The ethereal filtrate from above gave a deep purple color when a sample of it in EtOH was treated with a few drops of 5% aqueous $FeCl_3$ solution. This test is indicative of the presence of a hydroxamic acid (such as **5**).[4] The solution was distilled at reduced pressure in order to remove the ether solvent, and the dark oily residue was crystallized from hot aqueous EtOH. The colored solid thus obtained, **5**, gave a positive test with $FeCl_3$ solution and was identical with an authentic sample of **5**[3] when these samples were compared by tlc. The yield of **5** was 84 mg (43.5%).

α-Methyl-α-(*o*-aminophenoxy)propionylglycine Ethyl Ester (7, R = H, R′ = Et).—A solution of 0.7868 g (2.54 mmol) of **3** (R = H, R′ = Et) in 25 ml of THF and 15 ml of water was treated with Al(Hg)[8] made from 0.685 g (0.0254 g-atom) of Al. The resultant mixture was stirred at room temperature and a tlc was run after 90 min. The only zone visible had an R_f of ~0.6, which was smaller than that of the starting material. After being stirred for 105 min, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure in order to remove the THF. The aqueous residue contained a relatively large amount of crystals which gave a negative test with $FeCl_3$ in aqueous alcohol.[7] These were collected, washed with water, and dried. The yield of **7** (R = H, R′ = Et) was 0.5763 g (81%): mp 100.0–101.5°; ir (CH_2Cl_2) 3457 (NH), 1745 (ester C=O), 1681 (amide I), 1502 (amide II), and 1617 (aromatic stretching); nmr ($CDCl_3$) consistent with kind and number of protons present in **7** (R = H, R′ = Et). One recrystallization from benzene and petroleum ether (bp 30–60°) (1:5) afforded an antlytically pure sample: mp 101.0–101.5°.

Anal. Calcd for $C_{14}H_{20}N_2O_4$: C, 59.98; H, 7.19; N, 10.00. Found: C, 60.34, 60.54; H, 7.43, 7.28; N, 10.32, 10.13.

Compound **7** (R = H, R′ = Et) was converted into H-Gly-OEt·HCl by a procedure similar to that used on **4** (R = H, R′ = Et) above. The time required for cyclization and fragmentation to **8** and **6** (R = H, R′ = Et), however, was 18 hr, and the yield of the second product was 62%. Comparable figures *via* the hydroxylamino derivative **4** (R = H, R′ = Et) were 2½ hr and 72.8%.

Registry No.—**3** (R = H, R′ = Et), 20178-13-6; **3** (R = i-Bu, R′ = Et), 20178-14-7; **3** (R = CH_3, R′ = Et), 20178-15-8; **3** (R = CH_3, R′ = Me), 20178-16-9; **3** (R = $C_6H_5CH_2$, R′ = Me), 20178-17-0; **3** (R = i-Pr, R′ = Me), 20178-18-1; **7** (R = H, R′ = Et), 20178-19-2; zinc chloride, 7646-85-7; ammonium chloride, 12125-02-9.

Acknowledgment.—Support of this work in part by a Frederick Gardner Cottrell Grant in Aid of the Research Corporation, New York, N. Y., is gratefully acknowledged.

(8) I. Vogel, *J. Chem. Soc.*, 597 (1927).

Resin Acids. XVI. Some Transformations of Methyl 12α-Hydroxy-13β-abiet-8(9)-en-18-oate[1,2]

