[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF G. D. SEARLE & CO.]

Thiosteroids. III.[1] The Transannular Addition of Hydrogen Disulfide to the Steroid A Ring

BY ROBERT C. TWEIT AND R. M. DODSON

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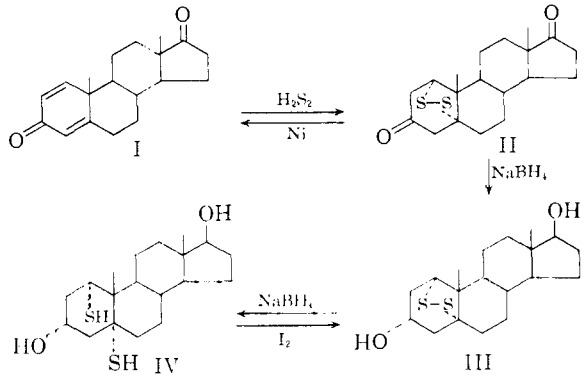
A number of $\Delta^{1,4}$-3-oxosteroids have been converted to 1α,5α-epidithio-3-oxosteroids[2] by the addition of hydrogen disulfide. The proof of structure of these steroid disulfides and the mechanism of the addition of hydrogen disulfide are discussed.

In recent years a number of transannular reactions and interactions involving non-adjacent atoms have been discovered.[3] The larger rings, where various conformations can enable atoms at opposite sides of the ring to approach each other closely, seem especially prone to this type of reaction. In the reactions which have given good yields of anomalous products in the larger rings, transannular effects in six-membered rings have been observed only as very minor side reactions. However, other interactions involving non-adjacent atoms have been found in the cyclohexane system; for instance, the formation of 1,4-epoxycyclohexane in the alkaline hydrolysis of *trans*-4-chlorocyclohexanol,[4] the rearrangement of *cis*-3-methoxy-cyclohexanecarboxylic acid on treatment with acetic anhydride and acid to a mixture of 3- and 4-acetoxy esters,[5] and a number of others.[6] In the steroid series the 3α,9α-oxides,[7] the photoisopyrocalciferols[8] and the i-isteroids[9a] are examples of transannular interactions. The addition of oxygen across the $\Delta^{1,3}$, $\Delta^{2,4}$, $\Delta^{5,7}$ and $\Delta^{8(14),9(11)}$-systems[10,11,9b,12] seems to be analogous to transannular Diels–Alder reactions.

During our investigations of additions to double bonds in the A ring of steroids[1] a new type of transannular reaction was discovered. When an attempt was made to add hydrogen sulfide to the Δ^1-bond of 1,4-androstadiene-3,17-dione, a new compound (II), $C_{19}H_{26}O_2S_2$, was isolated. The yield of II was greatly improved by the addition of an atomic equivalent of sulfur to the pyridine solution of the steroid before the solution was saturated with hydrogen sulfide. The infrared and ultraviolet spectra of the new compound indicated a saturated six-membered ring ketone and a saturated five-membered ring ketone. The analysis, the failure of the compound to decolorize iodine solution, and the absence of a band in the 4 μ region in the infrared spectrum showed the absence of free sulfhydryl groups. A Rast molecular weight determination indicated that the molecule contained only one steroid nucleus.

Reduction of the dione-disulfide II with sodium borohydride gave two substances, a diol-disulfide III and a diol-dithiol IV, which could be oxidized to the diol-disulfide III with iodine. The diol-dithiol IV formed a tetraacetate. The diol-disulfide III was desulfurized with Raney nickel to 5-androstene-3α,17β-diol. In contrast the dione-disulfide II was converted to 1,4-androstadiene-3,17-dione, probably by the base present in the Raney nickel used. Methanolic sodium hydroxide alone converted the dione-disulfide II to 1,4-androstadiene-3,17-dione.



The positions (1 and 5), beta to the ketone, for the disulfide linkage are consistent with the ease of reversal of the addition, and the isolation of 5-androstene-3α,17β-diol from desulfurization is further evidence for the attachment of a sulfur at C-5. The relatively easy acetylation of the tertiary thiol at C-5 is an interesting contrast to the more vigorous conditions usually required for a C-5α-hydroxyl.[13] The difference can probably be best ascribed to the greater length of the carbon–sulfur bond and the greater ionization of the sulfur-hydrogen bond in pyridine compared to a 5-hydroxyl group.

