using other catalysts. Diacylated ferrocenes were not isolated from any of these reactions.

The mechanism of this metal carbonyl catalyzed reaction, assuming initial generation of **1**, is likely similar to those proposed for other catalysts.[3]

Experimental Section

General Procedure for $Mo(CO)_6$-Catalyzed Acylation of Ferrocene. A mixture of ferrocene (10–20 mmol), acid chloride (1.05/1.00 mole ratio of acid chloride/ferrocene), and $Mo(CO)_6$ (5–10 mol %) in *n*-heptane (80–200 ml) was refluxed with stirring under nitrogen for 1–2 days. The solution was cooled and filtered, and the filtrate was flash evaporated. The residue from flash evaporation was dissolved in benzene (or 1:1 hexane–benzene) and chromatographed on silica gel. Elution with benzene or hexane–benzene (1:1) gave unreacted ferrocene. The acylated ferrocene (**3**) was obtained on elution with benzene or benzene–ether. No diacylated ferrocene was isolated when ether, methylene chloride, or chloroform were used as eluents. The yields and melting points of **3** are listed in Table I. The acylated ferrocenes were identified on the basis of melting points, as well as infrared, nuclear magnetic resonance, and mass spectral results.

Acknowledgments. This research was supported by the Research Foundation of the State of New York. We are pleased to acknowledge gifts of generous quantities of $Mo(CO)_6$ by the Climax Molybdenum Co.

Registry No.—**3** (R = CH_3), 1271-55-2; **3** [R = $(CH_3)_2CH$], 41406-84-2; **3** (R = cyclohexyl), 51364-96-6; **3** (R = 1-adamantyl), 34699-71-3; **3** (R = C_6H_5), 1272-44-2; $Mo(CO)_6$, 13939-06-5; ferrocene, 102-54-5; acetyl chloride, 75-36-5; isobutyryl chloride, 79-30-1; cyclohexanecarbonyl chloride, 2719-27-9; adamantane-1-carbonyl chloride, 2094-72-6; benzoyl chloride, 98-88-4.

References and Notes

(1) H. Alper and C. C. Huang, *J. Org. Chem.*, **38**, 64 (1973).
(2) J. J. McDonnell and D. J. Pochopien, *J. Org. Chem.*, **36**, 2092 (1971).
(3) For a recent discussion of proposed mechanisms for electrophilic substitution of ferrocene, see E. G. Perevalova and T. V. Nikitina in "Organometallic Reactions," Vol. 4, E. I. Becker and M. Tsutsui, Ed., Wiley-Interscience, New York, N. Y., 1972, p 163.

Epimerization of Mestranol Acetate on Alumina

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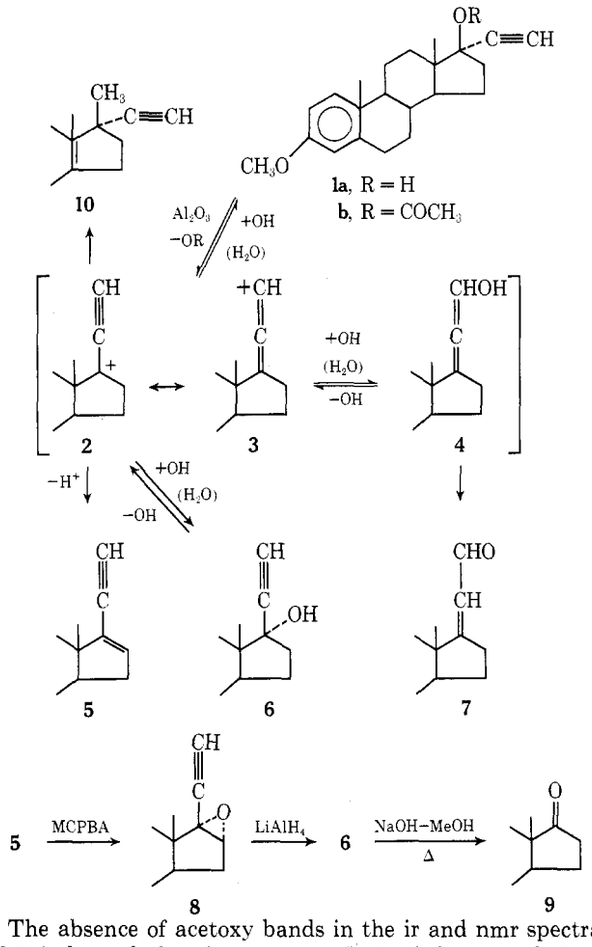
The preparation of 3-methoxy-19-nor-17α-pregna-1,3,5(10)-trien-20-yn-17β-ol (**1a**, mestranol) by ethynylation of the corresponding 17-ketone **9** is well known.[1] However, the epimeric 17β-ethynyl-17α-ol compound **6** (epimestranol) has apparently not been characterized.[2] During the course of a continuing investigation of the reactions of steroidal tertiary 17β-acetates on alumina, we observed the formation of other polar products in addition to the previously reported enynes arising from deacetoxylation.[4] We wish to report the formation of epimestranol **6** by an unexpected epimerization of mestranol acetate (**1b**) on alumina.

