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EQUILIBRIUM RELATIONSHIP OF D-HOMO KETOLIC SYSTEMS[1]

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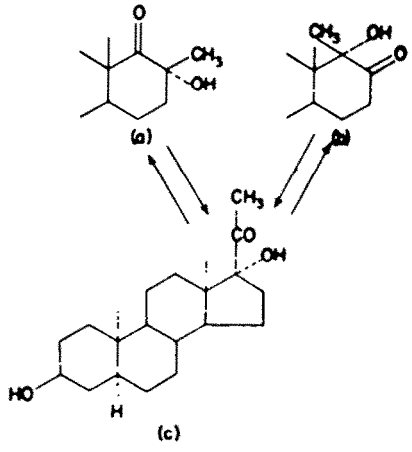
Abstract—The ability of the various D-homo ketolic isomers arising from 17-hydroxy-20-keto steroids to equilibrate with each other under alkaline as well as Lewis acid conditions has been demonstrated and discussed.

THE D-homoannulation rearrangement of 17-hydroxy-20-keto steroids had, until very recently, been considered to pursue a relatively well-defined reaction course as predetermined in large measure by reagent control. In the latter regard either alkali, heat or Lewis acids had been generally employed to evoke this change. These transformations and their mechanistic significance, in fact, have been discussed at some length just recently.[1c] In 1958 Elphimoff-Felkin and Skrobek published a paper[2] in which they reported the important observation that the isomeric ketolic systems A and B, derived from Reichstein's substance L (C), could be interconverted by aluminum t-butoxide or boron trifluoride. The conclusion was made, moreover, that this interconversion arose by retrogression to the normal steroid C.



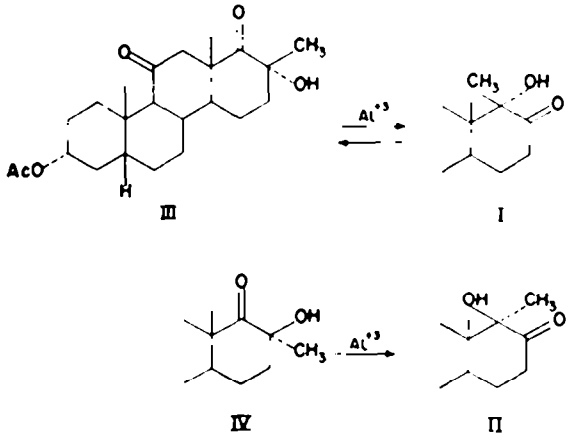
These findings were the first indication of the complexity and lack of unidirectional character of this ring expansion reaction.

Independent of Elphimoff-Felkin and Skrobek, we had made the same

[1] For preliminary accounts of this work see [a] D. Taub and N. L. Wendler, *Chem. & Ind.* 902 (1959); [b] N. L. Wendler, D. Taub and R. W. Walker, *Ibid.* 903 (1959); [c] N. L. Wendler, D. Taub and R. Firestone, *Experientia* XV, 237 (1959).

[2] I. Elphimoff-Felkin and A. Skrobek, *C.R. Acad. Sci., Paris* **246**, 2497 (1958). For details, *Idem*, *Bull. Soc. Chim.* 742 (1959). Through inadvertence on our part we had overlooked in our earlier communications, the contributions of Madame I. Elphimoff-Felkin to the general knowledge of the D-homo rearrangement. See also ref. 4; and W. Klyne and C. W. Shoppee, *Chem. & Ind.* 470 (1952).

observation.[1a] We found that 3α-acetoxy-17α-hydroxy-17β-methyl-D-homo-5β-androstane-11,17a-dione (III)[3] and 3α-acetoxy-17aα-hydroxy-17aβ-methyl-D-homo-5β-androstane-11,17-dione (I)[3] could be interconverted by refluxing either pure isomer with aluminum t-butoxide in toluene for 20 hours; there was produced, thereby, an equilibrium mixture consisting of approximately 65 per cent III and 35 per cent I. We further examined the remaining D-homo isomers and found that the 17aβ-hydroxy ketol (II)[3] remains unchanged under the equilibrating conditions with aluminum t-butoxide whereas the 17β-hydroxy ketol (IV)[3] is converted completely to II; there was no evidence of an equilibrium relationship between II and IV.



