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Measurements on Isolated Double Bond Systems: Ultraviolet Absorption Spectra of Steroids and Triterpenoids¹

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Received September 5, 1961

Absorption due to nonconjugated double bonds in derivatives of steroids and triterpenoids has been examined in the ultraviolet by use of a commercially available recording spectrophotometer operating down to 170 m μ . Problems concerned with such measurements are discussed. The results are compared with those of several related studies, and relationships between spectra and structure are considered.

Accurate and reproducible determination of ultraviolet absorption spectra of isolated olefinic systems and related chromophores (in particular, the nonconjugated carbonyl functions) is a problem to many investigators. Conventional spectrophotometers are inherently limited, specifically by their optics and the interference due to oxygen bands. Investigation in the far-ultraviolet has been limited usually, down to approximately 190 m μ unless the somewhat onerous vacuum technique was employed. The region down to 160 m μ was studied by Turner² who used a vacuum spectrophotometer. Although this system affords accurate data over the desired range (160–210 m μ), vacuum spectrometers are not readily available and are inconvenient to use if one desires rapid results with a minimum of instrumentation problems. The Extended-Range Beckman DK-2 recording spectrophotometer³ now has made possible routine investigation of ultraviolet absorption spectra down to approximately 175 m μ with minimum effort.

Polycyclic substances, such as the triterpenoids and steroids, warranted primary consideration especially in view of recent publications^{2,4–7}

that deal with ultraviolet spectra of such compounds. Lack of agreement between the results obtained on the vacuum instrument by Turner² and those reported by the Swiss⁴ and British^{5,6} workers, who used conventional spectrophotometers with nitrogen flushing, indicated that a re-evaluation of the methods was in order. Especially obvious were the discrepancies below 195 m μ for isolated ethylenic bonds with respect to the Δ^7 -compounds, as well as for saturated ketones.

The Extended-Range DK-2 produced spectra¹ that, in general, agreed with those from the vacuum instrument, and the variations noted^{2,4–7} were possibly a consequence of the well recognized difficulties of measurement (energy loss due to oxygen and solvent absorption, scattered light, mirror deterioration, etc.⁸) in the end-absorption

(4) K. Stich, G. Rotzler, and T. Reichstein, *Helv. Chim. Acta*, **42**, 1480 (1959).

(5) P. S. Ellington and G. D. Meakins, *J. Chem. Soc.*, 697 (1960).

(6) J. H. Chapman and A. C. Parker, *J. Chem. Soc.*, 2075 (1961).

(7) (a) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, 1959; (b) an excellent coverage of the pertinent literature is presented in chapters 1 and 5.

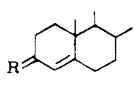

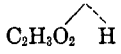

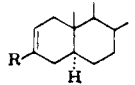


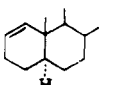
(8) For example, early in this study the Extended-Range instrument failed to have sufficient reference energy below 190 m μ . A consequence of this was a shift towards longer wave lengths of the apparent maximum of cholesterol acetate. The difficulty was overcome by replacement of a slightly blackened hydrogen lamp by one of improved design supplied by the manufacturer.

(1) A preliminary account of this work was presented by T. H. Applewhite and R. A. Micheli, *Tetrahedron Letters*, No. 16, 560 (1961).

(2) D. W. Turner, *J. Chem. Soc.*, 30 (1959).

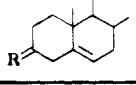
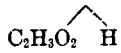


(3) Reference to a company or product by name does not imply approval or recommendation of the product by the Department of Agriculture to the exclusion of others which may also be suitable.

TABLE I
SPECTRA AND PROPERTIES OF A-RING UNSATURATED STEROIDS

	R	Curve No.	M.P. ^a	$\lambda_{\text{max}}^{\text{Cyclo}^b}$ m μ (ϵ)
				
Δ^4 -Cholestene-3 β -ol		I	129-130 Kof. (132) ^a	199.5 (8700)
Δ^4 -Cholestene-3 β -ol acetate		II	85-86 Kof. (85)	196 (13,500)
Δ^4 -Cholestene		III	82.5-83 (83)	193 (10,000)
				
Δ^2 -Cholestene-3-ol acetate		IV	89.5-92 (90-90.5)	180 ^c (8400)
		V		182 (8740) ^d
Δ^2 -Cholestene		VI	75.5-76.5 Kof. (74-75)	180 ^c (6600)
				
Δ^1 -Cholestene	—	VII	68.5-69.5 Kof. (68-69)	180 ^c (10,300)

^a Capillary m.p. except those designated Kof. (Kofler hot stage); m.p. in parenthesis are taken from refs. 7a, 14, or original literature. ^b Cyclo. = cyclohexane; Alc. = 95% ethanol. ^c Cut-off point of the solvent. ^d V was run in 0.1-cm. cells; corrected for solvent absorbance.

TABLE II
SPECTRA AND PROPERTIES OF Δ^4 -CHOLESTENE AND DERIVATIVES

	R	Curve No.	M.P. ^a	λ_{max} m μ (solvent) (ϵ)
				
Cholesteryl acetate		VIII	112.5-113 (115)	190 (Alc.) ^b (9400)
		IX		187 (Cyclo.) ^b (9700)
		X ^c		189 (Cyclo.) (10,000)
Cholesterol		XI	146-147 (149)	191 (Alc.) (9400)
		XII		189.5 (Cyclo.) (9900)
Δ^4 -Cholestene		XIII	90-91 (88-90)	190.5 (Alc.) (8900)
		XIV		189 (Cyclo.) (8900)

^a Footnote (a), Table I. ^b Footnote (b), Table I. ^c X was run in 0.1-cm. cells.

