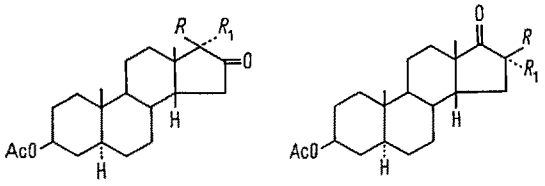
Optical Rotatory Dispersion and Spectral Data of some Steroidal Ring D Ketol Acetates of the 14β-Series[1]

Optical rotatory dispersion measurements[2] as well as other spectral data[3] on α-haloketones of the 16- and 17-keto steroid series have led to useful information on the conformation of fused cyclopentanones. The corresponding data[4,5] with α-acetoxyketones of this group proved to be in qualitative agreement with these conclusions and it appeared of interest to accumulate similar information on the recently synthesized[6] C-17-epimeric 16-ketosteroids (II, III) and C-16-epimeric 17-ketosteroids (V, VI) with the 14β-configuration (rings C/D *cis*).

All of the spectral data are collected in the Table and the rotatory dispersion and ultraviolet spectroscopic measurements were conducted in dioxane solution in order to make them directly comparable to the earlier reported[4,5] figures of the corresponding 14α-analogs (rings C/D *trans*). The infrared spectra were obtained in carbon tetrachloride solution with a Beckman IR 7 instrument and it will be noted that the position of the relevant infrared carbonyl band does not differ greatly for a given pair of epimers (e.g. II *vs.* III). A similar correspondence in frequency shifts was also observed with the appropriate ketol acetates of the 14α-series (see footnotes d–i in the Table).

Of particular interest are the rotatory dispersion properties of the four ketol acetates (II, III, V, VI) when compared with those of their parent ketones (I, IV). In contrast to the strong negative Cotton effect characteristic[7] of the 16-keto steroids of the standard 14α-series, 14β-androstan-3β-ol-16-one 3 acetate (I) exhibits a positive Cotton effect. If one attempts to analyze the situation in terms of the octant rule[8] as has been done recently by KLYNE[9] for various fused cyclopentanones, then one must conclude that the governing factor responsible for the positive Cotton effect is C-13 and C-14, rather than rings A, B and part of C. If we now examine the wavelength shifts (both in terms of the ultraviolet absorption maximum or of the position of the first rotatory dispersion extremum) accompanying introduction of an acetoxy substituent, then we can assign a quasi-equatorial orientation to the 17α-acetoxy isomer (III), while the 17β-isomer (II) appears to possess a more axial character. The sign of the positive Cotton effect is not altered upon introducing an adjacent acetoxy substituent (I, II, and III all exhibit positive Cotton effects), but it is surprising – and possibly indicative of conformational distortion – that the 17β-acetoxy ketone II has a stronger amplitude than the 17α-isomer (III) or the parent ketone (I).

An even more complicated situation seems to exist with the analogous 17-keto steroids. Turning first to the parent ketone, 14β-androstan-3β-ol-17-one 3-acetate (IV)[10], an octant projection[8] of the type performed[9] for the 14α-isomer would lead to the conclusion (see above discussion of positive Cotton effect of I) that C-14 and C-15 should make the dominant contribution, which would result in a negative Cotton effect. In actual fact, a moderate positive Cotton effect was measured (Table), indicating that rings A, B, and C – all of them being situated in a positive octant – exert the dominant influence. Introduction of a 16β-acetoxy substituent as in V results in an extra-



I R=R_1=H
II R=AcO; R_1=H
III R=H; R_1=AcO

IV R=R_1=H
V R=OAc; R_1=H
VI R=H; R_1=OAc

[1] Paper LXI of *Optical Rotatory Dispersion Studies*. For Paper LX see C. DJERASSI, Science *134*, 649 (1961).
[2] J. FISHMAN and C. DJERASSI, Exper. *16*, 138 (1960).
[3] F. V. BRUTCHER, T. ROBERTS, J. J. BARR, and N. PEARSON, J. Amer. chem. Soc. *81*, 4915 (1959). – J. FAJKOS and J. JOSKA, Chem. and Ind. *1960*, 1162. – J. FISHMAN, Chem. and Ind. *1961*, 1678.
[4] C. DJERASSI, O. HALPERN, V. HALPERN, O. SCHINDLER, and C. TAMM, Helv. chim. Acta *41*, 250 (1958).
[5] C. DJERASSI, *Optical Rotatory Dispersion: Applications to Organic Chemistry* (McGraw-Hill, New York 1960), chapter 8.
[6] J. FISHMAN and T. NAMBARA, J. org. Chem., in press.
[7] C. DJERASSI, W. CLOSSON, and A. E. LIPPMAN, J. Amer. chem. Soc. *78*, 3163 (1956).
[8] See chapter 13 in [4]; W. KLYNE in *Advances in Organic Chemistry* (Ed. by R. A. RAPHAEL, E. C. TAYLOR, and H. WYNBERG, Interscience, New York 1960), p. 333. – W. MOFFITT, R. B. WOODWARD, A. MOSCOWITZ, W. KLYNE, and C. DJERASSI, J. Amer. chem. Soc. *83*, in press (1961).
[9] W. KLYNE, Bull. Soc. Chim. France *1960*, 1396; Tetrahedron *13*, 29 (1961).
[10] Another noteworthy feature is the hypsochromic shift (in terms of the ultraviolet absorption maximum or the position of the rotatory dispersion extremum) in going from the 16-ketone (I) to the 17-ketone (IV) in the 14β-series, or in comparing the 14α-17-keto steroid (ref. [4] and [5]) with the 14β-17-keto isomer (IV).

