582. *Studies in Nuclear Magnetic Resonance. Part III.* Assignment of Configurations of αβ-Unsaturated Esters and the Isolation of Pure* trans-β-*Methylglutaconic Acid.*†

By L. M. Jackman and R. H. Wiley.

Chemical-shift data for a number of *cis-trans*-pairs of αβ-unsaturated esters show that β-olefinic protons are specifically deshielded by 0·5—0·9 p.p.m. by a *cis*-alkoxycarbonyl group. Similarly, the protons of a β-methyl group are deshielded by 0·25 p.p.m. Pure *trans*-β-methylglutaconic acid is described for the first time, and its configuration established by nuclear magnetic resonance spectroscopy.

In the preceding paper we showed that, in substituted ethylenes, certain substituents can so shield a *cis*-β-proton or the protons of a *cis*-β-methyl group that significant differences in the chemical shifts of these protons in *cis*- and *trans*-isomers are to be expected. The most effective substituents in this respect are those containing the carbonyl function (*e.g.*, –COR). To confirm this we have examined a number of geometrically isomeric pairs of αβ-unsaturated esters, and the results clearly show how nuclear magnetic resonance spectroscopy can be used to establish the relative configurations of such isomers, irrespective of the degree of substitution of the double bond.

The chemical shifts for a number of αβ-unsaturated esters are assembled in the Table. The spectra of some of these compounds require comment. The olefinic region of the spectrum of methyl *trans*-crotonate is typical of the AB region of an ABX_3 spin system. However, the chemical shift, $\Delta\nu_{AB}$ (46·0 c./sec.), between the two olefinic protons is sufficiently larger than the coupling constant J_{AB} (15—16 c./sec.) to permit the spectrum to be analysed approximately by a first-order treatment. The spectrum of methyl *cis*-crotonate was obtained with a sample containing 7·5% of the *trans*-isomer. The *cis*-ester also gives rise to an ABX_3 spectrum, but in this case the chemical shift is much closer to the value of the coupling constant J_{AB} ($\Delta\nu/J_{AB} \sim 1{\cdot}9$). The presence of the *trans*-isomer complicated the spectrum and discouraged us from attempting an accurate analysis by the procedure outlined by Fessenden and Waugh.[1] An approximate correction was

* Part II, preceding paper.

† For a preliminary communication see *Proc. Chem. Soc.*, 1958, 196.

[1] Fessenden and Waugh, *J. Chem. Phys.*, 1959, **30**, 944.

Chemical-shift data (τ-values) for αβ-unsaturated esters.

Ester	β-H	Δ [a]	β-CH_3	Δ [a]
Me methacrylate	4·51 3·96	0·55		
Me ββ-dimethylacrylate			8·16 7·88	0·28
Me_2 maleate	3·86	0·53		
Me_2 fumarate	3·33			
Me_2 citraconate	4·25	0·94	7·96	0·24
Me_2 mesaconate	3·31		7·72	
Me_2 dimethylmaleate			8·11	0·10
Me_2 dimethylfumarate			8·01	
Me *cis*-crotonate	3·57	0·62	7·86	0·25
Me *trans*-crotonate	2·95		8·11	
Me angelate	4·02	0·85	8·03	0·25
Me tiglate	3·27		8·27	

Ester	β-CH_3	Δ [a]
Me_2 *cis*-β-methylglutaconate	8·04	0·24*
Me_2 *trans*-β-methylglutaconate	7·80	
Et *cis*-β-ionylideneacetate	7·98	0·27
Et *trans*-β-ionylideneacetate	7·71	
Me *cis*-geranate [b]	8·27	0·25
Me *trans*-geranate [b]	8·02	
Me *cis*-phytenoate [b]	8·14	0·25
Me *trans*-phytenoate [b]	7·89	
Me *cis*-αβ-dimethylcinnamate [c]	8·05	0·30
Me *trans*-αβ-dimethylcinnamate [c]	7·75	
Me_2 *cis*(αβ)-*trans*(γδ)-β-methylmuconate [d]	8·00	0·25
Me_2 *trans*(αβ)-*trans*(γδ)-β-methylmuconate [d]	7·75	

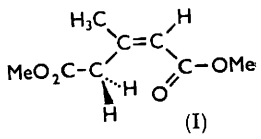
[a] $\tau_{trans} - \tau_{cis} = \Delta$, where *cis* and *trans* refer to the relation of the proton(s) to the carboxylate group and not necessarily to the configuration of the ester. [b] Ref. 4. [c] Ref. L. M. Jackman and J. W. Lown, unpublished work. [d] Ref. 3.