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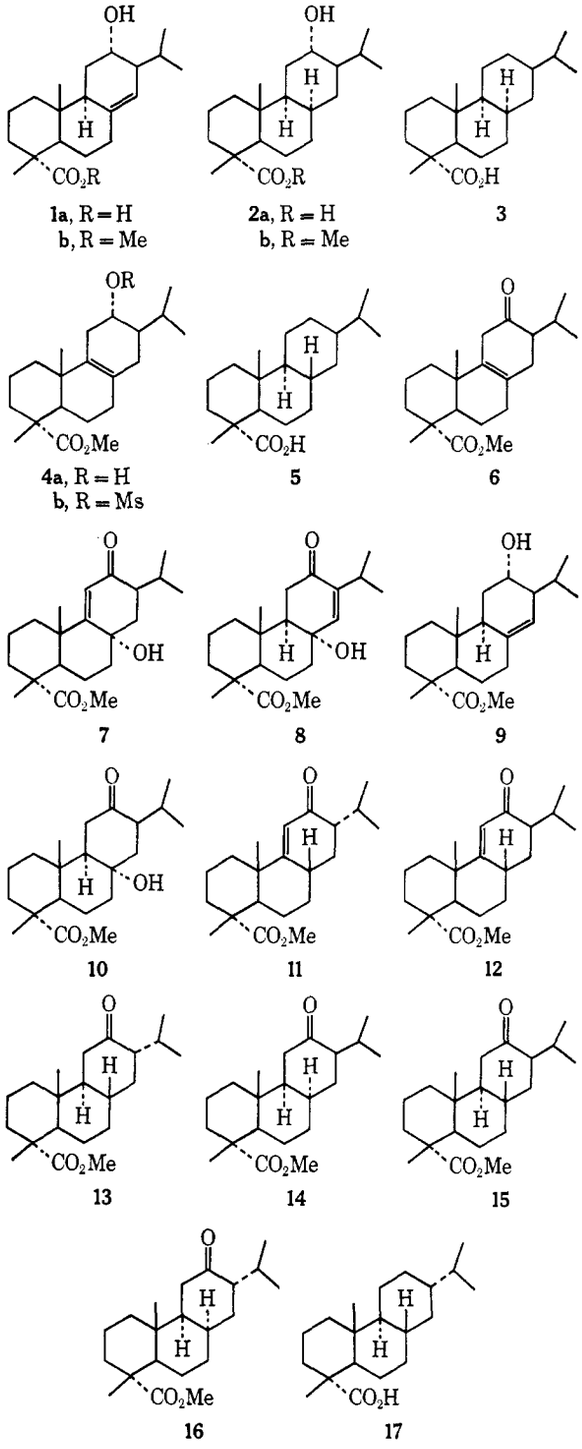
Received January 14, 1968

In an earlier[4] paper we reported the hydrogenation of **1a** to **2a** in acetic acid solution. The corresponding methyl ester **2b** was utilized[5] for our synthesis of authentic 8α,13β-abietan-18-oic acid (**3**),[6] and was generally prepared by hydrogenation of **1b**[8] in ethanol.



In an effort to improve the yield, the reduction was carried out in acetic acid, with the result that partial

(1) Previous paper, W. Herz and R. C. Blackstone, *J. Org. Chem.*, **34**, 1257 (1969).

(2) Supported in part by a grant from the National Science Foundation (GP-6362).

(3) National Science Foundation Fellow 1967–1968.

(4) W. Herz, H. J. Wahlborg, W. D. Lloyd, W. H. Schuller, and G. W. Hedrick, *J. Org. Chem.*, **30**, 3190 (1965).

(5) J. M. Huffman, T. Kamiya, L. H. Wright, J. J. Schmid, and W. Herz, *ibid.*, **31**, 4128 (1966).

(6) Numbering and nomenclature used in this paper are based on a recent proposal (third revision, October 1968) by J. W. Rowe, "The Common and Systematic Nomenclature of Cyclic Diterpenes," subscribed to by most workers in the area. The parent abietane skeleton possesses the *trans-anti-trans* configuration with a 13α-isopropyl group.[7] Inverted configurations are designated by the position number and the correct stereochemistry just before the skeletal name.

(7) E. Fujita, T. Fumita, and H. Katayama, *Chem. Commun.*, 968 (1967).

(8) W. G. Dauben and R. Coates, *J. Org. Chem.*, **28**, 1698 (1963).

isomerization (20%) to a new hydroxy ester took place.[9] The new compound was identified as **4a** because of the nmr spectra which had no signals characteristic of vinyl protons. It exhibited the resonance of an axial (H-12) proton as a broad multiplet ($W_{1/2}$ = 19 Hz) and the C-10 methyl signal at 0.97 ppm, 6 Hz downfield relative to **5** in accordance with the postulated structure.[10] Some transformations of this compound which cast additional light on stability relationships in the abietane series are reported in this note.