Substance	$\lambda_{max}^{diox.}$	$\Delta\lambda$ (mμ)	Optical rotatory dispersion (dioxane solution) First extremum	Second extremum	$\Delta\lambda$ (mμ)	Infrared C=O absorption (CCl_4) $\bar{\nu}_{max}$ cm^{-1}	$\Delta\bar{\nu}$ cm^{-1}
16-Ketone (I)	297	–	$[\alpha]_{323}$ + 2220°[a]	$[\alpha]_{275}$ – 1620°	–	1743[d]	–
17β-AcO (II)	312	+ 15	$[\alpha]_{341}$ + 2900°[b]	$[\alpha]_{287}$ – 1975°	+ 18	1760[e]	+ 17
17α-AcO (III)	292	– 5	$[\alpha]_{320}$ + 1300°	$[\alpha]_{278}$ – 1165°	– 3	1762[f]	+ 19
17-Ketone (IV)	280	–	$[\alpha]_{302}$ + 913°[c]	$[\alpha]_{267}$ + 155°	–	1739[g]	–
16β-AcO (V)	303	+ 23	$[\alpha]_{341}$ – 463°	$[\alpha]_{292}$ + 1009°	+ 39	1756[h]	+ 17
16α-AcO (VI)	300	+ 20	$[\alpha]_{323}$ + 857°	$[\alpha]_{280}$ – 457°	+ 21	1757[i]	+ 18

[a] As with many cyclopentanones in a non-polar solvent, there can be observed some resolution of this extremum with a second peak at $[\alpha]_{313}$ + 2000°. [b] Second peak at $[\alpha]_{339}$ + 2670°. [c] The rotatory dispersion curve of IV has been measured earlier (C. DJERASSI, R. RINIKER, and B. RINIKER, J. Amer. chem. Soc. *78*, 6362 (1956)) in methanol. [d] 14α-isomer, 1747 cm^{-1}. [e] 14α-isomer, 1767 cm^{-1}. [f] 14a-isomer, 1763 cm^{-1}. [g] 14β-isomer, 1743 cm^{-1}. [h] 14α-isomer, 1764 cm^{-1}. [i] 14α-isomer, 1763 cm^{-1}.

ordinarily large bathochromic shift of the rotatory dispersion extrema (+ 39 mμ), which must be attributed to a very strong axial character[11] of the acetoxy group, not anticipated by inspection of DREIDING models[12]. Even more surprising is the inversion of the sign of the Cotton effect of V, an observation for which we can offer no ready explanation other than to propose a substantial conformational deformation; rotatory contributions of free-rotational rotomers of the acetoxy group may also need to be considered. The 16α-acetoxy-17-ketone (VI) still possesses a positive Cotton effect and the bathochromic shift of its rotatory dispersion extremum (as compared to that of IV) suggests a slightly more axial orientation than in a 17β-acetoxy-16-ketone (II).

In conclusion, we can state that the optical rotatory dispersion data collected in the Table indicate the present difficulties in analyzing complex fused hydrindanones in terms of the octant rule and they also suggest some conformational distortion accompanying introduction of adjacent acetoxyl substituents[13].

Zusammenfassung. Die optische Rotationsdispersion sowie die UV- und IR-Spektren der Epimeren von 17-Acetoxy-16-keto- bzw. 16-Acetoxy-17-keto-14β-steroiden wurden gemessen. Mögliche Beziehungen zwischen Rotationsdispersion und Stereochemie der untersuchten Verbindungen werden diskutiert.

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Department of Chemistry, Stanford University, Stanford (California), and Sloan Kettering Institute for Cancer Research, New York, August 23, 1961.

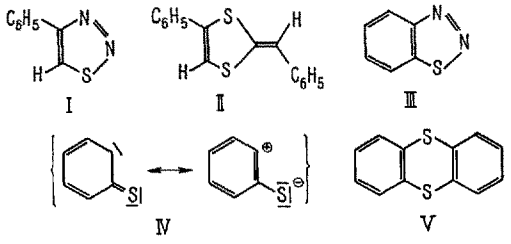
[11] The work of J. FISHMAN and T. NAMBARA, Chem. and Ind., 79 (1961), on 16-halogenated 14β-17-ketosteroids supports the attribution of axial character to a 16β-substituent in this series.