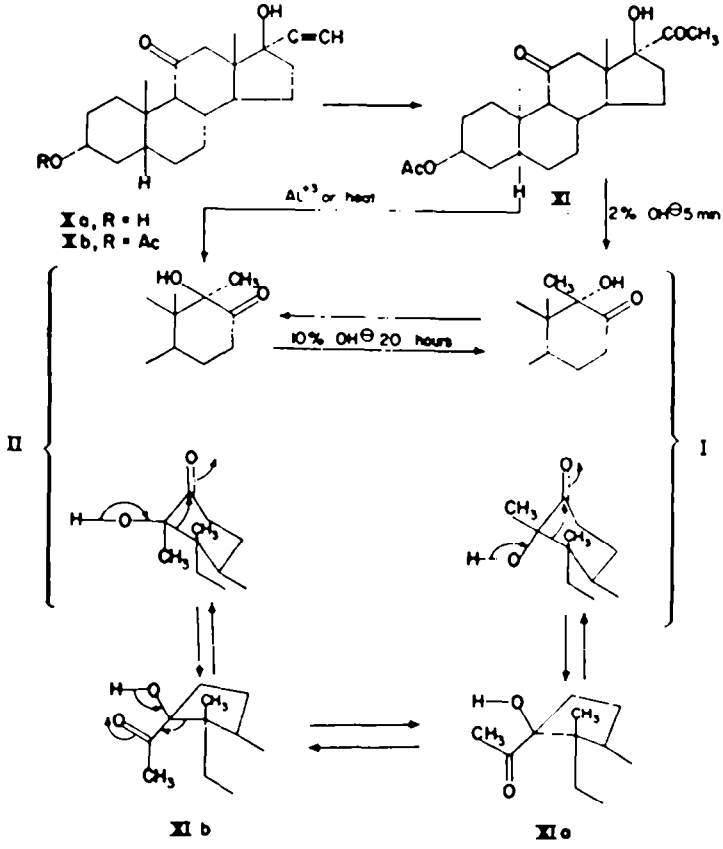
In the light of the fact that tracer studies have precluded the possibility of methyl migration in the formation of these D-homo systems,[4] the fact of their interconvertibility emphasizes their capacity to exist in a reversible relationship with a 17-hydroxy-20-keto steroid precursor.

Several years ago Madame Elphimoff-Felkin[5] had considered the role of conformational control of bond migration in the D-homo rearrangement with Lewis-acids. More recently we discussed this same concept and extended it to the alkaline catalyzed ring expansion reaction.[1c] Several considerations have been introduced into this general area however, which make the conformational argument less definitive than originally anticipated. Recent findings, for example, suggest the possibility at least that the 17α-ketol (III) may have its D-ring in the boat conformation.[6] Further, the conformational argument is unable to accommodate identical bond movement in the nitrous acid-amine rearrangement of C17-epimeric 17-hydroxy 20-amino pregnane derivatives.[7]

In studies on the alkaline catalyzed D-homo rearrangement we found that kinetic as well as equilibrium products are to be expected.[1b] Earlier studies had demonstrated, for example, that D-homoannulation of 17β-hydroxy-20-keto-17-isopregnane

[3] N. L. Wendler and D. Taub, *Chem & Ind.* 505 (1955); N. L. Wendler, D. Taub, S. Dobriner and D. Fukushima, *J. Amer. Chem. Soc.* **78**, 5027 (1956).
[4] R. B. Turner, M. Perelman and K. T. Park, Jr., *J. Amer. Chem. Soc.* **79**, 1108 (1957).
[5] I. Elphimoff-Felkin, *Bull. Soc. Chim.* 1845 (1956).
[6] [a] N. L. Wendler, *Chem. & Ind.* 1652 (1958); *J. Amer. Chem. Soc.* In press; [b] R. Rosenfeld, *Ibid.* **77**, 6585 (1957).
[7] [a] N. L. Wendler, D. Taub and H. L. Slates, *J. Amer. Chem. Soc.* **77**, 3559 (1955); [b] F. Ramirez and S. Stafiej, *Ibid.* **77**, 134 (1955); **78**, 644 (1956).