Oxidation of **4a** with Jones reagent[12] gave two products (9:1) readily separable by chromatography. The major product appeared to be **6** (ir bands at 1720 and 1712 cm^{-1}). The nmr spectrum possessed a somewhat broadened ($W_{1/2}$ = 7 Hz) two proton signal at 2.73 ppm which was ascribed to the 11-methylene group. The minor product, $C_{21}H_{34}O_4$, was a hydroxylic α,β-unsaturated keto ester (ir bands at 3600, 1658, and 1605 cm^{-1}, λ_{max} 236, ϵ 19,800), whose nmr displayed a very sharp singlet at 5.83 ppm ascribable to a vinyl proton α to the carbonyl groups. The absence of other low-field signals required that the hydroxyl group be tertiary and attached to C-8, since a proton at C-8 would have been expected to couple allylically to H-11 (*vide infra*). Moreover the observed chemical shift of the C-10 methyl group (1.26 ppm) corresponded approximately to the expected deshielding effect of the $\Delta^{9(11)}$-12-oxo function (16 Hz);[11] hence the hydroxyl group was assigned the 8α configuration as in **7**.

The formation of an analogous α,β-unsaturated γ-hydroxy ketone (**8**) as a minor product in the oxidation of **9** has been reported previously. Hydrogenation of **8** gave **10**.[4] Hydrogenation of **7** also afforded **10**, thus confirming the postulated structure.

It was expected that isomerization of **6** would result in predominant formation of one of the two possible 8β-H isomers **11** or **12**. However base treatment of **6** or exposure to acid-washed alumina produced a 1:1 mixture of *two* α,β-unsaturated keto esters (A and B) which were separated by preparative tlc. The less polar keto ester A (ir bands at 1722, 1658, and 1605 cm^{-1}; λ_{max} 238 nm, ϵ 12,500, vinyl proton signal at 5.78 ppm, $J_{H\text{-}11,H\text{-}8}$ = 2 Hz) could be hydrogenated to the known[4,8] keto ester **13**. Hence hydrogenation of A took place exclusively from the α face and ketone A had to be **11**.

Hydrogenation of the more polar keto ester B (ir bands at 1719, 1660, and 1609 cm^{-1}, λ_{max} 241 nm, ϵ 15,000, vinyl proton signal at 5.70 ppm, $J_{H\text{-}11,H\text{-}8}$ = 1.8 Hz) in a similar fashion gave a new saturated keto ester C (ir bands at 1716 and 1700 cm^{-1}) different from **13** and the previously reported **14**.[4] On the assumption that hydrogenation of B, like that of A, had taken place from the α face, keto ester C had to be formulated as either **15** or **16**.

The octant rule predicts a fairly strong positive Cotton effect for **15**, almost all of the contributing atoms of ring B and C being located in the upper left rear octant, whereas **16** might be expected to exhibit a negative Cotton effect even if ring C were somewhat distorted.[4] Since the observed Cotton effect was positive and of moderately strong amplitude, formula **15**, in which the isopropyl group is axial and should be epimerizable, was strongly favored. Indeed, base-catalyzed equilibration of C resulted in quantitative conversion to **13**. Hence C was **15** and B was **12**.[13]

(9) Treatment of a chloroform solution of **2a** with gaseous hydrogen chloride was somewhat more efficient for producing the new isomer (40% of **4a**, 20% of starting material and 40% of a mixture of unidentified substances).

(10) In the steroid series, $\Delta\delta$ $\Delta^{8,9}$ = 7 and $\Delta\delta$ 12α-OH = −0.5 Hz.[11]

(11) R. F. Zürcher, *Helv. Chim. Acta*, **46**, 2054 (1963).

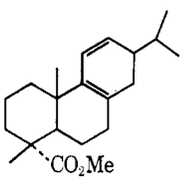
(12) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, New York, N. Y., 1967, p 142.