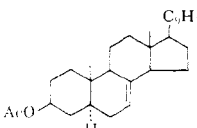
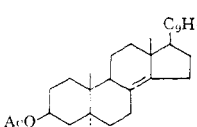
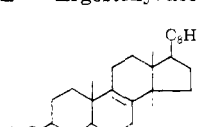
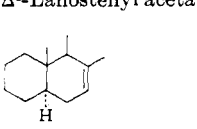
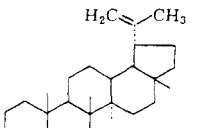
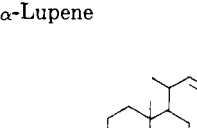
region. Compounds that might be expected to exhibit an absorption maximum in the 175-195-m μ region and some of the more highly strained ethylenic systems (195-205 m μ) were examined. The latter allowed interrelation and comparison of results from the various laboratories.

EXPERIMENTAL

Spectral determinations. Spectra were determined with a Beckman Model DK-2 "Extended-UV-Range" spectrophotometer³ that provides for operations down to 170 m μ . The equipment has been maintained under continuous dry nitrogen purge (ca. 2 cu. ft./hr.), which is necessary to

TABLE III

SPECTRA AND PROPERTIES OF B-RING, C-RING, AND SIDE CHAIN UNSATURATED COMPOUNDS

	Curve No.	M.P. ^a	$\lambda_{\max}^{\text{Cyclo}^b}$ $m\mu$ (ϵ)
 C ₂₇ H ₄₄ AcO H Δ ⁷ -Ergostenol acetate ^d	XV	156-158 (158-160; 157-159)	179.5 ^c (10,500) 203.5 (5770)
 C ₂₉ H ₄₈ AcO H Δ ⁸⁽¹⁴⁾ -Ergostenyl acetate	XVI	106.5-108 (110)	206 (12,000)
 C ₂₈ H ₄₆ AcO H Δ ⁸ -Lanostenyl acetate	XVII	120-121 (120-121)	200 (8330)
 H Δ ⁷ -Cholestene ^d	XVIII	86.5-87.5 (87)	181 (9000) 205 (5370)
 H ₂ C=CH ₃ α-Lupene	XIX	163-164 (164)	195 (9100)
 C ₂₈ H ₄₆ HO Stigmasterol	XX	169-170 (170)	188 (21,700)

^a Footnote (a), Table I. ^b Footnote (b), Table I. ^c Footnote (c), Table I. ^d Chromatographically pure. One Spot on a chromatostrip [Silica gel "G" E. Merck, (A.G.)] observed under ultraviolet light after spraying with 2',7'-dichloro-fluorescein dye. R_f 0.35 (cyclohexane-benzene 1:1) for XV; R_f 0.88 (cyclohexane-petroleum ether 1:1) for XVIII.

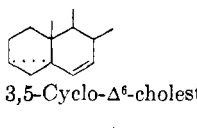
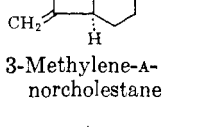
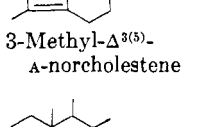
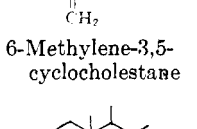
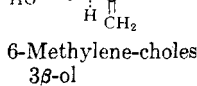
prevent oxidative deterioration of the aluminized surfaces and concomitant loss of energy.⁹ With a high purge rate (>1 cu. ft./min.) to remove oxygen and water vapor, the slits are operable (0.3 mm. at maximum sensitivity) to the 170- $m\mu$ limit. Stray light was estimated by procedures suggested by the manufacturer¹⁰; errors due to stray light have been discussed.¹ Typical control settings were: photomultiplier 20X, sensitivity 40, absorbance 0-1, period 0.2, speed 37 $m\mu$ /min., and 0-100% transmittance set at 250 $m\mu$, and base line checked with solvent in each path.

(9) "Preliminary Operating Instruction," August 1959, Beckman Instruments, Inc., Fullerton, Calif.

(10) Private communication, Beckman Instruments, Inc., Fullerton, Calif.

TABLE IV

SPECTRA AND PROPERTIES OF *exo* AND *endo* MONOUNSATURATED DERIVATIVES OF CHOLESTANE

	Curve No.	M.P. ^a	$\lambda_{\max}^{\text{Cyclo}^b}$ $m\mu$ (ϵ)
 3,5-Cyclo-Δ ⁶ -cholestene	XXI	70-71.5 (73)	207.5 (12,400)
 CH ₂ 3-Methylene-Δ-norcholestane	XXII	90-91.5 Kof. (90.6-91.8)	202.5 (6860)
 3-Methyl-Δ ³⁽⁵⁾ -Δ-norcholestene	XXIII	65-65.5 Kof. (65)	197.5 (10,600)
 CH ₂ 6-Methylene-3,5-cyclocholestane	XXIV ^c	58-61	196.5 (12,200)
 HO CH ₂ 6-Methylene-cholestane-3β-ol	XXV ^c	110-113	195.5 (13,200)

^a Footnote (a), Table I. ^b Footnote (b), Table I. ^c Ref. 17.

