, George Thieme, Stuttgart 1955, Vol. IX, pp. 704–737.

[11] R. M. Dodson and P. B. Sollman, U. S. Patents **2,763,669** and **2,837,539**. We are indebted to these investigators for additional experimental details.

[12] C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6377 (1956).

[13] E. W. Foltz, A. E. Lippman, and C. Djerassi, *J. Am. Chem. Soc.*, **77**, 4359 (1955).

[14] R. H. Levin and J. L. Thompson, *J. Am. Chem. Soc.*, **70**, 3140 (1948).



I II III

IV. R = O
V. R = $(SCH_2C_6H_5)_2$
VI. R = S

VII. R = OH
VIII. R = OAc
IX. R = H

octane and in methanol solution are recorded in the Experimental section.

By a similar reaction sequence, androstan-17-one (IV) was transformed into the previously undescribed dibenzylmercaptal V and thence by sodium-ammonia reduction into androstane-17-thione (VI). The latter exhibited a positive Cotton effect (see Experimental) in the visible region which was very similar to that of III (Fig. 1).

Attempts were also made to prepare cholestane-3-thione—either by reduction of cholestan-3-one dibenzylmercaptal or by hydrogen sulfide–hydrogen chloride treatment[11] of cholestan-3-one—and androstane-16-thione (by the dibenzylmercaptal reduction procedure[11]) in order to evaluate the Cotton effects of thione functions in other parts of the steroid molecule, but these attempts proved abortive.[15] Apparently such thiones without α-substituents are too reactive and undergo further reactions. It was, therefore, not possible to test the general applicability of the octant rule[16] to thiones, but the present rotatory dispersion results show that the long wave length absorption band of thiones can be optically active and that if optically active thio ketones were readily available, an extensive study of their rotatory dispersion behavior would be quite profitable.

EXPERIMENTAL[17]

Δ⁴-*Pregnen-3-one-20-thione* (I).[11] R. D. (Fig. 1) in dioxane (*c*, 0.042): $[\alpha]_{700}$ +162°, $[\alpha]_{589}$ +433°, $[\alpha]_{550}$ +1004°, $[\alpha]_{467.5}$ −772°, $[\alpha]_{400-382}$ *ca.* −300° (broad peak), $[\alpha]_{365}$ −528°, $[\alpha]_{360}$ −424°, $[\alpha]_{352.5}$ −572°, $[\alpha]_{307.5}$ +1543°.

Δ^5-*Androsten-3β-ol-17-thione* (III). A solution of 375 mg. of dehydroepiandrosterone dibenzylmercaptal[14] (m.p. 182–185°) in 50 cc. of anhydrous ether was added dropwise to a stirred solution of 320 mg. of sodium in 8 cc. of liquid ammonia. An additional 150 mg. of sodium was added over a period of 1 hr. and the mixture was then stirred for 3 hr. After careful dropwise addition of 2 cc. of absolute ethanol and 1.5 cc. of 95% ethanol, the mixture was poured cautiously into 50 cc. of water and the aqueous phase was separated. Acidification to *p*H 6 with acetic acid followed by ether extraction produced 127 mg. of pink solid, m.p. 127–140°, which was chromatographed in benzene solution on 10 g. of silica gel (28–300 mesh). Elution with benzene–ethyl acetate (95:5) and recrystallization from hexane provided orange-pink crystals of Δ^5-androsten-3β-ol-17-thione (III), m.p. 162–163°, $\lambda_{max}^{CH_3OH}$ 237.5 mμ (log ε 4.06) and $\lambda_{max}^{dioxane}$ 492.5 mμ (log ε 1.15); lit.[11] m.p. 168–170°, λ_{max} 237.5 and 495 mμ (log ε 3.98 and 1.19). R.D. (Fig. 1) in *dioxane* (*c*, 0.072): $[\alpha]_{700}$ +54°, $[\alpha]_{589}$ +162°, $[\alpha]_{530}$ +806°, $[\alpha]_{475}$ −892°, $[\alpha]_{375-425}$ *ca.* −500° (broad peak), $[\alpha]_{280}$ −1175°. R.D. in *methanol* (*c*, 0.086): peak, $[\alpha]_{532.5}$ +730°, trough, $[\alpha]_{473}$ −790°. R. D. in *n-octane* (*c*, 0.080): peak, $[\alpha]_{539}$ +846°, trough, $[\alpha]_{482.5}$ −860°.