The disulfide bridge was placed on the α-side of the molecule by analogy to other additions to C-1 of

(1) Paper I, R. M. Dodson and R. C. Tweit, THIS JOURNAL, **81**, 1224 (1959); Paper II, R. C. Tweit and R. M. Dodson, *J. Org. Chem.*, **24**, 277 (1959).

(2) This nomenclature was suggested to us by Dr. Leonard T. Capell of "Chemical Abstracts."

(3) For reviews see: *Ann. Repts. on Progr. Chem. (Chem. Soc. London)*, **54**, 181, 219 (1957), and R. Huisgen, *Angew. Chem.*, **69**, 341 (1957).

(4) H. W. Heine, THIS JOURNAL, **79**, 6268 (1957).

(5) D. S. Noyce and H. I. Weingarten, *ibid.*, **79**, 3098 (1957).

(6) E. L. Bennett and C. Niemann, *ibid.*, **74**, 5076 (1952); W. R. Hatchard and A. K. Schneider, *ibid.*, **79**, 6261 (1957); D. S. Noyce and H. I. Weingarten, *ibid.*, **79**, 3093 (1957); D. S. Noyce and B. R. Thomas, *ibid.*, **79**, 755 (1957); S. Archer, M. R. Bell, T. R. Lewis, J. W. Schulenberg and M. J. Unser, *ibid.*, **79**, 6337 (1957); W. G. Dauben, R. C. Tweit and R. L. Maclean, *ibid.*, **77**, 48 (1955); N. A. Nelson and G. A. Mortimer, *J. Org. Chem.*, **22**, 1146 (1957); L. N. Owen and P. A. Robins, *J. Chem. Soc.*, 320, 326 (1949); E. F. Ullman, *Chemistry & Industry*, 1173 (1958); H. K. Hall, Jr., THIS JOURNAL, **80**, 6412 (1958); and other references.

(7) V. R. Mattox, R. B. Turner, L. L. Engel, B. F. McKenzie, W. F. McGuckin and E. C. Kendall, *J. Biol. Chem.*, **164**, 569 (1946).

(8) W. G. Dauben and G. J. Fonken, THIS JOURNAL, **79**, 2971 (1957).

(9) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd Edition, Reinhold Publishing Corp., New York, N. Y., 1949; (a) pp. 256–261, (b) pp. 163–164.

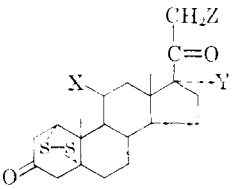
(10) H. B. Henbest and R. A. L. Wilson, *Chemistry & Industry*, 86 (1956).

(11) W. Bergmann, F. Hirschmann and E. L. Skau, *J. Org. Chem.*, **4**, 29 (1939).

(12) G. D. Laubach, E. C. Schreiber, E. J. Agnello and K. J. Brunings, THIS JOURNAL, **78**, 4746 (1956).

(13) P. A. Plattner, T. Petrzilka and W. Lang, *Helv. Chim. Acta*, **27**, 513 (1944).

TABLE I



X	Y	Z	M.p., dec., °C.	$[\alpha]_D$	ΔM_D[a]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
H	H	H	221–222	− 4°	−397°	66.62	66.72	7.99	8.00
H	H	OAc	188–190	+ 4	−412	63.27	62.97	7.39	7.60
H	OH	OAc	222–223	−16	−309	61.03	61.12	7.13	7.18
O=	OH	OAc	235–237	− 4	−403	59.20	58.80	6.48	6.15
β-OH	OH	OAc	222–224	+ 1	−274	59.29[b]	59.10	7.27	7.48

[a] ΔM_D = M_D (3C=O,1α,5α-epidithio) − M_D (3C=O,5α-pregnane). [b] Contains one mole of acetone of crystallization.

the A ring.[1] The reduction of the 3-ketone to give a 3α-hydroxyl group, in contrast to the usual reductions of 3-ketones to give mainly the 3β-isomer, also supported the α-configuration of the disulfide bridge. The two sulfur atoms apparently hindered the approach of the borohydride ion to the 3-ketone to a greater extent than the 10-methyl group.