Solvents employed were 95% ethanol and Eastman Kodak cyclohexane, m.p. 4.5°, further purified through Davison #923 silica gel, as described by Potts.¹¹ Cyclohexane so purified (capacity ca. 700 ml. per 300 g. of silica gel) did not show the peak at 185 $m\mu$ that was evident in the starting material, and was usable to ca. 177 $m\mu$. Since no effect of "dissolved" oxygen could be detected either by boiling or by nitrogen purging of the cyclohexane, exclusion of air from the solvent was not considered necessary. Ethanol (95%) leaves much to be desired as a solvent in this spectral region (cut-off point ca. 187 $m\mu$). Since most of the compounds studied were easily soluble in cyclohexane (except for a few triterpenoid carboxylic acids), there was little need to use ethanol as a solvent. In cases where it was used, no special purification was necessary.

Two pairs of cells were used: 0.01-cm. and 0.1-cm. path length with faces of high transmissivity, fused quartz.¹² Most of the measurements were made in the 0.01-cm. pair that had path lengths of 0.0110 cm. (sample cell) and 0.0100 cm. (reference cell) as determined by comparison with cells measured by interferometry.¹³ This 10% difference accounts for the upturn in the blank curves: the values noted are almost exactly 10% of the solvent-against-nitrogen path curves below the points where the solvents begin to absorb (*vide infra*).

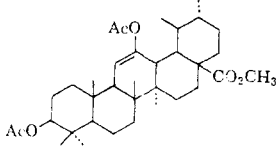
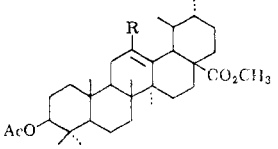
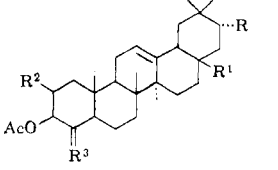
Solutions were prepared for spectral determinations either by direct weighing (to \pm 0.02 mg.) of 5 to 10 mg. of solute into 5- or 10-ml. volumetric flasks, or by difference weighings

(11) W. J. Potts, Jr., *J. Chem. Phys.* **20**, 809 (1952).

(12) American Instrument Co., Silver Springs, Md.

(13) We are indebted to Mr. Glen F. Bailey for these measurements.

TABLE V
 SPECTRA AND PROPERTIES OF TRITERPENOIDS

	R	Curve No.	M.P. ^a	$\lambda_{\text{max}}^{\text{Cyr.}^b}$ m μ (ϵ)
 Methyl Δ^{11} -ursene-3 β ,12-diol-28-oate diacetate	—	XXVI	216-218 (219-220)	198 (9600)
 Methyl Δ^{12} -ursene-3 β ,12-diol-28-oate diacetate	C ₂ H ₅ O ₂ —	XXVII	173-177 (175-179)	197.5 (7600)
Acetyl methyl ursolate	H—	XXVIII	246-247.5 (246-247)	193 ^c (7180)
 Soyasapoginol B triacetate R = C ₂ H ₅ O ₂ — R ¹ = CH ₃ — R ² = H— R ³ = C ₂ H ₅ O ₂ CH ₂ —CH ₃		XXIX	179-180 (180)	194.5 (9920)
Diacetoxy dimethyl medicagenate R = H— R ¹ = —CO ₂ CH ₃ R ² = C ₂ H ₅ O ₂ — R ³ = CH ₃ —CO ₂ CH ₃		XXX	248-250 (235-238) ^d	194.5 ^c (7570)
β -Amyrin acetate R = H— R ¹ = CH ₃ — R ² = H— R ³ = CH ₃ —CH ₃		XXXI	239-240.5 (241)	194.5 (8770)

^a Footnote (a), Table I. ^b Footnote (b), Table I. ^c Inflection. ^d See ref. 19.

of 1 to 2 mg. ($\pm 1 \mu\text{g.}$) into 1- or 2-ml. volumetric flasks. Concentrations of about 1 mg./ml. gave absorbances near 0.3. Since the 0.0110-cm. cell required only one drop of solution, the measurements could be carried out easily on less than 1 mg. samples if necessary.

Certain precautions must be noted in working with such short path cells of used quartz. The 0.01 cm. thick-film is tenaciously held by surface tension and must be dislodged with a sharp motion similar to that used with a clinical thermometer. Absorption of solutes and polar solvents also is troublesome. Adsorbed solutes can be displaced by methanol, and the adsorbed methanol then can be rapidly removed in high vacuum at room temperature. By using these techniques and by keeping exterior cell faces clean, reproducibility is possible.

Compounds. Significant structural features with respect to ultraviolet spectra and physical properties of the compounds are shown in Tables I-VII. References concerning the prep-

aration and physical properties of all compounds used, can be found in the Fiesers' *Steroids*^{7a} or in Elsevier's *Encyclopedia*,¹⁴ except for compounds IV,¹⁵ XXII,¹⁶ XXIV,¹⁷ XXV,¹⁷ XXVI,¹⁸ XXVII,¹⁸ XXXIII,¹⁸ XXXIV,¹⁸ and XXX.^{19,20}

(14) *Elsevier's Encyclopedia of Organic Chemistry*, Elsevier Publishing Co., Amsterdam, 1940-1959, Vol. 14 and supplements.

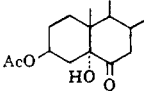
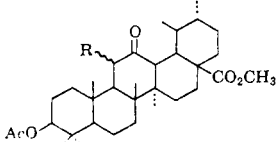
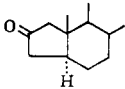
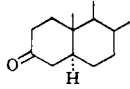
(15) W. G. Dauben, R. A. Micheli, and J. F. Eastham, *J. Am. Chem. Soc.*, **74**, 3852 (1952).