Androstane-17-thione (VI). To a solution of 686 mg. of androstan-17-one (IV) in 15 cc. of glacial acetic acid was added 4 cc. of benzyl mercaptan and 0.4 cc. of cond. hydrochloric acid. Upon swirling for 4 min., a colorless precipitate appeared and after chilling in ice for 2 hr., the solid was collected and washed with methanol; yield, 1.17 g., m.p. 143–147°. Chromatography on alumina and recrystallization from chloroform-methanol provided 0.88 g. of analytically pure *dibenzylmercaptal* V, m.p. 146–147.5°, $[\alpha]_{589}^{20}$ −1° (*c*, 0.2 in chloroform), no carbonyl absorption in infrared.

Anal. Calcd. for $C_{33}H_{44}S_2$: C, 78.51; H, 8.79; S, 12.70. Found: C, 78.53; H, 8.59; S, 13.05.

The reduction of 758 mg. of the above dibenzylmercaptal V in 90 cc. of ether was conducted with two 390-mg. portions of sodium in 30 cc. of liquid ammonia as described above except that the reaction mixture was stirred for 9 hr. and decomposition was effected with ammonium chloride. The crude pink thione (395 mg., m.p. 67–75°) was purified by silica gel chromatography and recrystallization from methanol affording 118 mg. of analytically pure, orange-pink *androstane-17-thione* (VI), m.p. 102–104°, $\lambda_{max}^{CHCl_3}$ 6.78 (m), 6.86 (s), 7.29 (m), 7.61 (s), 8.48 (s)μ, $\lambda_{max}^{dioxane}$ 239 and 492 mμ (log ε 3.94 and 1.11). R.D. in dioxane (*c*, 0.072): $[\alpha]_{700}$ +153°, $[\alpha]_{589}$ +372°, $[\alpha]_{530}$ +1293°, $[\alpha]_{475}$ −969°, $[\alpha]_{305}$ −139°.

Anal. Calcd. for $C_{19}H_{30}S$: C, 78.55; H, 10.41; S, 11.04. Found: C, 78.57; H, 10.26; S, 10.80.

Synthesis of androstan-16-one (IX). To a solution of 3.0 g. of androstan-17-one (IV) (m.p. 121–122°, $[\alpha]_D$ +94.2°, (chloroform), λ_{max}^{KBr} 5.72 μ, $\lambda_{max}^{C_2H_5OH}$ 292–294 mμ, log ε 1.64) and 2.526 g. of potassium in 125 cc. of *t*-butyl alcohol was added 10 cc. of isopropyl nitrite,[18] whereupon a cherry red color developed.

A precipitate appeared within an hour and after standing at room temperature overnight, the mixture was poured into water (all solids dissolved), acidified with acetic acid, and extracted with chloroform. Evaporation of the solvent and one recrystallization from isopropyl alcohol gave 1.91 g. of pale yellow crystals of *16-oximinoandrostan-17-one*, m.p. 170–176°, suitable for the next step. The analytical specimen was crystallized from the same solvent and exhibited a m.p. of 173–177°, $\lambda_{max}^{CH_3OH}$ 238.5 and 340 mμ, log ε 4.00 and 1.74, $\lambda_{max}^{1N\ KOH-CH_3OH}$ 288 mμ, log ε 4.19, $\lambda_{max}^{CHCl_3}$ 2.80, 3.06, 5.74, and 6.08μ; R.D. in methanol (*c*, 0.11): $[\alpha]_{589}$ +11°, $[\alpha]_{385}$ +705°, $[\alpha]_{302.5}$ −2418° (infl.), $[\alpha]_{292.5}$ −2636°, $[\alpha]_{275}$ −2000°.

Anal. Calcd. for $C_{19}H_{29}NO_2$: C, 75.20; H, 9.63; N, 4.62; 0, 10.55. Found: C, 74.92; H, 9.60; N, 4.79; O, 10.77.