The reduction of the disulfide bridge with sodium borohydride provided some information about the strain involved in the molecules containing it. The disulfide link in lipoic acid was cleaved by sodium borohydride at 5°,[14] while only the carbonyl groups of the dione-disulfide II were reduced below 30°. When the temperature was allowed to rise to 60°, the mixture of diol-dithiol IV and diol-disulfide III mentioned above was obtained. Little information is available on the reduction of linear disulfides with sodium borohydride, although Brown and Subba Rao[15] reduced diphenyl disulfide with sodium borohydride and aluminum chloride in diethylene glycol dimethyl ether at 25°. Thus the stability of the steroidal disulfide bridge is apparently greater than that of the trimethylene disulfides.[16]

The ultraviolet absorption spectrum of II indicated that the stability of the dione-disulfide was probably closer to that of the linear disulfides than to trimethylene disulfide. Calvin's[17] studies of the ultraviolet spectra of various disulfides showed that trimethylene disulfide had a maximum at 334 mμ, while the maximum for linear disulfides was at 250 mμ. The dione-disulfide II had a maximum at 268 mμ, much closer to the value which Calvin found for the linear disulfides, than to the value for trimethylene disulfide.

The mechanism for the formation of the disulfide bridge in II probably involves the addition of hydrogen disulfide, rather than separate additions of hydrogen sulfide to the Δ^1- and Δ^4-bonds, followed by oxidation to the disulfide bond. On chromatography of the crude product, no products corresponding to the addition of hydrogen sulfide to only one double bond were found. This conclusion was bolstered by the failure of other monofunctional compounds, such as ethanethiolic acid[1] and methyl mercaptan, to add to the Δ^4-bond in various steroids.

Rough calculations indicate that, in a pyridine solution of hydrogen sulfide, an appreciable fraction of the sulfide is present as monohydrogen sulfide ions. Addition of sulfur should produce a mixture of monohydrogen disulfide ions and hydrogen disulfide, just as addition of sulfur to a sodium sulfide solution gives sodium disulfide. The sulfur–sulfur bond in hydrogen disulfide was reported to be 2.05 Å.[18] The two sulfur atoms can interact with the orbitals of the C-1 and C-5 atoms (indicated by calculation to be 2.5 Å. apart) to form the disulfide linkage in either one or two steps. No choice can be made between a concerted or stepwise mechanism on the basis of available evidence.

Attempts to add hydrogen disulfide to santonin, benzoquinone and 2,6-diphenyl-4-pyrone failed. The failure of santonin to react is particularly interesting, since this is a very close analog of the steroid A and B rings. The lack of reactivity is probably due to the 4-methyl group, and the lactone ring. 17β-Hydroxy-1α,5α-epidithioandrostan-3-one, 1α,5α-epidithio-17α-oxa-D-homoandrostane-3,17-dione and the other steroid adducts listed in Table I were prepared by similar methods.

As can be seen from the table and the experimental section ΔM_D values for the adducts were consistent. The values for the reduction products III and IV are worthy of note. The ΔM_D value for the disulfide-diol III relative to 5α-androstane-3α,17β-diol was −235°. Reduction of III to the dithiol IV produced a change in M_D of +436°, evidence for a rather striking shift in the conformation of the molecule and comparable in magnitude to a ΔM_D of −244° for the reduction of the disulfide bond in lipoic acid.[14,19]

Experimental[20]

1α,5α-Epidithioandrostane-3,17-dione (II).—A solution of 46 g. of 1,4-androstadiene-3,17-dione and 5.2 g. of sulfur

(14) I. C. Gunsalus, L. S. Barton and W. Gruber, THIS JOURNAL, **78**, 1763 (1956).

(15) H. C. Brown and B. C. Subba Rao, *ibid.*, **78**, 2582 (1956).

(16) S. Sunner [*Nature*, **176**, 217 (1955)] has shown trimethylene disulfide to be 4 kcal. less stable than linear disulfides.

(17) J. A. Barltrop, P. M. Hayes and M. Calvin, THIS JOURNAL, **76**, 4348 (1954).