(16) W. G. Dauben and J. A. Ross, *J. Am. Chem. Soc.*, **81**, 6521 (1959).

(17) Unpublished work by W. G. Dauben and G. H. Berezin.

(18) From unpublished work by L. F. Fieser and R. A. Micheli. A note is *in press* which describes the preparation of these derivatives of ursolic acid.

TABLE VI
 SPECTRA AND PROPERTIES OF POLYCYCLIC KETONES

	R	Curve No.	M.P. ^a	Solvent λ_{\max} m μ (ϵ)
	—	XXXII	231.5–233 (232–233)	Cyclo. ^b 182 (6160)
	HO—	XXXIII	237 (242)	Cyclo. 178 ^c (8550)
Methyl ursan-3β-ol-12-one-28-oate acetate	H—	XXXIV	245–251 (246–248; 246–250)	Cyclo. 178 ^c (~7500)
	—	XXXV XXXVI	102–102.5 (100–100.5; 98)	Alc. ^b 186.5 ^c (1560) Cyclo. 178 ^c (3230)
	—	XXXVII XXXVIII	128–129 (129)	Alc. 186.5 ^c (2210) Cyclo. 178 ^c (4500)

^a Footnote (a), Table I. ^b Footnote (b), Table I. ^c Footnote (c), Table I.

RESULTS AND DISCUSSION

Compounds are grouped in Tables I through VII on the basis of structural similarities. The observed λ_{\max} and $(\epsilon)_{\max}$ values and the structural formulas of significant portions of the molecules are presented. The λ_{\max} and corresponding absorption intensity (ϵ) values in the tables have been supplemented by curves (Figs. 1–3), because the shape of the curves was of utmost significance especially for substances that exhibit maxima near or below the limit of the system; for example, certain Δ^1 - or Δ^2 -steroids (compounds IV, V, VI, and VII,

(19) C. Djerassi, D. B. Thomas, A. L. Livingston, and C. R. Thompson, *J. Am. Chem. Soc.*, **79**, 5292 (1957), reported m.p. 235–238° for this substance. Sample XXX was obtained by direct crystallization of the diacetate dimethyl ester from a methanolic solution of the crude saponin mixture. Recrystallization from the same solvent afforded the analytical sample with m.p. 248–250°. We are grateful to Professor C. Djerassi for a sample of his preparation, m.p. 246–249°, for comparison.

(20) Compounds were donated as follows: Professor W. G. Dauben; I, II, XVI, XXI–XXV, XXXV, and a sample of cholestane-3 β ,5 α -dihydroxy-6-one. Dr. T. G. Halsall; XVII. Dr. G. D. Meakins; III, XV, XVIII, and XIX. Professor R. B. Turner; VI and VII.

Table I) and the saturated ketones (compounds XXXII–XXXVIII, Table VI).²¹

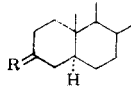
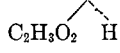


Unless otherwise noted all spectra were run in cyclohexane. Subtraction of the solvent absorption curve has been carried out. Curves XLIV–XLVII are included to show the shapes of the solvent blank and solvent absorbance curves.

To establish the reliability of our measuring system, wave length and molecular extinction coefficient values were compared with those obtained with a vacuum spectrometer (*e.g.*, by Turner²). Unlike earlier reports,^{4–6} our results (particularly in regard to λ_{\max}) are comparable to Turner's, down to the cut-off point of our system. Representative values for identical compounds used in both studies are included here for com-

Compound	Found λ_{\max} (ϵ_{\max})	Turner ² λ_{\max} (ϵ_{\max})
Cyclohexene	183.5 (7750) ¹	~183 (7500)
Δ^4 -Cholestene	193 (10000)	~192 (8860)
Δ^8 -Lanostenyl acetate	200 (8330) ¹	~201 (7000)

(21) The same Roman numeral is used for a compound and its corresponding curves.

TABLE VII
 SPECTRA AND PROPERTIES OF CHOLESTANE AND DERIVATIVES

	R	Curve No.	M.P. ^a	$\lambda_{\max}^{\text{Cyclo}^b}$ m μ (ϵ)
Cholestan-3 β -ol acetate		XXXIX	110-110.5 (111)	178 ^c (3910) ^d
Cholestan-3 β -ol		XL	141-142 (142)	178 ^c (3120) ^d
Cholestane		XLI	79.5-80 (80)	178 ^c (2310) ^d

^a Footnote (a), Table I. ^b Footnote (b), Table I. ^c Cut-off point of solvent. ^d Corrected for solvent absorbance.

parison (Turner's values were taken from his published curves). Other comparisons were made of related ethylenic systems. The over-all shape of the curves, as well as the coincidence of maxima and minima, for the Δ^7 -compounds are offered as additional evidence that our system is reliable and comparable to the results obtained with a vacuum instrument, down to approximately 180 m μ . Furthermore, at 178 m μ (the cut-off point of our system) the intensity values for cholestane derivatives (Table VII) are in good agreement with the ϵ values at 176 m μ reported by Turner²²; for example, 3120 (rep.²² 3140) for XL, 2310 (rep.²² 2760) for XLI.