Experimental Section[14]

Methyl 12α-Hydroxy-13β-abiet-8(9)-en-18-oate (4a).—Gaseous hydrogen chloride was bubbled through a chloroform solution of 4.0 g of **2a** for 3 hr. The solution was washed thoroughly with water, dried, and evaporated. The residue, 3.8 g, was chromatographed over alumina. Elution with hexane–benzene (1:1) gave nonhydroxylic material. Elution with benzene gave **4a** (40%) followed by **2a** (20%). Elution with ether gave small amounts of unidentified products. Recrystallization of **4a** from cold ether gave crystals which had mp 95–98°, $[\alpha]^{25}D$ ($CHCl_3$, *c* 0.92), ir 3600 (hydroxyl) and 1720, 1240 cm^{-1} (ester); nmr 3.62 (methoxyl), 3.56 m ($W_{1/2}$ 19, βH-12), 2.42 (hydroxyl), 1.18 (C-4 methyl), 0.97 (C-10 methyl), 0.91 d and 0.82 d (J = 7, isopropyl). The reaction was capricious, the 40% yield of **4a** being difficulty to reproduce.

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25; O, 14.35. Found: C, 75.33; H, 10.26; O, 14.36.

Treatment of 80 mg of **4a** with methanesulfonyl chloride–pyridine at 0° for 15 hr, dilution with water, extraction with ether, washing and drying the ether extract, and evaporation at reduced pressure gave the mesylate **4b** as a gum (85 mg) which solidified on standing but could not be recrystallized satisfactorily: ir 1715, 1250 (ester) and 1340, 1170 cm^{-1} (mesylate); nmr 4.78 m ($W_{1/2}$ = 19, βH-12), 3.62 (methoxyl), 2.99 (mesylate), 1.17 (C-4 methyl), 0.97 (C-10 methyl), 0.93 and 0.87 d (J = 6.8, isopropyl). In an attempt to prepare the unknown resin acid ester **18** the mesylate was placed on a column of alumina, but was recovered unchanged after 18 hr. Attempts to eliminate the mesylate function by refluxing with collidine or sodium acetate–acetic acid resulted in complex mixtures.



18

Oxidation of 4a.—Jones reagent[12] was added to a solution of 0.5 g of **4a** in acetone at room temperature until the brown color persisted. Work-up in the usual manner[1] gave a gum, tlc analysis of which showed the presence of two components. Preparative tlc afforded 0.37 g of **6** and 0.050 g of **7**. The major product (**6**) was a gum, $[\alpha]^{25}D$ +32° ($CHCl_3$, *c* 3.76); ir 1720, 1220 (ester), and 1712 cm^{-1} (ketone), nmr 3.61 (methoxyl), 2.73 br (2 protons, $W_{1/2}$ = 7, 11-methylene), 1.19 (C-4 methyl), 0.99 (C-10 methyl), 0.91 d and 0.88 d (J = 6.5, isopropyl).

The minor product **7** was recrystallized from methanol and had mp 196–198°; $[\alpha]^{25}D$ +6° ($CHCl_3$, *c* 635); uv λ_{max} 236 nm (ϵ 19,800); ir 3600 (hydroxyl), 1720, 1250 (ester), and 1658, 1615 cm^{-1} (conjugated enone); nmr 5.83 (H-11), 3.62 (methoxyl),

(13) The observed chemical shifts of the C-10 methyl resonances of **11** and **12** were in excellent agreement with the predicted values ($\Delta\delta$ $\Delta^{9(11)}$-12-oxo function 16 Hz,[11] observed for **11** 17 Hz relative to **17**, observed for **12** 17 Hz relative to **5**.

(14) Melting points are uncorrected. Analyses were by Dr. F. Pascher, Bonn, Germany. Nmr spectra were run on a Varian A-60 instrument in deuteriochloroform with tetramethylsilane as internal standard. Line positions are expressed in ppm from tetramethylsilane. Signals are characterized in the usual way: d doublet, br somewhat broadened singlet, m multiplet. Coupling constants are expressed in Hz. Infrared spectra were run on Perkin-Elmer Infracord or Model 257 spectrophotometers in chloroform solution. Ultraviolet spectra were run on a Cary 14 recording spectrometer in 95% ethanol solution. Ord curves were obtained with a Jasco ORD/UV-5 recording spectrophotometer in methanol solution. Column chromatograms were performed on Alcoa F-20 alumina. Silica gel G was used for analytical tlc, silica gel $PF_{254+366}$ (Merck) for preparative tlc.