(18) D. P. Stevenson and J. Y. Beach, *ibid.*, **60**, 2872 (1938).

(19) E. Walton, A. F. Wagner, F. W. Bachelor, L. H. Peterson, F. W. Holly and K. Folkers, *ibid.*, **77**, 5144 (1955).

(20) All melting points were taken on a Fisher-Johns melting point apparatus. We are indebted to Dr. R. T. Dillon and his staff of the Analytical Division, G. D. Searle and Co., for the analytical and optical data reported. The rotations were taken in chloroform at 24 ± 2°, and the infrared spectra were taken in potassium bromide disks. The methods of preparation of starting materials were discussed in a previous paper.[1] The ΔM_D values listed refer to: ΔM_D = M_D (1α,5α-epidithiosteroid)-M_D (1,5α-unsubstituted steroid).

in 1.0 l. of pyridine was saturated with hydrogen sulfide. The last of the sulfur dissolved rapidly as the hydrogen sulfide was added. The reaction stood overnight and was then concentrated under vacuum. Toluene was added to the residue and removed under reduced pressure. The residue was crystallized from methylene chloride–acetone to yield 39 g. of 1α,5α-epidithioandrostane-3,17-dione, m.p. 210–214° dec. to a red melt. This material was contaminated with a trace of sulfur. The filtrates were concentrated under vacuum and chromatographed on 900 g. of silica gel. The column was washed with benzene and 5% ethyl acetate in benzene and then eluted with 10% ethyl acetate in benzene. The first 10% ethyl acetate in benzene eluates contained 1α,5α-epidithioandrostane-3,17-dione and were concentrated under vacuum. After crystallization from methylene chloride–acetone, the product, 2 g., melted at 214–218° dec., turned red, $[\alpha]_D$ −21 ± 2°, ΔM_D −400°, $\lambda_{max}^{methanol}$ 268 mμ ε 240. The infrared spectrum had carbonyl bands at 5.76 and 5.82 μ and no sulfhydryl bands around 4 μ. The spectrum was identical with that of the main fraction of material.

Anal. Calcd. for $C_{19}H_{26}O_2S_2$: C, 65.10; H, 7.48; S, 18.29; mol. wt., 350.5. Found: C, 64.77, 65.28; H, 7.47, 7.67; S, 18.51; mol. wt. (Rast), 350.

Reduction of 1α,5α-Epidithioandrostane-3,17-dione.—The steroid, 10.00 g., was mixed with 800 cc. of methanol and a solution of 10.0 g. of sodium borohydride in 100 ml. of water was added. The temperature of the mixture rose to about 60°, gas was evolved and the solid dissolved. The resulting solution was cooled to room temperature and allowed to stand for 0.5 hour. Then, the solution was concentrated under vacuum to one-third liter, cooled, and the solid which had formed was separated by filtration and washed with water. Another fraction of material was obtained on concentration of the filtrate. This solid had the same infrared spectrum as the first fraction. Finally, two more crops, whose infrared spectra did not match those of the first two fractions, were separated by filtration.

The first two fractions were combined and partially dissolved in 100 ml. of methanol–acetone. The undissolved material was separated and the solution was concentrated to yield 2.25 g. of 3α,17β-dihydroxyandrostane-1α,5α-dithiol (IV), m.p. 216–218°, $[\alpha]_D$ +67 ± 1°, ΔM_D +201°.

Anal. Calcd. for $C_{19}H_{32}O_2S_2$: C, 64.00; H, 9.05. Found: C, 64.07; H, 9.21.

The infrared spectrum of the undissolved material, 2.7 g., m.p. 211–213°, was identical with that of the analytical sample. The spectrum had a broad hydroxyl band at 2.94 μ and a sulfhydryl doublet at 3.90 and 3.97 μ. There were no bands in the infrared between 5 and 6.7 μ (the carbonyl region).

The last two fractions from the original solution were dissolved in the methanol–acetone filtrate from the 1α,5α-dithiol. On concentration, a solid was obtained which was recrystallized from methylene chloride–methanol to yield 2.20 g. of 1α,5α-epidithioandrostane-3α,17β-diol (III), m.p. 238–239° dec., $[\alpha]_D$ −56 ± 1°, ΔM_D −235°.