derivatives is catalyzed by Lewis acids to give 17aβ-ketols (type II) and by alkali to yield 17aα-ketols (type I) as the major, if not exclusive, product.[8] We had prepared 3α-acetoxy-17β-hydroxy-17-isopregnane-11,20-dione (XI) by Stavely[9] hydration of the ethinyl carbinol (Xb).[10] The 17-isopregnanolone was found to be quite unstable, melting at 120-130° with phase change and total rearrangement, to the 17aβ-ketol (II), m.p. 223-226°. Similarly, compound XI was converted to the 17aβ-ketol (II) essentially quantitatively an alumina. On the other hand, treatment of the 17-isopregnanolone (XI) with boiling 2 per cent methanolic potassium hydroxide for 5 minutes produced the known 17aα-ketol (I) in essentially quantitative yield. The latter represents the kinetic product of rearrangement since both the 17-isopregnanolone (XI) as well as the 17aα-ketol (I), when boiled for 20 hours with methanolic potassium hydroxide, yield the same 50 : 50 ± 10 per cent equilibrium mixture of 17aα-ketol (I) and 17aβ-ketol (II). Likewise, treatment of the 17aβ-ketol (II) also produced the same equilibrium product I $\rightleftharpoons$ II.



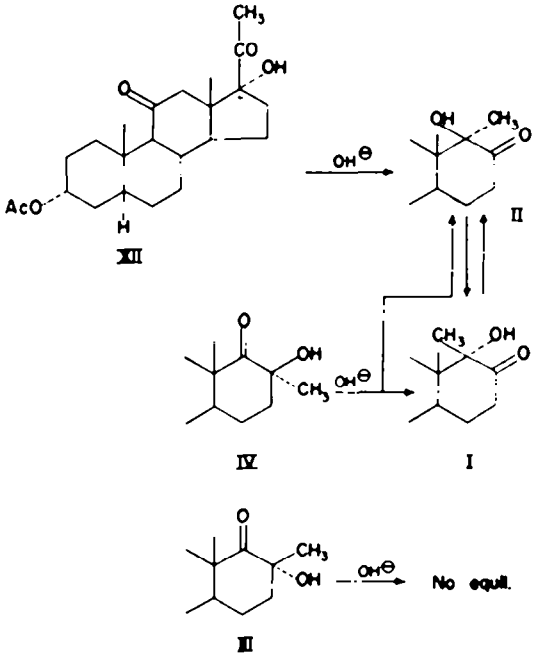
[8] [a] C. W. Shoppee and D. A. Prins, *Helv. Chim. Acta* **26**, 185, 201, 1004 (1943); [b] R. B. Turner, *J. Amer. Chem. Soc.* **75**, 3484 (1953). R. B. Turner, R. Anliker, R. Helbling, J. Meier and H. Heusser, *Helv. Chim. Acta* **35**, 411 (1955).

[9] H. E. Stavely, *J. Amer. Chem. Soc.* **62**, 489 (1940); see also ref. 8*b*.

[10] [a] L. H. Sarett, *J. Biol. Chem.* **162**, 601 (1946); [b] N. L. Wendler, R. P. Graber and G. G. Hazen, *Tetrahedron* **3**, 144 (1958).

Again the formation of an equilibrium product requires that the pertinent D-homo isomers be capable of existing in a reversible relationship with a 17-hydroxy-20-keto pregnane; only through mediation of the latter can a configurational inversion reasonably occur at C-17a. Further, assuming that these D-homo systems possess chair conformations and rearrange from same, it follows that the equilibration of the 17aα-ketol (I) and 17aβ-ketol (II) would take place by way of starting 17-isopregnanolone (XI) and not its C-17α-OH isomer (XII). The formation of the 17aα-ketol (I) as the kinetic product is in accord with the postulates expressed by Turner[8b] wherein the probable *trans* OH *vs* C O alignment in the transitional species (compare XIa) predicts the formation of I.