1.26 (C-10 methyl), 1.17 (C-4 methyl), 0.93 d and 0.87 d (J = 7, isopropyl).

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26; O, 18.37. Found: C, 72.15; H, 9.25; O, 18.48.

Catalytic hydrogenation of 60 mg of **7** in 10 ml of absolute ethanol (15 psi, 10% Pd-C) for 10 hr gave 60 mg of **10**, mp 161–164°, mmp with authentic material[4] 162–164°, ir and nmr spectra superimposable.

Isomerization of 6.—Treatment of **6** with sodium methoxide–methanol in the usual fashion[4] or chromatography over alumina gave a 1:1 mixture of **11** and **12** which was separated by preparative tlc. The less polar substance **11** was recrystallized from methanol–water and had mp 99–100°; $[\alpha]^{25}D$ +47° ($CHCl_3$, c 0.256); ir 1722, 1225 (ester), and 1658, 1605 cm^{-1} (conjugated enone); uv λ_{max} 238 nm (ϵ 12,500); nmr 5.87 d (J = 2, H-11), 3.60 (methoxyl), 1.22 (C-4 methyl), 1.13 (C-10 methyl), 0.92 and 0.79 d (J = 7.1, isopropyl).

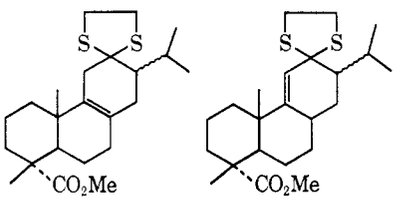
Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70; O, 14.44. Found: C, 75.64; H, 9.69; O, 14.62.

Hydrogenation of 50 mg of **11** in absolute ethanol (10 psi, 5% Pd–C) for 1 hr gave 50 mg of **13**,[4,8] mp 96–97°, mmp 96–97°, ir and nmr spectra superimposable.

The more polar ketone **12** was recrystallized from methanol–water and had mp 103–104°; $[\alpha]^{25}D$ +163° ($CHCl_3$, c 0.33); ir 1719, 1225 (ester), and 1660, 1609 cm^{-1} (conjugated enone); uv λ_{max} 241 nm (ϵ 15,000); nmr 5.70 d (J = 1.8, H-11), 3.60 (methoxyl), 1.22 (C-4 methyl), 1.14 (C-10 methyl), 0.91 d and 0.83 d (J = 6, isopropyl).

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70; O, 14.44. Found: C, 75.90; H, 9.71; O, 14.50.

In an attempt to form the thioketal of **11** for the purpose of eventually removing the ketone group, a solution of 130 mg of **11** in 1.5 ml of ethanedithiol was allowed to stand with 0.75 ml of boron trifluoride for 4 hr, poured into water, and extracted with ether. The washed and dried ether extracts were evaporated at reduced pressure. The residue could not be induced to solidify. Preparative tlc afforded separation of the two major components as gums. The major product, *ca.* 70%, appeared to be **19** since the nmr spectrum did not display signals characteristic of vinyl protons, but had signals at 3.63 (methoxyl), 3.22 m (4 protons, $-CH_2S-$), 2.53 (2 protons, 11-methylene group), 1.17 (C-4 methyl), 1.01 (C-10 methyl), and 0.92 d (J = 6.7, isopropyl). The minor product, less than 20%, appeared to be **20**, nmr 5.55 br ($W_{1/2}$ = 2.2, H-11), 3.62 (methoxyl), 3.20 m (4 protons, $-CH_2S-$), 1.19 (C-4 methyl) and 0.92 d (J = 7.5, isopropyl). The nmr spectrum of the crude product also indicated that a small amount, *ca.* 10%, of a third product was present, possibly a C-13 epimer.