When a benzene solution of **1b** was allowed to remain in contact with a column[5] of neutral alumina[6] at room temperature for 5–10 days, the principal transformation product **5** (30–50%) was eluted as the least polar component, followed by a mixture of unchanged acetate **1b**, two closely moving products **6** and **7**, and finally by mestranol (**1a**). Repeated chromatography of this mixture on silica gel, followed by fractional crystallization, afforded **6** and **7**, each in 5% yield.



The absence of acetoxy bands in the ir and nmr spectra of **5** indicated that it was a product of deacetoxylation. The presence of a vinylic proton at δ 6.13 and a deshielded ethynyl proton at δ 3.07 in the nmr spectrum, as well as an augmented uv absorption at 225 nm (ϵ 19.200), established the conjugated enyne structure for **5**. The same enyne was obtained by treatment of **1a** with $POCl_3$ in pyridine.[7] An isomeric enyne detected by nmr in trace amounts in the mother liquors from **5** was identified as the product **10** formed by Wagner–Meerwein migration of the C_{13} methyl group to C_{17}, by comparison with an authentic sample obtained by dehydration of **1a** with formic acid.[8] Compound **6** appeared to be an ethynylcarbinol on the basis of its microanalysis and ir and nmr spectral data. The location of the ethynylcarbinol functions of **6** at C_{17} became evident from its conversion to the 17-ketone **9** *via* the base-induced reversal[10] of ketone ethynylation. Finally, **6** was also prepared by an alternate synthesis. Treatment of enyne **5** with *m*-chloroperoxybenzoic acid (MCPBA) afforded the epoxide **8**[11] (49%), which on reduction with $LiAlH_4$ furnished **6** (~15%), identical with that obtained by transformation of mestranol acetate (**1b**) on alumina. These results confirmed the epimeric relationship of **6** and **1a** at C_{17}. A conjugated aldehyde structure for **7**, as suggested by its spectral properties, was confirmed by comparison with authentic material.[9] Unlike the acetate **1b**, the parent carbinol **1a** failed to give transformation products on alumina.

The formation of the observed alumina-transformation products from **1b** can be explained by invoking a carbonium ion mechanism. The mesomeric carbonium ion **2** ↔ **3** can be formed by a loss of acetate ion[12] on the dipolar[13] surface of alumina. Formation of the conjugated aldehyde **7** *via* the enol **4**, by reaction of the allenic form **3** of the mesomeric cation with water from alumina, is recogniz-

able as a Meyer–Schuster[14] rearrangement product. Reaction of the propargylic cation[15] **2** with water could then account for the formation of **6** and **1a**.[16] Formation of the enyne **5** and the appearance of compounds such as **10** have been previously noted in such acid-catalyzed reactions.[8,17] Such transformations on alumina appeared generally to occur with other 17α-ethynyl-17β-acetoxy steroids lacking a Δ^4-3-ketone function in ring A. The apparent inertness of 17α-ethynyl-17β-acetoxy-Δ^4-3-keto steroids presently remains unexplained, since the corresponding 17α-methyl-17β-acetoxy-Δ^4-3-keto steroids do indeed undergo deacetoxylation.[4]