Derivatives of Δ^5 -cholestene (Table II) were studied in both of the commonly employed solvents (cyclohexane and ethanol) and with different path lengths (0.1- and 0.01-cm. cells). Although we did not find great variation among the three members of this series, under identical conditions, there was considerable difference between the absorption maxima reported^{4,5} and our values, especially in the case of cholesteryl acetate (VIII-X). We have compared¹ the ϵ values at 5-m μ intervals from 210 m μ to 190 m μ for our curve IX with those from the plots published by Ellington and Meakins (ref. 5, Fig. 3, p. 700) and Stich, Rotzler, and Reichstein (ref. 4, Fig. 1, p. 1484). We are in excellent agreement down to \sim 197 m μ , at which point their values begin to diverge from ours. The λ_{\max} values of 193 m μ ⁴ and 195 m μ ⁵ are apparently artifacts due to instrumental limitations. Consequently, we must doubt the validity of such λ_{\max} and ϵ_{\max} values as well as the statement (ref. 4, footnote 46a, p. 1485): "... Die in Cyclohexan über 191 m μ gefundenen Maxima halten wir für reel. ..." In a more recent report by Chapman and Parker,⁶ the value for λ_{\max} at 189 m μ was close to our figure, but their ϵ_{\max} of 8000 is about 18% below ours. This conceivably was due to their admitted lack of precision of cell length and concentration. A further possible contribution to error could be from "near" stray light

or other energy losses. In view of such varied sources of error, no further comment seems necessary with respect to their values.

Many of the centers of unsaturation in steroids and triterpenoids can be determined by means of ultraviolet absorption spectra. However, the results should be supplemented by physical and chemical knowledge, in order to recognize positional as opposed to neighboring group effects.

The Δ^1 - and Δ^2 -cholestenes (Table I), because of their low λ_{\max} (<180 m μ), are readily distinguishable from the other monounsaturated compounds that we have considered. Moreover, the much higher ϵ value for the Δ^1 -steroids (\sim 10,000) compared to the Δ^2 - (\sim 7000) makes it possible to differentiate between these two classes of *cis*-disubstituted double bonds.

Trisubstituted double bonds, characteristic of the Δ^4 -, Δ^5 -, and Δ^7 -compounds (Tables I-III), impart spectra that are distinguished by their λ_{\max} and by the shape of the curves. For example, the identification of Δ^4 -cholestene [λ_{\max} 193 m μ (ϵ 10,000)] is possible because its curve differs sufficiently from that of corresponding Δ^5 -steroid [λ_{\max} 189 m μ (ϵ 8900)]. Absorption spectra of Δ^7 -compounds are unique in that they exhibit a maximum at 200-205 m μ (ϵ 5000-6000), a minimum at 195-200 m μ , and then rapidly rise until the intensity values are 9000-10,000 units at the lower limit of this measuring system.

The trisubstituted Δ^{12} -bond, which is so prevalent in triterpenoids, has been studied with typical examples of simple as well as polyfunctional members of the α - and β -amyrin series (Table V). Although considerable variation in the molecular extinction coefficients was observed, the consistency of the absorption maxima at approximately 194 m μ may prove useful in determining the presence of such a position of unsaturation. The curve for the terpene hydrocarbon α -pinene (XLII),²³ λ_{\max} 204.5 m μ (ϵ 4630), is included for comparison.

(23) We are indebted to Dr. Roy Teranishi for this sample of α -pinene, purified by preparative vapor phase chromatography.

(22) D. W. Turner, *Chem. and Ind.*, 626 (1958).

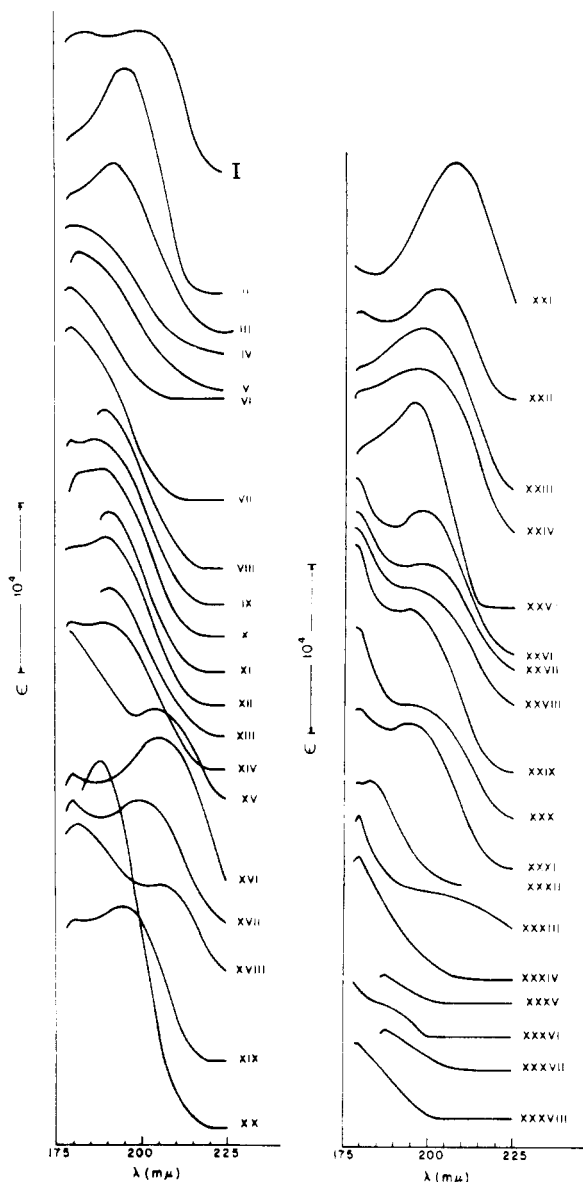


Fig. 1. Molecular extinction coefficient curves of A-ring unsaturated steroids I-VII (Table I); Δ^5 -cholestene and derivatives VIII-XIV (Table II); and B-ring, C-ring, and side chain unsaturated compounds XV-XX (cf. Table III)

Fig. 2. Molecular extinction coefficient curves of *exo* and *endo* mono-unsaturated derivatives of cholestane XXI-XXV (Table IV), triterpenoids XXVI-XXXI (Table V), and polycyclic ketones XXXII - XXXVIII (Table VI)

Platt and Klevens²⁴ have reported λ_{\max} 204 $m\mu$, and Turner² has discussed the high λ_{\max} value observed in his work with this compound.