19 **20**

Methyl 12-Oxo-13β-abietan-18-oate (15).—A solution of 70 mg of **12** in absolute ethanol was hydrogenated (9 psi, 5% Pd-C) for 4 hr, filtered, and evaporated. Recrystallization of the residue from methanol–water afforded 60 mg of **15** which had mp 123–125°; ir 1716, 1230 (ester), and 1710 cm^{-1} (ketone); nmr 3.62 (methoxyl), 1.10 (C-4 methyl), 0.92 (C-10 methyl), 0.97 d and 0.88 d (J = 7, isopropyl); ord curve (c 0.048), $[\alpha]_{400}$ +274°, $[\alpha]_{304}$ +1880°, $[\alpha]_{255}$ −1580°.

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25; O, 14.35. Found: C, 75.45; H, 9.95; O, 14.34.

A solution of 55 mg of **15** in 20 ml of aqueous methanol containing 250 mg of potassium hydroxide was allowed to stand for 2 hr, acidified, diluted with water, and extracted with ether. The washed and dried ether extracts on evaporation furnished 50 mg of **13** identical in all respects with authentic material.

Registry No.—**4a**, 20104-28-3; **4b**, 20104-29-4; **6**, 20144-61-0; **7**, 20104-30-7; **11**, 20104-31-8; **12**, 20104-32-9; **15**, 20104-33-0; **19**, 20104-34-1; **20**, 20104-35-2.

The Rates of Hydrolysis of Two Thiol Esters in Water[1]

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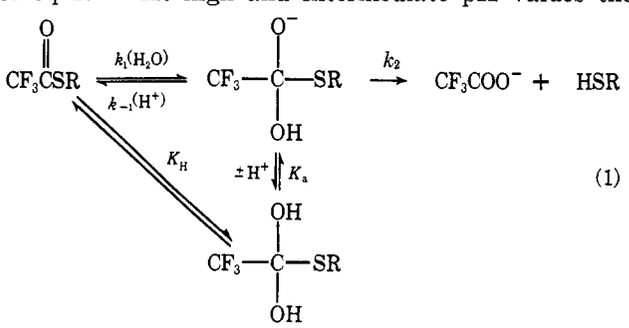
Received December 9, 1968

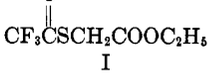
The purpose of this note is to point out that limiting values of the rate constants for decomposition of the tetrahedral addition intermediate in thiol ester hydrolysis to starting materials and products may be calculated from the observed rate constants at a pH value near that at which a change in rate-determining step occurs. In the case of a thiol ester of trifluoroacetic acid the value of these rate constants approach those expected for a diffusion-controlled reaction, reflecting the low stability of the tetrahedral intermediate.

Kinetic evidence for a change in rate-determining step with changing pH, the absolute values of the rate constants required for alternative mechanisms, and a dependence on pH of the exchange of ^{18}O from labeled ester into the solvent that agrees with the behavior predicted from the kinetic data provide convincing evidence that the hydrolysis of ethyl trifluorothiolacetate proceeds with the formation of a kinetically significant intermediate according to the mechanism of eq 1.[2,3] At high and intermediate pH values the



(1)

rate-determining step is the attack of hydroxide ion or the general base catalyzed attack of water on the ester, whereas below pH 2 the breakdown of the anionic tetrahedral addition intermediate becomes rate determining. Calculations of limiting values for the rate constants of eq 1, based upon estimates of the equilibrium constants for formation and ionization of the neutral tetrahedral intermediate, suggested that these rate constants approach the magnitude expected for diffusion-controlled reactions[4] and led us to examine the hydrolysis of ethyl S-trifluoroacetylmercaptoacetate I. This thiol ester has a better leaving group (pK =



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(1) Contribution No. 653 from the Graduate Department of Biochemistry, Brandeis University, Waltham, Mass. 02154. Supported by grants from the National Science Foundation (GB-5648) and the National Institute of Child Health and Human Development of the National Institutes of Health (HD-1247). R. B. was a National Science Foundation Predoctoral Fellow, 1965–1968.

(2) L. R. Fedor and T. C. Bruice, *J. Amer. Chem. Soc.*, **86**, 5697 (1964); **87**, 4138 (1965).

(3) M. L. Bender and H. d'A. Heck, *ibid.*, **89**, 1211 (1967).

(4) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill Book Co., New York, N. Y., 1969, p 521.