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus (unless otherwise indicated) and are uncorrected. The ir spectra were recorded on a Beckman IR-8 spectrophotometer in KBr pellets; the uv spectra were determined on a Cary Model II recording spectrophotometer in ethanol; and the nmr spectra were recorded on a Varian A-60 spectrometer in $CDCl_3$. Chemical shifts are reported in parts per million relative to TMS. Mass spectra were recorded on a Finnigan MS 1015-D spectrometer. Optical rotations were determined on a Rudolph Model 70 polarimeter attached to a Model 200 photoelectric unit for 1% solutions in $CHCl_3$ unless otherwise indicated. Tlc analyses were performed on Uniplate Silicar 7-GF (Analtech Inc.). For column chromatography Silic-AR-CC-7 (Mallincrodt Chemical Co.) was used. All evaporations were carried out *in vacuo*. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

3-Methoxy-19-norpregna-1,3,5(10)-trien-20-yn-17α-ol (Epimestranol, 6). A. From the Reaction of 1b on Alumina. A solution of **1b** (10 g) in benzene (50 ml) was adsorbed on a column of neutral alumina (1 kg) in benzene and allowed to stand for 10 days at room temperature. The column was then eluted with benzene containing increasing proportions of EtOAc and finally stripped with EtOAc and 125-ml fractions were collected. These were pooled into three major fractions on the basis of tlc. The least polar fraction (4.16 g, 50%), consisting mainly of the enyne **5**, was recrystallized from CH_2Cl_2–MeOH to afford an analytical sample of **5** (3.5 g): mp 156–157°; $[\alpha]^{26}D$ +63°; uv 225 nm (ε 19,200), 277 (2200), 286 (2100); nmr δ 7.3–6.5 (m, 3 H, aromatic), 6.13 (t, 1 H, J = 2.5 Hz, 16-H), 3.75 (s, 3 H, OCH_3), 3.07 (s, 1 H, C≡CH), and 0.87 (s, 3 H, 18-CH_3).

Anal. Calcd for $C_{21}H_{24}O$: C, 86.25; H, 8.27. Found: C, 86.47; H, 8.15.

A trace amount of the enyne **10** detected by tlc in the mother liquors from **5** was identified by the presence of a signal at δ 1.31 in the nmr spectrum (C-13 methyl migrated to C-17) by comparison with a sample obtained by dehydration of **1a** with formic acid (as described below).

The middle fraction (2.7 g) consisted of a mixture of **1b**, **6**, **7**, and **1a** (in the order of their decreasing R_f value on tlc). Repeated chromatography of this fraction on silica gel columns using 2–5% EtOAc in C_6H_6 for elution, followed by fractional crystallization from MeOH, afforded **6** (0.44 g, 5%) and **7** (0.45 g, 5%) as analytical samples. Epimestranol (**6**) had mp 136–137°; ir 2.8 (OH), 3.04 μ (C≡CH); nmr δ 6.5–7.3 (m, 3 H, aromatic), 3.76 (s, 3 H, OCH_3), 2.51 (s, 1 H, C≡CH) and 0.90 (s, 3 H, 18-Me); mass spectrum m/e 310 (molecular ion).

Anal. Calcd for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 81.01; H, 8.39.

Aldehyde **7** had mp 173–175°; $[\alpha]^{24}D$ +60° (reported[9] mp 175–177°; $[\alpha]D$ +63.5°).

The most polar fraction was largely mestranol (**1a**, 1.5 g) on the bsis of tlc and ir.

B. From the Reduction of 8 with $LiAlH_4$. $LiAlH_4$ (10 g) was slowly added at room temperature to a stirred solution of **8** (10 g) in THF (800 ml) and the mixture was heated at reflux under nitrogen for 1.5 hr. The reaction mixture was then cooled in an ice bath, stirred vigorously, and treated cautiously in succession with H_2O (10 ml), 15% aqueous NaOH (10 ml), and H_2O (30 ml). The granular precipitate was separated by filtration and washed several times with ether. The combined organic solutions were taken to dryness and the residue was chromatographed on a silica gel (500 g) column. The enyne **5** (4.42 g) was eluted with benzene followed by **6** (1.5 g, 15%) eluted with 1% EtOAc–C_6H_6. These were identical (melting point, ir, nmr) with the products obtained by transformation of **1b** on alumina.