* β-CH_2·CO_2Me = 6·28 and 6·935, respectively; Δ = 0·655.

therefore made by taking the centres of gravity of the A and the B submultiplets and treating the problem as a simple AB system. It is unlikely that the errors in the τ-values thus calculated can exceed 0·05 p.p.m. Some difficulty was encountered in determining the τ-values of the β-methyl protons in methyl angelate and tiglate. In both isomers the appropriate absorption line is split as a doublet by the adjacent olefinic proton, and each component of the doublet is further split as a quarter (J ~1·0 c./sec.) by long-range coupling between the α- and the β-methyl protons. The high-frequency quartet in the case of methyl angelate and the low-frequency quartet in the case of methyl tiglate overlap the absorption due to the α-methyl group. For this reason it is difficult to locate the true centres of gravity of the β-methyl groups, and the τ-values in the table are subject to an error of 0·06 p.p.m.

It is noteworthy that the coupling constant between the *C*-methyl and the olefinic protons has the same value (1·60 ± 0·07) in methyl citraconate as in methyl mesaconate. This equality in the coupling constants between methyl protons and a β-olefinic proton in *cis*- and *trans*-isomers is observed with other compounds in the Table and is in direct contrast to the observation, made in Part I, that the analogous coupling constants in *cis*- and *trans*-2-substituted propenes differ significantly.

The τ-values of β-olefinic protons are seen (Table) to depend markedly on stereochemistry, being deshielded by 0·5—0·9 p.p.m. in the isomer in which they are *cis* to the alkoxycarbonyl substituent. Too few examples are available to relate the magnitude of the differential shift to structural variations. The deshielding of the protons of a *cis*-β-methyl group is fairly constant, being of the order of 0·25 p.p.m. A shift of this magnitude is appreciable, particularly when it is realised that the net shielding effect is the average for the three equivalent conformations of the methyl group. It is noteworthy that the differential shift (0·60 p.p.m.) of the β-methylene protons in the β-methylglutaconic esters is much larger than that of the β-methyl protons. This suggests that the conformation (I) is heavily populated. The shift of the methylene protons is of the order observed for *cis*-β-olefinic protons which are rigidly fixed. This is to be expected because, although the methylene protons are not rigidly orientated, they can approach closer to the magnetically anisotropic carbonyl than does the olefinic proton.



(I)

The above examples clearly demonstrate that, provided both isomers are available, nuclear magnetic resonance spectroscopy can be used to establish the geometric configurations of αβ-unsaturated esters. The method is likely to prove of considerable use with tri- and tetra-substituted derivatives, for in such cases there are no infrared bands which

can be reliably correlated with configuration, and ultraviolet spectra can seldom be used to make a definite assignment of configuration. Already several examples [2-4] of the successful application of nuclear magnetic resonance in this field have followed our preliminary communication.[5]

In the present work it was necessary to re-investigate the two reported β-methylglutaconic acids. We found that a *trans*-configuration had been erroneously assigned to a mixture of isomers. This provided a basis for the revision of earlier conclusions concerning configuration and led to the isolation of the pure *trans*-isomer. Because there is considerable confusion in the literature, the existing information will be restated.