Tetrasubstituted double bonds are characterized by absorption maxima at high wave lengths. That due to a Δ^8 -ethylenic center [e.g., Δ^8 -lanostenyl acetate (XVII)] is found at $\lambda_{\max} \sim 200 m\mu$, whereas the $\Delta^{8(14)}$ -steroids not only exhibit a

(24) J. R. Platt and H. B. Klevens, *Rev. Mod. Phys.*, **16**, 182 (1944).

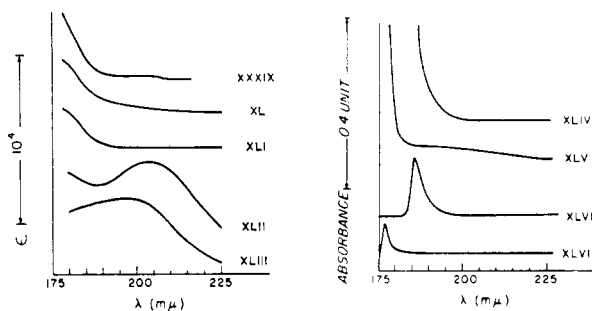


Fig. 3. Molecular extinction coefficient curves of cholestane and derivatives XXXIX-XLI (Table VII), α -pinene XLII, and dihydropyran XLIII; and absorption curves for 95% ethanol (XLIV) and cyclohexane (XLV) with nitrogen reference, ethanol with ethanol reference (XLVI), and cyclohexane with cyclohexane reference (XLVII), all in 0.01-cm. cells

maxima at even higher wave lengths but also have a very intense absorption coefficient [e.g., λ_{\max} 206 $m\mu$ (ϵ 12,000) for XVI]. Bladon *et al.*²⁵ noted similar results for this class of compound.

The values reported here for the diunsaturated compound stigmaterol (XX), λ_{\max} 188 $m\mu$ (ϵ 21,700), permit us to determine typical values for the side chain ethylenic center, to discuss the summation of intensity values, and to correlate our results with Turner's² (*vide supra*). At the λ_{\max} (estimated value 187 $m\mu$ from his published curves), Turner reported the intensities to be 11,300 and 11,600 for stigmast-22-en-3-yl acetate and ergost-22-en-3-yl acetate, respectively. Summation of either of these two intensity values with that of a typical Δ^5 -sterol [e.g., cholesteryl acetate (VIII), λ_{\max} 187 $m\mu$ (ϵ 9700)] compares favorably to the ϵ_{\max} for XX. Consequently, it seems likely that the ultraviolet spectra of a 1,2-disubstituted, *trans*-double bond, typified in the $\Delta^{22(23)}$ -sterols discussed above, would have $\lambda_{\max} \sim 187 m\mu$ ($\epsilon \sim 11,000$ -12,000) in our system. Although summation of intensity values at approximately equal wave lengths was noted by Ellington and Meakins⁵ in the range 193-198 $m\mu$, they find $\lambda_{\max} \sim 196 m\mu$ and $\epsilon_{\max} \sim 6000$ for the 1,2-disubstituted *trans*-ethylenic center. These values differ considerably from either our results or Turner's.² Furthermore, Platt and Klevens²⁴ have reported *trans*-9-octadecenoic acid to have λ_{\max} 188 $m\mu$ and $\log \epsilon$ 3.9, as determined with a vacuum instrument.²⁶

Interpretation of carbonyl absorption spectra in the far ultraviolet is difficult, for even under optimum conditions the curves can be very misleading. Since the maxima for the type of ketones examined here are generally $< 180 m\mu$, a judicious approach requires that the data be supplemented

(25) P. Bladon, H. B. Henbest, and G. W. Wood, *J. Chem. Soc.*, 2737 (1952).

(26) In unpublished work T. H. Applewhite and L. A. Goldblatt have found 12-hydroxy-*trans*-9-octadecenoic acid to have λ_{\max} 187 $m\mu$ and $\epsilon_{\max} \sim 12,000$ in the system described here.

by the solvent curves (see XLIV to XLVII). As Turner's²² work has indicated, a correction can be made for the absorption due to the hydrocarbon residue. Such corrections have not been indicated in the data presented here, but the spectra (XXX-IX-XLI) of selected cholestane derivatives (Table VII) are included. A consideration of the ϵ values (Tables VI and VII) shows that the hydrocarbon skeleton generally contributes about half the absorption; however, the shapes of the curves down to the cut-off point (*cf.* XXXIV to XXXVIII and XXXIX to XLI) suggest that no indication of maxima can be gained by subtraction. The saturated ketone curves (XXXIV to XXXVIII) included here (Table VI) make it apparent that, in general, no true absorption maxima are to be expected in the 178-205-m μ region. Thus, the values reported⁴⁻⁶ near 190 m μ are simply portions of lower intensity regions of the true curves and are of little, if any, diagnostic value. At the higher wave lengths good agreement is noted. As an example, for cholestanone (in alcohol) (XXXVII) at 194 m μ we found ϵ 1620 (1570 when corrected for solvent absorbance) and the reported values are 1670⁴ and 1600.⁵