3-Methoxy-16α,17-epoxy-19-norpregna-1,3,5(10)-trien-20-yne (8). A solution of MCPBA (8.0 g) in $CHCl_3$ (300 ml) was slowly added over a period of 0.5 hr to a stirred solution of **5** (5.5 g) in $CHCl_3$ (250 ml) at room temperature. Stirring was continued for an additional 5 hr, after which the excess peracid was destroyed by the addition of an aqueous 10% $NaHSO_3$ solution. The $CHCl_3$ layer was washed successively with aqueous 10% $NaHCO_3$ and H_2O, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel and eluted with benzene–petroleum ether (35:65) to give unreacted **5**. Further elution with benzene–petroleum ether (50:50) afforded **8** (2.85 g, 49%). Recrystallization from CH_2Cl_2–MeOH gave an analytical sample: mp 199.5°; $[\alpha]^{26}D$ +103° (*c* 0.5, $CHCl_3$); uv 278 nm (ε 1980), 287 (1850); ir 3.03 (C≡CH), 3.31 μ (16α-H); nmr δ 3.65 (s, 1 H, 16β-H), 2.41 (s, 1 H, C≡CH), and 0.94 (s, 3 H, 18-Me).

Anal. Calcd for $C_{21}H_{24}O_2$: C, 81.78; H, 7.84. Found: C, 81.91; H, 7.81.

Conversion of 6 to 9. Deethynylation of **6** (50 mg) following the method of Langecker[10] by heating at reflux with methanolic NaOH (10 ml, 1 *N*) afforded **9** (15 mg), mp 172°, identical with an authentic commercial sample (ir, tlc).

3-Methoxy-19-norpregna-1,3,5(10),16-tetraen-17-yne (5). A solution of **1a** (5 g) in dry pyridine (50 ml) and freshly distilled $POCl_3$ (2.6 ml) was heated at reflux for 2 hr, cooled, and poured into ice and concentrated HCl. The suspension was extracted with a mixture of ether and CH_2Cl_2 (3:1), washed with aqueous 10% Na_2CO_3 and H_2O, dried (Na_2SO_4), and evaporated. Chromatography of the dark residue on a column of silica gel and elution with benzene afforded a colorless, crystalline solid, mp 156–157°, identical (ir, nmr) with that obtained by deacetoxylation of **1b** on alumina.

3-Methoxy-17β-methyl-18,19-dinorpregna-1,3,5(10),13(14)-tetraen-20-yne (10). A mixture of **1a** (1.0 g) and formic acid (50 ml, 90%) was heated under reflux for 1.5 hr. The red solution was cooled, poured into ice, and extracted with CH_2Cl_2. The organic layer was washed with aqueous 10% $NaHCO_3$ and H_2O, dried (Na_2SO_4), and evaporated. The residue (1.0 g) was chromatographed on a column of silica gel in hexane. Following an initial oily fraction, elution with increasing proportions of C_6H_6 in hexane afforded **10** as a crystalline solid (0.282 g, 30%) which upon recrystallization from MeOH gave mp 108–112°; $[\alpha]^{24}D$ −26°; ir 3.08 μ (C≡CH); nmr δ 7.3–6.4 (m, 3 H, aromatic), 3.80 (s, 3 H, OCH_3), 2.18 (s, 1 H, C≡CH), and 1.31 (s, 3 H, 17β-Me).

Anal. Calcd for $C_{21}H_{24}O$: C, 86.25; H, 8.27. Found: C, 86.07; H, 8.31.

Acknowledgment. We wish to thank Drs. S. D. Levine and J. A. Settepani for their helpful comments, members of our Analytical Research Group for spectral and other analytical data, and Mr. R. E. Adams and our Pilot Plant Group for technical assistance.

Registry No.—**1a**, 72-33-3; **1b**, 10382-22-6; **5**, 23640-47-3; **6**, 4502-08-3; **7**, 19683-43-3; **8**, 51510-21-5; **10**, 24742-97-0.