The alkaline D-homoannulation of 17α-hydroxy-20-ketopregnanes (XII) has by past experience[8,3] resulted in the predominant formation of the 17aβ-ketol (II), with the 17aα-ketol (I) being formed as a minor product. The product expected by conformational considerations, on the other hand, is the 17β-ketol (IV). The fact that until very recently[11] this isomer had never beeen identified from a D-homo rearrangement reaction was in itself mysterious. The present authors construed this to indicate the possible instability of this isomer, IV, under the alkaline rearrangement conditions in analogy with the behavior of I[1c]. In fact it was later demonstrated that this isomer, IV, is indeed unstable to the 20 hour equilibration conditions with alkali and does give I and II in the same essential ratio as that previously observed to be produced from the latter isomers themselves. The suggestion was therefore made that IV, like I, is the kinetic product of rearrangement. This conclusion is now known



[11] Dr. Fukushima of the Sloan Kettering Institute for Cancer Research has informed us recently that he has synthesized 3β,17β-dihydroxy-17α-methyl-D-homoandrostane-17a-one (see method, ref. 3) and found this compound to be identical with an unknown product isolated in about 7% yield from the reaction of base with Reichstein's Substance L. [See also *J. Amer. Chem. Soc.* 77, 6585 (1955).]

not to be true. Under conditions less than those necessary to produce equilibrium, the isomer, IV, is recovered largely unchanged whereas the parent steroid (XII) is converted to II (major) and I (minor). Only under the more prolonged conditions of alkaline treatment is IV, in turn, converted to the equilibrium product. Consequently, since IV is finally ruled out as the kinetic product of rearrangement of XII, the conformational argument in whose support it was originally employed is correspondingly invalidated. The kinetic product of rearrangement of XII appears to be the 17aβ-ketol (II). This is suggested by the observation that when XII is refluxed for 4 hours with 5 per cent methanolic potassium hydroxide the product by infrared analysis consisted of 68 per cent 17aβ-ketol (II) and 32 per cent 17aβ-ketol (I). On the other hand, under the 20 hour conditions of alkaline equilibration, a product ratio of 50 : 50 : 10 per cent was realized.

In contrast to the other D-homo isomers, the 17α-hydroxy ketol (III) is in large measure unaffected by the conditions of base equilibration although traces of the ketols I and II are nonetheless indicated by paper partition chromatography and infrared spectroscopy. Prolonged treatment (4–5 days) with alkali, however, failed to increase the amount of I and II, but resulted, on the other hand, in considerable decomposition of an undetermined character.

The methods employed for analyzing the products obtained from the equilibration experiments described were threefold. Paper partition chromatography on Whatman No. 1 or 4 paper utilizing benzene–cyclohexane 1 : 3 as the mobile phase and formamide as the stationary phase, effected good resolution of the 17aα and 17aβ-ketols, both of which give positive Zimmermann color reactions.[12] The 17α and 17β-hydroxy ketols, which were also easily separated, do not give a positive Zimmermann reaction but can be detected by the iodine vapor technique.[13]

Analysis of the isomeric mixtures was carried out by means of infrared spectrophotometry. The working curve method was used, in which a series of known mixtures of the various isomers was made up, the infrared curves of which were compared directly with the unknowns. This procedure, besides establishing the percent isomer ratio within the desired limits (± 5 per cent), also afforded a direct comparison of the entire spectrum in the 2–15 micron region and thus served as a control in establishing the absence of impurities or other isomers which might invalidate the results.

The experimental work was carried out on a Baird double beam infrared spectrophotometer with NaCl optics (Model B), using a cell of 0·10 mm path length and at a fixed concentration of 10 mg solute/78 mg chloroform. Listed below are the most characteristic absorption bands of the four isomers. In most instances, only two isomers were present in any given unknown. With the few cases where more than two isomers were present, it was sometimes necessary to utilize both characteristic bands listed.

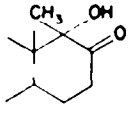
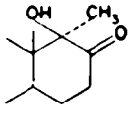
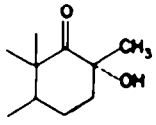
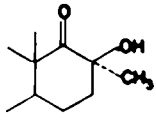
Finally, in many of the cases, direct isolation of the components of the isomeric product was carried out either by alumina chromatography, which was less satisfactory, or by chromatography on Whatman No. 3 paper. In the instances where the 17β-hydroxy ketol and 17aβ-ketol preponderated direct crystallization sufficed to separate these compounds.

[12] Procedure of K. Savard, *J. Biol. Chem.* **202**, 457 (1953)
[13] G. B. Marini-Bettolo-Marconi and S. Guarino, *Experientia* **6**, 309 (1950)

In conclusion it may be said that the D-homoannulation rearrangement has revealed itself to be much more diverse in character than previously appreciated. It is a transformational type subject to all manner of directional control giving as it does kinetic products, products of reagent control and equilibrium products. The lack of parallelism in the behavior to alkali of the 17 ketones *cis-a-cis* the 17a ketones is mystifying as is the unique stability, for example, of the isomer III. Consequently, at the present time, no single concept seems adequate to embrace logically and consistently all facets of this transformation.