The characteristic displacement of the weak carbonyl absorption band, found in the 280 m μ region, is often useful in determining the conformation of the α -substituent responsible for this shift.²⁷ Preliminary studies were made with two α -hydroxy ketones (XXXII and XXXIII) in order to determine the feasibility of applying this effect to the more intense carbonyl band at shorter wave lengths. Cholestanone-3 β -acetoxy-5 α -hydroxy-6-one (XXXII) which contains an axial α -hydroxy function is known to exhibit a positive shift of 20.5 m μ (λ_{\max} 299.5) over that of the parent ketone. That this compound also exhibits a true maximum at 182 m μ (ϵ 6160) is quite evident from curve XXXII. On the other hand, the triterpenoid derivative XXXIII, whose complete stereochemistry has not been established, does not exhibit a maximum within the limits of our system; the only change from the parent ketone XXXIV being an increase of intensity at 178 m μ and a change in the shape of the curve. Although the ursolic acid derivative XXXIII does not show a maximum and the implication is that an equatorial α -hydroxy ketone is present, insufficient data prevents a more positive identification at present.²⁸ Other model compounds were not readily available.

(27) See ref. 7a, pages 175-176, for a discussion and pertinent references.

(28) A comparison of $\Delta M_D - 141^\circ$ (M_D XXXIII + 7° ; M_D XXXIV + 148°). See ref. 19) for the ursolic acid derivatives with the $\Delta M_D - 117^\circ$ (equatorial) and + 63° (axial) of a similar set of compounds, *e.g.*, methyl 3 α -acetoxy-11 α -hydroxy-12-ketocholanoate ($M_D + 350^\circ$), methyl 3 α -acetoxy-11 β -hydroxy-12-ketocholanoate ($M_D + 530^\circ$), and methyl 3 α -acetoxy-12-ketocholanoate ($M_D + 467^\circ$) [G. Baumgartner and Ch. Tamm, *Helv. Chim. Acta*, **38**, 441 (1955)] strongly favors the equatorial conformation.

The solvent effect²⁹ has been studied on two ketones with cyclohexane and alcohol. A comparison of the spectra for A-norcholestane-2-one (XXXV and XXXVI) and those for cholestanone (XXXVII and XXXVIII) make it quite evident that any change in λ_{\max} brought about by using alcohol as the solvent is not visible in our system. In both cases the ϵ value at the cut-off point of alcohol is approximately half of the corresponding value at the cut-off point of cyclohexane, and if any shift in λ_{\max} occurs it is obscured by solvent absorption.

Several examples of shifts in λ_{\max} or ϵ_{\max} due to interaction of adjacent groups were observed. The marked bathochromic shift (>6 m μ) in conjunction with the variation in molecular extinction coefficients for the Δ^4 -cholestene derivatives (*cf.* I-III) appears to be an example of neighboring group participation.³⁰ This effect was not observed for the Δ^5 -sterols (Table II). While the pronounced change in absorption intensity between the Δ^2 -cholestene derivatives VI and IV may well be attributed to interaction of the neighboring π -electron system³⁰ of the 3-acetate, it seems quite possible that the very high ϵ value for Δ^1 -cholestene (VII) is a consequence of the auxochromic character of the adjacent, angular methyl group. The influence of an acetoxy group juxtaposed to an ethylenic center was noticeable in the few examples that were available and seems comparable in the enol acetates (compare XXVI, XXVII, and XXVIII) and the homoallylic system (compare II and III). Although the λ_{\max} of Δ^2 -cholestene (VI) and the related enol ester (IV) could not be determined more precisely, because of the solvent cut-off point, the $\Delta\epsilon$ at 180 m μ seems to follow the pattern set by the other two groups of compounds. The curve for the cyclic enol ether dihydropyran (XLVIII) [λ_{\max} 196 m μ (ϵ 4500)] is also included for comparison.³¹

It is interesting to compare the values for the two cyclosteroids (XXI and XXIV) with those for the related 6-methylene-cholestane-3 β -ol (XXV) listed in Table IV. Although the absorption intensities are essentially equal for all three compounds, the pronounced bathochromic shift of 12 m μ between XXI and XXV indicates a conjugation effect³² on the part of the cyclopropane ring and Δ^6 -ethylenic system³³—a phenomenon that does not occur markedly in the case of the noncoplanar exocyclic double bond of XXIV.

(29) L. Dorfman, *Chem. Revs.*, **53**, 49-50 (1953).

(30) C. F. Wilcox, Jr., S. Winstein, and W. G. McMillan, *J. Am. Chem. Soc.*, **82**, 5450 (1960).

(31) J. R. Platt, H. B. Klevens, and W. C. Price, *J. Chem. Phys.*, **17**, 466 (1949), found the values λ_{\max} 195 m μ (ϵ 3800) with a vacuum spectrometer.

(32) (a) S. Winstein, L. De Vries, and R. Orloski, *J. Am. Chem. Soc.*, **83**, 2020 (1960); (b) R. C. Cookson, R. R. Hill, and J. Hudec, *Chem. and Ind.*, 589 (1961).

(33) I. M. Klotz, *J. Am. Chem. Soc.*, **66**, 88 (1944), has discussed the ultraviolet properties of compound XXI.