A mixture of 3.03 g. of the oximino ketone, 120 cc. of acetic acid, 120 cc. of water and 9.3 g. of zinc dust was heated with stirring to 80°.[19] At this point, a vigorous exothermic reaction started and after it had subsided, heating was con-

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(15) The synthesis of the required androstan-16-one (IX) by calcium–liquid ammonia reduction of the 17β-acetoxy-16-ketone VIII is described in the Experimental section.

(16) It has been suggested (see ref. 3, p. 184) that the octant rule should also be applicable to thioketones.

(17) All optical rotatory dispersion curves were determined by Mrs. T. Nakano using a manual Rudolph photoelectric spectropolarimeter (Model 200AS/800/650) with a mechanically oscillating polarizer.

(18) N. Levin and W. H. Hartung, *Org. Syntheses*, Coll. Vol. III, 192 (1955).

(19) Procedure of M. N. Huffman and M. H. Lott, *J. Biol. Chem.*, **207**, 433 (1954).

tinued at 94° for 1.25 hr., whereupon all the zinc had dissolved. Dilution with water, filtration, and recrystallization from hexane afforded 1.94 g. of *androstan-17β-ol-16-one* (VII), m.p. 137–139.5°, $[\alpha]_D$ −144.7° (chloroform). The analytical specimen showed a m.p. of 139–141°, $\lambda_{max}^{CHCl_3}$ 2.84 and 5.72 μ, $\lambda_{max}^{CH_3OH}$ 297 mμ, log ε 1.67; R.D. in methanol (*c*, 0.10): $[\alpha]_{589}$ −162°, $[\alpha]_{322.5}$ −4158°, $[\alpha]_{277.5}$ +4055°, $[\alpha]_{256}$ +2665°.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.22; H, 10.57.

Acetylation of 5.33 g. of VII with acetic anhydride–pyridine and crystallization from methanol provided 5.16 g. of *androstan-17β-ol-16-one acetate* (VIII), m.p. 152.5–153.5°. The analytical specimen, obtained by double sublimation at 130°/0.02 mm., exhibited a m.p. of 153–153.5; $\lambda_{max}^{CHCl_3}$ 5.68, 5.73, and 8.05 μ, $\lambda_{max}^{CH_3OH}$ 294–300 mμ, log ε 1.59.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70; O, 14.44. Found: C, 75.82; H, 9.73; O, 14.94.

A solution of 3.00 g. of the above acetate VIII in 100 cc. of dry tetrahydrofuran was added dropwise over a period of 15 min. to a stirred solution of 5.77 g. of calcium in 750 cc. of liquid ammonia. The mixture was stirred for an additional 15 min. and the blue color was discharged with methanol.

The ammonia was allowed to evaporate overnight and the residue was taken up in ethyl acetate, washed with water, and evaporated. The resulting semisolid (2.24 g.) containing an appreciable amount of androstan-16-ol[20] was directly oxidized for 15 min. at 7° in acetone solution (160 cc.) in the presence of 3.0 g. of anhydrous sodium sulfate with 3.00 cc. of 8*N* chromium trioxide in sulfuric acid.[21] The crude product was chromatographed on neutral alumina and the hexane eluted material was recrystallized from methanol to give 1.52 g. of *androstan-16-one* (IX), m.p. 108–109.5°. Two distillations at 150°/0.02 mm. yielded the analytical sample, m.p. 109–110°, λ_{max}^{KBr} 5.74 μ, $\lambda_{max}^{CH_3OH}$ 290 mμ, log ε 1.55; R.D. in methanol (*c*, 0.114): $[\alpha]_{589}$ −224°, $[\alpha]_{322.5}$ −4050°, $[\alpha]_{320}$ −4003°, $[\alpha]_{312.5}$ −4592°, $[\alpha]_{272.5}$ +4203°, $[\alpha]_{260}$ +3407°.

Anal. Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 82.74; H, 10.86.