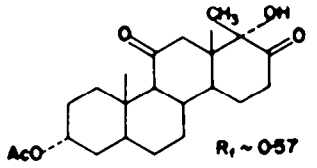
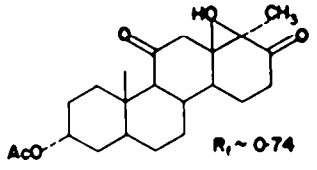
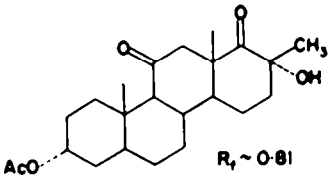
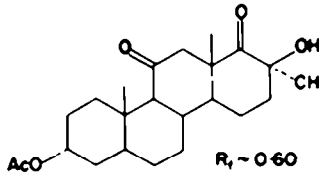
EXPERIMENTAL

3α-Acetoxy-17β-hydroxy-17-isopregnane-11,20-dione (XI). Acetylation of 4·9 g of the 3α-hydroxy-ethinyl carbinol (Xa)[19] gave the corresponding 3α-acetate (Xb), 4·88 g, m.p. 184–186°. A mixture of 4·78 g Xb, 9·0 g mercuric chloride and 1·5 cc freshly distilled aniline in 200 cc benzene and 50 cc water was stirred at 60° for 20 hr. The mixture was cooled, filtered, washed with water, dil hydrochloric acid, dil potassium bicarbonate solution, saturated sodium chloride solution and dried over magnesium sulfate. The yellow residue which showed no tendency to crystallize was partitioned as follows:[14]

Isomer	Major characteristic absorption bands	For detection in isomer
 I	10·35 μ	IV
	10·85 μ	II, III
 II	10·69 μ	I, III, IV
 III	9·40 μ	IV
	9·98 μ	I, II
 IV	9·95 μ	I
	10·82 μ	II, III

[14] Procedure of R. F. Hirschmann of these laboratories.

It was dissolved in 150 cc formamide and extracted successively with hexane, cyclohexane, cyclohexane-benzene 1 : 4, cyclohexane–benzene 1 : 1, benzene and benzene–chloroform 1 : 2. Each extract was washed with water, dried over sodium sulfate and concentrated to dryness. The benzene-cyclohexane 1 : 1 and benzene extracts crystallized from 50% ether–pet ether to give 2·01 g of the 17-isopregnane (XI) which melted nearly completely at 120–135°, resolidified and finally melted at 223–226°. This behavior indicated thermal D-homoannulation to the 17aβ-hydroxy ketol (II) (see below). XI had $[\alpha]_D^{Chf.}$ · 46°,[15] $\lambda_{max}^{Chf.}$: 2·74, 2·85–2·90, 5·78, 5·86, 8·0 μ. (Found: C, 70·94; H, 8·64. Calc. for $C_{23}H_{34}O_3$: C, 70·74; H, 8·71%).

Isomer equilibrated	Reagent	Product composition	Component isolated
 I	Al^{+3}	65% III; 35% I	III -Al_2O_3—chromatography
	$OH^{\ominus}$	55% I; 45% II	II - Chromatography & crystallization
 II	Al^{+3}	~100% II	II—direct crystallization
	$OH^{\ominus}$	50% I; 50% II	I Paper chromatography
 III	Al^{+3}	60% III; 40% I	III- Al_2O_3 -chromatography
	$OH^{\ominus}$	70% III; 20% I ~10% II	III –Al_2O_3—chromatography
 IV	Al^{+3}	95% II	II Crystallization
	$OH^{\ominus}$	60% I; 40% II	I and II—Paper Chromatography

The hexane and cyclohexane fractions consisted primarily of a U.V. absorbing, non-crystalline yellow material which gave an instantaneous strong Zimmermann test and which was very mobile on paper. By analogy with Turner's[16] this material could be a 17a-methyl, 17a-anilino-17-keto-D-homo-5β-androstane.