Anal. Calcd. for $C_{19}H_{30}O_2S_2$: C, 64.36; H, 8.53. Found: C, 64.52; H, 8.66.

The infrared spectrum had a hydroxyl doublet at 2.92 and 3.00 μ and neither sulfhydryl bands around 4.0 μ nor carbonyl bands in the 5 to 6.5 μ region. When the reaction was repeated with the sodium borohydride added slowly and the temperature kept below 30°, only the epidithiodiol III was obtained in 72% yield.

Oxidation of 3α,17β-Dihydroxyandrostane-1α,5α-dithiol.—The steroid, 0.05 g., was dissolved in 3 ml. of methanol and a solution of iodine in ethanol was added dropwise until the color persisted. On evaporation of the solution, crystals of 1α,5α-epidithioandrostane-3α,17β-diol formed and were separated by filtration to yield 0.02 g., m.p. 235–237° dec. A mixture of the compound with authentic material melted 235.5–237.5° dec.; the infrared spectrum also confirmed the identity.

3α,17β-Diacetoxy-1α,5α-diacetylthioandrostane.—3α,17β-Dihydroxyandrostane-1α,5α-dithiol, 1.4 g., was dissolved in 10 cc. of pyridine and 10 cc. of acetic anhydride and allowed to stand at room temperature for one day. Then the solution was poured into water; the mixture was filtered; and the solid was crystallized twice from acetone–petroleum ether (b.p. 60–70°) to yield 1.08 g. of 3α,17β-diacetoxy-1α,5α-diacetylthioandrostane, m.p. 235–238°, $[\alpha]_D$ −71 ± 1°, $\lambda_{max}^{methanol}$ 238 mμ, ε 9750. The infrared spectrum had bands at 5.73, 5.91, 8.00–8.03 and 9.00 μ and no sulfhydryl bands in the 4 μ region.

Anal. Calcd. for $C_{27}H_{40}O_6S_2$: C, 61.80; H, 7.68; S, 12.22. Found: C, 62.13; H, 8.00; S, 12.35.

Reduction of 1α,5α-Epidithioandrostane-3α,17β-diol.—The steroid, 1.9 g., was mixed with 40 ml. of methanol and a solution of 2 g. of sodium borohydride in 20 ml. of water was added. A heavy precipitate formed and 40 ml. of methanol was added. The mixture was heated on the steam-bath, gas was evolved and the solid dissolved. About 50 ml. of methanol was distilled and on cooling a solid formed. The material was separated by filtration and recrystallized from methanol to yield 1.1 g. of 3α,17β-dihydroxyandrostane-1α,5α-dithiol, m.p. 213–216°. The infrared spectrum identified the compound.

Raney Nickel Desulfurization of 1α,5α-Epidithioandrostane-3α,17β-diol.—The steroid, 5.25 g., was dissolved in 100 ml. of 95% ethanol and three teaspoons of Raney nickel from a suspension in water was added. The mixture was heated under reflux for 7 hours and then filtered through charcoal. The solid on the filter was washed twice with hot methanol and the filtrates were concentrated. The residue was dissolved in benzene and chromatographed on 200 g. of silica gel. The column was washed with benzene and from the 5% ethyl acetate–benzene eluents a solid was obtained in low yield. The analysis was close to that of a monohydroxyandrostene, but since the amount of material was small, it was not characterized further.

The 15% ethyl acetate–benzene eluates were concentrated and the residue was crystallized from methanol to yield a total of 0.94 g. of 5-androstene-3α,17β-diol (20%) and 0.10 g. of recovered starting material. The dihydroxy compound was recrystallized twice from methanol–methyl ethyl ketone to yield the analytical sample, m.p. 196–199° (a methyl ethyl ketone solvate), $[\alpha]_D$ −52° (ethanol) and −71° (chloroform, both values calculated to non-solvated material).

Anal. Calcd. for $C_{19}H_{30}O_2 \cdot C_4H_8O$: C, 76.19; H, 10.56. Found: C, 75.95; H, 10.31.