[12] A. DREIDING, Helv. chim. Acta *42*, 1339 (1959).

[13] *Acknowledgment.* We are indebted to Mrs. RUTH RECORDS for the optical rotatory dispersion measurements and to the National Cancer Institute of the National Institutes of Health for financial support (grants No. CRTY-5061 and CY-3207).

1,3-Dipolare Additionen der Thioketocarbene

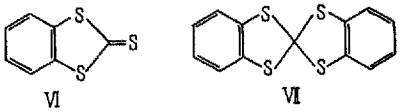
Die erfolgreiche Verwendung von Ketocarbenen als 1,3-Dipole[1] legte nahe, auch die Fähigkeit der geschwefelten Abkömmlinge zur 1,3-Dipolaren Addition[2] zu prüfen. Die von KIRMSE und HORNER[3] beobachtete Bildung des Dithiafulven-Derivats II bei der Photolyse von I wies bereits auf eine 1,3-Addition des Phenyl-thioketocarbens an Phenyl-thioketen, das Produkt der Wolff-Umlagerung. Aus 1,2,3-Benzo-thiadiazol (III) erhielt JACOBSON[4] beim Erhitzen auf 200–220° das Thianthren (V), was auf eine Dimerisation des intermediären aromatischen Thioketocarbens IV deutet.



I II III

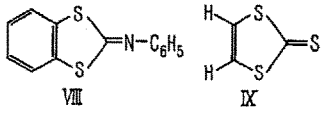
IV V

Unsere Versuche sprechen für eine erstaunliche Reaktionsträgheit von IV, verglichen mit dem Sauerstoffanalogen[1]. Beim Zerfall von III in Fumarsäurediäthylester oder α-Naphtylisocyanat bei 220° oder in siedendem Benzonitril liess sich die Bildung des Thianthrens nicht zugunsten einer Wechselwirkung von IV mit dem Lösungsmittel unterdrücken. Die für die Stickstoffabspaltung aus III nötige hohe Temperatur – wir fanden keine geeigneten Katalysatoren – begrenzt die Auswahl der Dipolarophilen. Einzig Verbindungen mit CS-Doppelbindung nehmen das Thioketocarben IV relativ glatt auf. Der Zerfall von III in Schwefelkohlenstoff im Autoklaven bei 220° lieferte 84% 1,3-Benzodithiol-2-thion (VI)[5], das auf diesem Wege, ebenso wie das aus VI mit Lithiumaluminiumhydrid erhaltene Dithiobrenzcatechin, bequem zugänglich ist.



VI VI

Beim erneuten Zerfall von III in VI bei 200° vermag die CS-Doppelbindung eine weitere Molekel des Thioketocarbens IV aufzunehmen. Das zu 69% Ausbeute entstandene Produkt ist vermutlich das noch nicht beschriebene Spirobi-[1,3-benzodithiol] (VII). Mit Phenylsenföl vereinigte sich zerfallendes III zu 38% 2-Phenylimino-1,3-benzodithiol (VIII), dessen Struktur durch unabhängige Synthese aus Dithiobrenzcatechin und Phenylisocyaniddichlorid in Gegenwart von Triäthylamin gesichert wurde.



VIII IX

Auch bei der Thermolyse oder Photolyse des 4-Phenyl-1,2,3-thiadiazols (I) trat das Thioketocarben nicht mit Alkenen, Alkinen oder Nitrilen zusammen. Der Zerfall des unsubstituierten 1,2,3-Thiadiazols in Schwefelkohlenstoff bei 200° lieferte zu nur 0,2% das bekannte 1,3-Dithiol-2-thion (IX)[6]

Summary. The aromatic thioketocarbene IV, generated by thermolysis of 1,2,3-benzothiadiazole at 200°, undergoes 1,3-dipolar additions with the CS-double bond of carbon disulfide, 1,3-benzodithiole-2-thion and phenyl isothiocyanate.

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[3] W. KIRMSE und L. HORNER, Liebigs Ann. Chem. *614*, 4 (1958).

[4] P. JACOBSON und H. JANSSEN, Liebigs Ann. Chem. *277*, 209, 218 (1893).

[5] W. R. H. HURTLEY und S. SMILES, J. chem. Soc. [London] *1926*, 1821, bereiteten VI aus Dithiobrenzcatechin, Schwefelkohlenstoff und Alkali.

[6] F. CHALLENGER, E. A. MASON, E. C. HOLDSWORTH und R. EMMOTT, J. chem. Soc. [London] *1953*, 292.