References and Notes

(1) F. B. Colton, U. S. Patent 3,666,769 (1954).
(2) The formation of **6** in trace amounts during the process of ethynylation of **9** would not be surprising in view of similar results reported for other 17-keto steroids.[3] The nmr chemical shifts of the C_{18} and ethynyl protons for **6**, identical with those obtained by us, were reported by O. Engelfried, H. Gibian, F. Newman, K. Prezewowsky, G. Schutz, and R. Weichert, *Arzneim.-Forsch.*, **16**, 1518 (1966). However, neither the source of the compound nor other physical properties were noted.
(3) A. T. Reichstein and C. Meyster, *Helv. Chim. Acta*, **22**, 728 (1939).
(4) R. Kanojia, S. Rovinsky, and I. Scheer, *Chem. Commun.*, 1581 (1971).
(5) Subsequently, the transformation was also demonstrated by stirring a slurry of alumina with a benzene solution of **1b**.
(6) M. Woelm, neutral alumina, activity I. Basic and acidic alumina also gave these transformation products.
(7) E. Ghera, *J. Org. Chem.*, **33**, 1042 (1968).
(8) (a) C. Quannes, M. Dvolaitzky, and J. Jacques, *Bull. Soc. Chim. Fr.*, 776 (1964); (b) P. Crabbe and E. Eisneras, *Rev. Soc. Quim. Mex.*, **9**, 185 (1965); *Chem. Abstr.*, **64**, 12749h (1966).
(9) W. R. Benn, *J. Org. Chem.*, **33**, 3113 (1968).
(10) H. Langecker, *Naturwissenschaften*, **46**, 601 (1959).
(11) The 16α,17 stereochemistry of the epoxide is believed to be consistent with the known stereochemical course of epoxidation of 17-substituted 16-enes. See (a) C. W. Shoppe, *Nature (London)*, **166**,

107 (1950); (b) G. J. Mathews and A. Hassner in "Organic Reactions in Steroids," Vol. II, J. Fried and J. A. Edwards, Ed., Van Nostrand-Reinhold, Princeton, N. J., 1972, p 2, and references cited therein.
(12) In view of the more facile leaving nature of an acetate group as compared to a hydroxyl group, the relative inertness of **1a** under the circumstances is not surprising. Moreover, possible transient existence of the relatively strongly bound carbinol **1a** on alumina as an alkoxide could also prevent the formation of such a cationic species.
(13) (a) S. E. Tung and E. Meinich, *J. Catal.*, **3**, 229 (1964); (b) B. D. Flockhart, C. Naccachi, J. A. N. Scott, and R. C. Pink, *Chem. Commun.*, 238 (1965); (c) G. M. Schwab and H. Kral, *Proc. Int. Congr. Catal., 3rd*, **1**, 433 (1964).
(14) K. Meyer and K. Schuster, *Ber.*, **55**, 819 (1922).
(15) The first direct observation of such a cation by treatment of an ethynylcarbinol with sulfuric acid was reported by H. G. Rickey, Jr., J. C. Phillips, and L. E. Rennick, *J. Amer. Chem. Soc.*, **87**, 1381 (1965).
(16) Hydrolysis of **1b** on prolonged contact with alumina must contribute to the greater abundance of **1a**.
(17) N. L. Wendler in "Molecular Rearrangements," Part 2, P. de Mayo, Ed., Interscience, New York, N. Y., 1964, p 1019.

Structures of Suaveolic Acid and Suaveolol[1]

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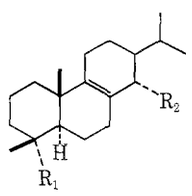
Several species of *Hyptis* have been found to possess significant pharmacological properties.[3] An investigation of *Hyptis suaveolens* (L) Point (Labiatae), a species widespread throughout tropical America[4] and reputed to possess medicinal properties,[5] has led to the isolation of two novel diterpenes for which the names suaveolic acid and suaveolol are proposed.

Suaveolic acid (**1**) was obtained by extraction of the dried leaves and stems of *H. suaveolens* with either acetone or methanol, and its infrared spectrum revealed the presence of both COOH and OH groups. Although its nmr spectrum showed that no vinyl protons were present, a strong absorption in the Raman spectrum of **1** at 1650 cm^{-1} indicated that the structure contained a C=C bond. The nmr spectrum, in addition to confirming the presence of two exchangeable hydrogens, indicated that suaveolic acid contained an isopropyl group and two quaternary methyl substituents. Furthermore, a one-proton signal at δ 3.81 (d, J = 7 Hz) suggested that the alcohol function was secondary.