Comparison of the ϵ_{\max} values of 3-methylene-A-norcholestane XXII and 3-methyl- $\Delta^{8(5)}$ -A-norcholestene XXIII again indicates an effect due to the methyl groups adjacent to the unsaturated center (see the discussion for the Δ^1 - and Δ^2 -cholestenes).

We conclude that routine examination of ultraviolet absorption spectra below 205 $m\mu$ of isolated double bonds and certain carbonyl functions, as well as the effects which substituents and neighboring groups impart, is now possible by means of commercially available purged instruments. The results are comparable to those obtained with vacuum spectrometers, down to about 180 $m\mu$, if

suitable solvents are used, and if certain rigid requirements of sufficient energy, low stray light, etc., are met. When considering the shorter wave length region, one must be cognizant of the fact that the apparent maximum often coincides with the cut-off point of the instrument and does not reflect the true variation of λ_{\max} and ϵ_{\max} with structure.

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ALBANY 10, CALIF.

[CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES, MERCK & CO., INC.]

A Novel Cleavage Reaction of Steroid 20,21-Oxalolactones. Synthesis of 16,16-Dimethylprednisone

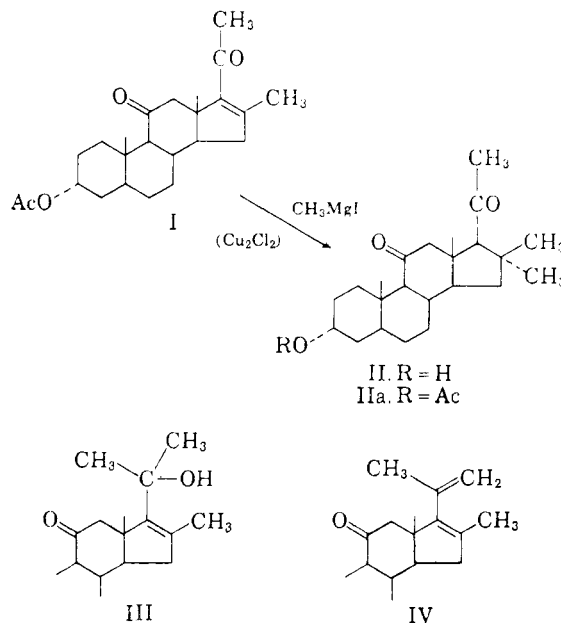
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Cleavage of steroid 17 α ,20-oxidooxalolactones (*e.g.*, VII) with bifunctional amines achieves quantitative release of the corresponding 17 α -hydroxy 20-ketone otherwise prone to D-homoannulation under the usual conditions of hydrolysis. This reaction made possible the synthesis of 16,16-dimethylprednisone.

The enhanced anti-inflammatory activity and lack of sodium retention associated with cortical steroid systems possessing a 16 α -¹ or 16 β -²-methyl group made it of interest to ascertain the effect of dimethyl substitution at that position. To this end 16,16-dimethylprednisone was synthesized,³ and the chemistry pertaining to its preparation is the subject of this paper.

The conjugate addition of methylmagnesium iodide to 3 α -acetoxy-16-methyl-16-pregnene-11,20-dione (I)⁴ in the presence of cuprous chloride⁵ proceeded in part by 1,4-addition to give 3 α -hydroxy-16,16-dimethylpregnane-11,20-dione (II). Although the maximum yield of II realized was 34%, this figure was difficult to achieve and average conversions were in the order of 20–25%. The for-



(1) (a) G. E. Arth, J. Fried, D. B. R. Johnston, D. R. Hoff, L. H. Sarett, R. H. Silber, H. C. Stoerk, and C. A. Winter, *J. Am. Chem. Soc.*, **80**, 3161 (1958); (b) E. P. Oliveto, R. Rausser, L. Weber, A. L. Nussbaum, W. Gebert, C. T. Coniglio, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman, and M. M. Pechet, *J. Am. Chem. Soc.*, **80**, 4431 (1958).

(2) (a) D. Taub, R. D. Hoffsommer, H. L. Slates, and N. L. Wendler, *J. Am. Chem. Soc.*, **80**, 4435 (1958); *J. Am. Chem. Soc.*, **82**, 4012 (1960); (b) E. P. Oliveto, R. Rausser, A. L. Nussbaum, W. Gebert, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman, and M. M. Pechet, *J. Am. Chem. Soc.*, **80**, 6627 (1958).

(3) R. D. Hoffsommer, H. L. Slates, D. Taub, and N. L. Wendler, *J. Org. Chem.*, **24**, 1617 (1959).

(4) H. L. Slates and N. L. Wendler, *J. Am. Chem. Soc.*, **81**, 5472 (1959).

(5) Metal chloride-catalyzed 1,4-additions of Grignard reagents to $\Delta^{\alpha,\beta}$ -ketones in general was first introduced by M. Kharasch and P. O. Tawney [*J. Am. Chem. Soc.*, **63**, 2308 (1941)]. The conjugate addition of methyl Grignard to Δ^{12} -20-keto steroids, which was first explored by R. E. Marker and H. M. Crooks [*J. Am. Chem. Soc.*, **64**, 1280 (1942)], has been utilized to an increasing extent more recently. In this connection see ref. 1, also R. P. Graber and M. B. Meyers, *Chem. & Ind.*, 1478 (1960); K. Heusler, J. Kebrle, C. Meystre, H. Uberwasser, P. Wieland, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **42**, 2043 (1959).