That ring D in XI is 5-membered was demonstrated by successive treatment of XI with lithium

[15] The ΔM_D XII–XI is −148°. This compares with values of +135°, + 91° and −191° (in various solvents) for three pairs of normal and iso-17-hydroxy-20-ketopregnanes. Data from Pouvoir Rotatoire Naturel I, J. P. Mathieu and A. Petit, *Stéroides*. Masson et Cie., Paris (1956).

aluminum hydride in refluxing tetrahydrofuran and sodium periodate in aqueous methanol to give in excellent yield 3α,11β-*dihydroxy*-5β-*androstane*-17-*one*, m.p. 231–234°, identical with an authentic specimen.[16]

Rearrangement of 3α-*acetoxy*-17β-*hydroxy*-17-*isopregnane*-11,20-*dione* (XI)

(a) *Treatment with* 2% *alkali.* A solution of 100 mg XI in 5 cc methanol was brought to boiling and treated with 1 cc of a solution containing 1 g potassium hydroxide in 10 cc water. The reaction mixture was allowed to reflux for 5 min, then chilled and acidified with dil aqueous hydrochloric acid. The quenched reaction mixture was evaporated *in vacuo* and the residue extracted with ethyl acetate. The ethyl acetate extract was washed neutral with bicarbonate, the solvent evaporated, and the residue acetylated in 0·5 cc pyridine with 0·5 cc acetic anhydride. The product from the acetylation crystallized spontaneously from ether to give 3α-*acetoxy*-17aα-*hydroxy*-17aβ-*methyl* D-*homo*-5β-*androstane*-11,17-*dione* (I), m.p. 179–181°; mixed m.p. with authentic I not depressed. The infrared spectra of the two samples were identical. A sample of the total product before crystallization analysed in the infrared for 95% 17aα-hydroxy ketol (I).

(b) *Prolonged treatment with* 10% *alkali.* A solution of 100 mg XI in 10 cc methanol was treated with 1 g potassium hydroxide in 1 cc water and the reaction mixture refluxed for 20 hr in a nitrogen atmosphere. The product was acetylated and analyzed in the infrared for 55% 17aβ-hydroxy ketol (II) and 45% 17aα-hydroxy ketol (I). Chromatography followed by crystallization afforded crystalline II, m.p. 220–225°; mixed m.p. with authentic II not depressed. The infrared spectra of the two samples were identical.

(c) *Alumina.* A 100 mg sample of XI dissolved in 10 cc benzene was slurried for 24 hr with 2·5 g neutral alumina. The total product analyzed in the infrared for at least 95% 17aβ-hydroxy ketol (II). The total product recrystallized from acetone–ether melted at 223–227°.

(d) *Rearrangement by heat.* A sample of XI was warmed in a capillary tube. It partly melted near 120°, resolidified and completely melted at 223°. Paper chromatography of the melt in the benzene cyclohexane 1 : 3 formamide system showed the presence only of the 17aβ-hydroxy ketol (II). On remelting, the sample had m.p. 223–226°; mixed m.p. with authentic II, 222–225°.

Equilibration experiments with the isomeric D-*homo ketols. General procedures*

(a) *Aluminum t-butoxide catalyzed equilibrations* were conducted by refluxing a solution of e.g. 500 mg of the pertinent ketol in 10 cc toluene with 500 mg aluminum t-butoxide in a nitrogen atmosphere for 20–24 hr. At the conclusion of this period of reflux, the reaction mixture was cooled, acidified and the toluene evaporated *in vacuo*. The residue was dissolved in ether and the ether extract washed with bicarbonate, dried and evaporated to dryness. The residue was in each instance analyzed for percent composition by infrared spectroscopy, submitted to paper partition chromatography and the components isolated in specific instances.

(b) *Alkali catalyzed equilibrations* were conducted by refluxing a solution of e.g. 500 mg of the pertinent ketol in 10 cc methanol containing 1 g potassium hydroxide and 1 cc water for 20–24 hr in a nitrogen atmosphere. At the conclusion of this period, the methanol was removed *in vacuo* and the product extracted with ethyl acetate. The ethyl acetate extract was evaporated and the residue acetylated with acetic anhydride in pyridine. The total product was subsequently submitted to paper partition chromatography and analyzed by infrared spectroscopy for component composition. In specific instances the isomers were isolated.

[16] N. L. Wendler, D. Taub and R. P. Graber, *Tetrahedron* 7, 173 (1959).