Ruzicka[21] reported that the ethyl acetate solvate of 5-androstene-3α,17β-diol melts unsharply about 200° and that a sublimed sample has a m.p. of 207–208°, $[\alpha]_D$ −56° (ethanol). The infrared spectrum of our compound has an hydroxyl band at 2.98 μ and a weak ketone band at 5.81 μ. Our compound did not form a precipitate with digitonin. A diacetate prepared by the usual method melted at 154–155°, lit.[21] m.p. 155–155.5°. The infrared spectrum had no hydroxyl band in 3 μ region, and ester bands at 5.77, 7.87 and 8.03 μ.

When the dihydroxy compound was oxidized with chromium trioxide in pyridine, 4-androstene-3,17-dione was obtained.

Basic Treatment of 1α,5α-Epidithioandrostane-3,17-dione.—The steroid, 2.00 g., was dissolved in 100 ml. of methanol containing 5 ml. of 8 *N* aqueous sodium hydroxide. The solution was allowed to stand overnight; some solid formed. The solvent was partially evaporated under nitrogen and water was added. The precipitate was separated by filtration to yield 1.38 g. of 1,4-androstadiene-3,17-dione, m.p. 142–144°. The infrared spectrum was identical with that of an authentic sample.

17β-Hydroxy-1α,5α-epidithioandrostan-3-one.—17β-Hydroxy-1,4-androstadien-3-one, 2.00 g., was dissolved in 60 ml. of pyridine, and the solution was saturated with hydrogen sulfide. Then 2 drops of piperidine was added and air was bubbled through the solution for one minute. After 3 days, the reaction mixture was poured into one-half l. of water and extracted three times with ether. The ether solution was washed five times with water; then petroleum ether, b.p. 35–40°, was added, and the solution was concentrated on the steam-bath. When the residue was triturated with ether, a solid formed. It was crystallized from acetone–ether and then from acetone to give 0.24 g. of 17β-hydroxy-1α,5α-epidithioandrostan-3-one, m.p. 217–219° dec., turned red, $[\alpha]_D$ −81 ± 2°, ΔM_D −301°. The infrared spectrum had bands at 2.93 and 5.83 μ.

Anal. Calcd. for $C_{19}H_{28}O_2S_2$: C, 64.73; H, 8.00. Found: C, 64.62; H, 7.55.

(21) L. Ruzicka, M. W. Goldberg and W. Bosshard, *Helv. Chim. Acta*, **20**, 541 (1937).

1α,5α-Epidithio-17a-oxa-D-homoandrostane-3,17-dione.—6D-Homo-17a-oxa-1,4-androstandiene-3,17-dione, 2.00 g., was dissolved in 60 ml. of pyridine and hydrogen sulfide was bubbled into the solution for two hours. Then 2 drops of piperidine was added and the reaction was allowed to stand for 3 days. After this time 200 ml. of water was added and the solution was extracted three times with ether. A solid formed in the aqueous layer and was separated by filtration. It was crystallized from ethyl acetate to give 0.34 g. of 1α,5α-epidithio-17a-oxa-D-homoandrostane-3,17-dione, m.p. 232–233° dec., red melt, $[\alpha]_D$ −140 ± 2°, ΔM_D −457°.

Anal. Calcd. for $C_{19}H_{26}O_3S_2$: C, 62.26; H, 7.15. Found: C, 62.06, 62.00; H, 6.76, 7.00.

CHICAGO 80, ILL.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY]

Glycinate Complexes of Zinc and Cadmium

BY BARBARA W. LOW,[1] F. L. HIRSHFELD AND F. M. RICHARDS[1]

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Crystals of $Zn(NH_2CH_2CO_2)_2 \cdot H_2O$ and $Cd(NH_2CH_2CO_2)_2 \cdot H_2O$ are approximately isomorphous. The latter, being of higher crystallographic symmetry, has been studied in somewhat greater detail although only one projection has been analyzed. In both complexes the metal coördination is octahedral, two glycine ligands chelating with the metal in *trans* planar array while the other two coördination positions are occupied by carboxyl oxygens of neighboring glycine ligands. The amino groups and the water are fully hydrogen bonded. The difference in symmetry of the two structures is not explained.