1, R_1 = CO_2H; R_2 = OH
2, R_1 = CO_2Me; R_2 = OH
3, R_1 = CO_2Me; R_2 = OAc
4, R_1 = CO_2Me; R_2 = =O
5, R_1 = CH_2OH; R_2 = OH
6, R_1 = CH_2OAc; R_2 = OAc

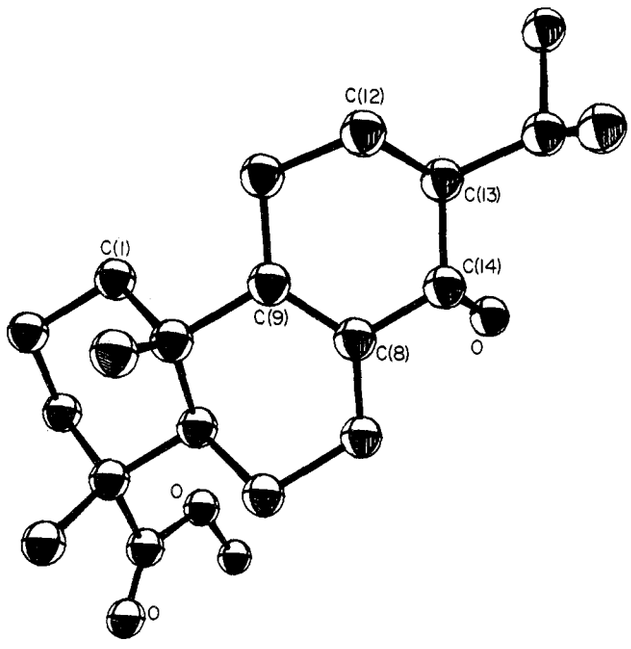


Figure 1. A perspective drawing of methyl suaveolate (relative configuration). All atoms are drawn with the same radius and hydrogens are omitted for clarity.

Treatment of **1** with diazomethane gave methyl suaveolate (**2**), which, upon exposure to acetic anhydride in pyridine, produced a secondary acetate (**3**) showing a one-proton doublet (J = 7 Hz) at δ 5.33. The low-field position of this signal[6] suggested that the CHOH proton in suaveolic acid might be allylic, and this was confirmed by oxidation of methyl suaveolate with Jones reagent to an α,β-unsaturated ketone **4**.[7] The chemical evidence implies a structure for **1** based upon 8-abieten-18-oic acid,[8] with placement of the OH at C-14 rather than C-11 dictated by the fact that in **1**, **2**, and **3** the CHOH proton appears as a well-defined doublet.

Suaveolol (**5**) was isolated after chromatography of the *Hyptis* extract on alumina and also by direct crystallization from the extract. It showed no carbonyl absorption, but its nmr spectrum revealed both primary and secondary alcohol functions. As in the case of **1**, the Raman spectrum (1670 cm^{-1}) of **5** clearly indicated the presence of a tetrasubstituted double bond. Treatment of suaveolol with acetic anhydride in pyridine gave a gummy diacetate **6**. The relationship between suaveolic acid and suaveolol was established by reduction of methyl suaveolate with lithium aluminum hydride, which gave **5** in high yield.

In order to confirm the structural hypothesis and to establish the relative stereochemistry of **1** and **5**, an X-ray determination of the structure of methyl suaveolate was undertaken. A computer-generated drawing of the final X-ray model is shown in Figure 1.[9] A double bond is clearly indicated between C-8 and C-9 in **2**. The OH group at C-14 is in the α configuration and hydrogen bonded to the methanol of crystallization, with an O–O distance of 2.65 Å. The isopropyl group at C-13 is in the β configuration.

Although oxygen substitution at C-12 of the abietane skeleton is commonplace,[10] oxygenation at C-14 is rare.[11] The structures of suaveolic acid (**1**) and suaveolol (**5**) are also unusual in that the oxygenated C ring is nonaromatic.

Experimental Section

General. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. Ultravio-