The *dibenzylmercaptal* was prepared as described above for androstan-17-one (IV) in acetic acid solution with benzyl mercaptan and concentrated hydrochloric acid. Recrystallization from isopropyl alcohol afforded colorless crystals, m.p. 79–81°, $[\alpha]_D$ +8.7° (chloroform), which did not exhibit any carbonyl band in the infrared.

Anal. Calcd. for $C_{33}H_{44}S_2$: C, 78.51; H, 8.79. Found: C, 78.38; H, 8.67.

DEPARTMENT OF CHEMISTRY
STANFORD UNIVERSITY
STANFORD, CALIF.

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(20) For similar results in some related calcium-ammonia reductions see J. A. Zderic and A. Bowers, *Ciencia* (*Mex*), 20, 23 (1960).

(21) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

New Catalysts for the Conversion of Isocyanates to Carbodiimides

ELIZABETH DYER AND ROBERT E. READ[1]

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Aluminum isopropoxide and a variety of metal naphthenates have been found to be catalysts for the conversion of isocyanates to carbodiimides and carbon dioxide, as shown in Table I.

$$2\,ArNCO \xrightarrow[cat.]{\Delta} CO_2 + ArN{=}C{=}NAr$$

Although these new catalysts appear less active than the phosphorus compounds,[2] they are somewhat more readily available.

At temperatures above 255° 1-naphthylisocyanate yielded the carbodiimide and carbon dioxide in the absence of an external catalyst.[3] The evolution of carbon dioxide was an autocatalytic reaction, accelerated by the carbodiimide. However, at these high temperatures the carbodiimide was unstable and formed oligomers.[3] In the metal ion-catalyzed reactions of Table I, on the other hand, carbon dioxide evolution followed a pseudo-first-order rate law, and high yields of carbodiimide were obtained at temperatures slightly above 135°.

Isocyanates are known to form complexes with metal alcoholates.[4] The intermediate leading to the formation of carbon dioxide might involve a complex of the metallic catalyst with the isocyanate or with the unsymmetrical isocyanate trimer.[5] The symmetrical isocyanate trimer is thought to be a coproduct rather than an intermediate in carbodiimide formation. A recent paper[6] reports that at room temperature the metal naphthenates are excellent catalysts for trimer formation; however, at the somewhat higher temperatures of the current work the predominant product was the carbodiimide.

The inactivity of 1,4-diaza[2.2.2]bicyclooctane (DABCO) as a catalyst (Table I) indicates that the ability to catalyze other reactions[7] of isocyanates is not always accompanied by the ability to catalyze the conversion of isocyanates to carbodiimides.

EXPERIMENTAL

To a mixture of freshly distilled isocyanate and solvent was added the catalyst, and the mixture was heated at reflux under a stream of dry nitrogen. Organic materials were removed from the sweep stream (postreaction system) by passing it through traps cooled by Dry Ice–acetone, and carbon dioxide was determined by passage through tared Ascarite-filled weighing tubes. Removal of unchanged isocyanate and solvent from the reaction mixture by evaporation under reduced pressure gave a mixture of catalyst and

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[1] From the Ph.D. thesis, University of Delaware, of Robert E. Read, Armstrong Cork Co. Research Fellow, 1957–1960.

(2) T. W. Campbell and J. J. Verbanc, U. S. Patent 2,853,473, Sept. 23, 1958, *Chem. Abstr.*, 53, 10126 (1959); W. J. Balon, U. S. Patent 2,853,518, Sept. 23, 1958, *Chem. Abstr.*, 53, 5202 (1959); K. C. Smeltz, U.S. Patent 2,840,589, June 24, 1958, *Chem. Abstr.*, 52, 16290 (1958).

(3) E. Dyer and R. E. Read, *J. Org. Chem.*, 26, 4388 (1961).

(4) M. Pestemer and D. Lauerer, *Angew. Chem.*, 72, 612 (1960).

(5) K. H. Slotta and R. Tschesche, *Ber.*, 60, 295 (1927).

(6) I. C. Kogon, *J. Org. Chem.*, 26, 3004 (1961).

(7) A. Farkas and K. G. Flynn, *J. Am. Chem. Soc.*, 82, 642 (1960).