Introduction

The marked effect of zinc ion on protein solubilities[2] suggested that a study of the coördination of this metal with amino acids would be of interest (for a review of other work in this field, see Gurd and Wilcox).[3] An X-ray crystallographic investigation of the zinc glycine complex was undertaken in an attempt to establish the nature of the metal coördination in this structure. At the same time, glycine complexes with several other metals were prepared, of which the cadmium complex proved to be crystallographically similar to the zinc complex. X-Ray diffraction photographs showed the two crystals to be nearly isomorphous. The cadmium complex, of much higher symmetry, was far the more amenable to crystallographic analysis. Accordingly, when work on the zinc complex had proceeded far enough to show the general nature of the metal coördination, attention was temporarily diverted to the cadmium complex, which offered greater promise of a more detailed structure determination.

Experimental

The zinc and cadmium complexes were both prepared in the same way. The metallic oxide (1 mole) and recrystallized glycine (2 moles) were dissolved together in boiling water. After filtration, the solution was allowed to cool slowly to room temperature. Large crystals were obtained by recrystallization from water and from water–alcohol (1:1) mixtures. Micro-Kjeldahl analyses and dry-weight determinations (air, 110°) of both complexes established the crystalline composition: $M(NH_2CH_2COO)_2 \cdot H_2O$.

Morphology and Optics.—The approximate isomorphism of the two preparations was immediately evident from the morphological and optical examination. Both the zinc and the cadmium glycinate monohydrate crystallize as colorless plates elongated along [010] and usually lying on (001) (see Table I for cell dimensions and space groups). Most crystals show {100}; other forms commonly observed include {110} and {1$\bar{1}$0} of the zinc complex (designated in terms of the triclinic holosymmetric class, as discussed below), {210} and {110} for the cadmium complex. The crystals frequently show etched lines parallel to [010] on the main face (001) with principal cleavage (100). Crystals of the zinc complex tend to grow radially in clumps so that single crystals with unbroken ends are somewhat rare. In well-developed specimens both like and unlike termination has been observed.

TABLE I

CRYSTAL LATTICE CONSTANTS

Lattice dimensions measured on a General Electric Spectrogoniometer fitted with a Eulerian cradle, Goniostat,[a] for single-crystal studies. Copper radiation employed: λ $K\alpha_1$ = 1.54051, λ $K\alpha_2$ = 1.54433.

	Cadmium glycinate monohydrate	Zinc glycinate monohydrate
a, Å.	14.862 ± 0.005	15.051 ± 0.006
b, Å.	5.297 ± .005	10.441 ± .008
c, Å.	10.006 ± .003	19.692 ± .012
α, degrees		89.89 ± .05
β, degrees	90.40 ± .03	87.15 ± .05
γ, degrees		90.39 ± .05
Space group	$I2/a$	$A1$ or $A\bar{1}$
Z	4	16
Density (calcd.), g./ml.	2.350 ± 0.004	1.990 ± 0.004
Density (flotation), g./ml.	2.338 ± 0.010	1.993 ± 0.005

[a] T. Furnas and D. Harker, *Rev. Sci. Instr.*, **26**, 449 (1955).

Viewed normally to the (001) face, crystals of both complexes give a slightly off-center optic-axis figure. They show high positive birefringence, with $\beta \| b$ and γ parallel to the trace of (101) for the zinc complex, (201) for the cadmium complex, in the plane perpendicular to b. Measurements on the zinc complex gave

$\alpha = 1.510 \pm 0.003$, $\beta = 1.547 \pm 0.003$, $\gamma = 1.648 \pm 0.003$, $2V = 67°$

Cadmium Glycinate Monohydrate.—The cadmium complex is monoclinic, with four molecules of cadmium glycinate and four of water in a cell

(1) Part of this work was carried out while (B.W.L., and F.M.R.) were members of the Department of Biophysical Chemistry, Harvard Medical School.

(2) E. J. Cohn, F. R. N. Gurd, D. M. Surgenor, B. A. Barnes, R. K. Brown, G. Derouaux, J. M. Gillespie, F. W. Kahnt, W. F. Lever, C. H. Liu, D. Mittelman, R. F. Mouton, K. Schmid and E. A. Uroma, THIS JOURNAL, **72**, 465 (1950).

(3) F. R. N. Gurd and P. E. Wilcox, *Advances in Protein Chem.*, 11, 311 (1956).