β-Methylglutaconic acid, m. p. 146°, was first prepared by the alkaline hydrolysis of ethyl isodehydroacetate.[6] The structure of ethyl isodehydroacetate was itself in question at the time, and a controversy over its structure involved a difference of opinion as to the characteristics of the acids obtained during this alkaline degradation. The possibility that the acid existed in *cis-trans*-forms was recognised [7] and apparently established with the isolation of two forms of the acid, m. p.s 115° and 141°. The 141° acid was described as the product readily formed by alkaline hydrolysis of the isodehydroacetate or from the anhydride on hydrolysis and was hence assigned the *cis*-structure. The 115° isomer was accordingly assigned the *trans*-configuration. A careful review of the evidence [8] established that there were apparently only two forms of the acid, m. p.s 147° and 115°. No evidence was available that indicated the existence of a third form or a difference between the products melting at 141° and 147°, and it was tacitly assumed that the two were the same material in different states of purity. The higher-melting acid was formed initially on opening of either the ethyl isodehydroacetate or the β-methylglutaconic anhydride ring. Prolongation of the alkaline hydrolysis resulted in a decrease in yield of the 147° form and an increase in that of the 115° form. Heating with alkali isomerised the 147° to the 115° form. Although questioned,[9]* the assignment of the *cis*-structure to the 147° acid has been generally accepted.[10] This acid can readily be obtained with a m. p. of 150° [11] or 152° [12] by recrystallisation from ether, and is also formed on saponification of the condensation product from malonic ester and ethyl tetrolate [8] or on condensation of ethyl cyanoacetate with acetoacetic ester.[13] It has been shown that the 115° form is,[14] and the 146° form is not,[15] incorporated into cholesterol by liver enzymes, and that this may take place without degradation to smaller fragments.[16] Paper-chromatographic studies [16] used to establish the presence of β-methylglutaconic acid have shown that the compound melting at 115° is " a mixture of the two isomers."

The methyl ester of the acid, m. p. 150°, gives rise to a doublet (J ~0·9 c./sec.) at 8·04 (C-Me) and bands at 6·28, 6·36 (CH_2 and OMe), and 4·27 (:CH). An aqueous solution of the acid itself shows bands with similar separations. That this acid is the true *cis*-form was shown by observing the spectrum of the anhydride dissolved in water. Even at room temperature, before hydrolysis is complete, the bands appear at the positions observed for the acid itself and no other lines possibly characteristic of the other isomer can be found.

* In Beilstein's "Handbuch," Vol. II, p. 777, the 147° form is designated *cis*. In the first supplement, assignment is left undecided. In the second supplement, the 147° form is designated *trans*.

[2] Morris, Vernon, and White, *Proc. Chem. Soc.*, 1958, 303.
[3] Elvidge, *J.*, 1959, 474.
[4] Burrell, Jackman, and Weedon, *Proc. Chem. Soc.*, 1959, 263.
[5] Jackman and Wiley, *Proc. Chem. Soc.*, 1958, 196.
[6] Hantzsch, *Annalen*, 1883, **222**, 31.
[7] Genvresse, *Ann. Chim. Phys.*, 1891, **24**, 108.
[8] Feist, *Annalen*, 1906, **345**, 60.
[9] Bland and Thorpe, *J.*, 1912, **101**, 856, 1557.
[10] Cawley, *J. Amer. Chem. Soc.*, 1955, **77**, 4125.
[11] Adams and Van Duuren, *J. Amer. Chem. Soc.*, 1953, **75**, 2377.
[12] Fichter and Schwab, *Annalen*, 1906, **348**, 254.
[13] Rogerson and Thorpe, *J.*, 1905, **87**, 1692.
[14] Rabinowitz and Gurin, *J. Amer. Chem. Soc.*, 1954, **76**, 5168.
[15] Bloch, Clark, and Harary, *J. Biol. Chem.*, 1954, **211**, 687.
[16] Adamson and Greenberg, *Biochim. Biophys. Acta*, 1957, **23**, 472.

The spectrum of the ester derived from the acid, m. p. 115°, was more complex. In addition to the bands observed with the *cis*-ester it contained a doublet (J ~0·9) at 7·80 and a band at 6·935. The two additional bands were attributable to the *trans*-isomer on the basis that the 115° isomer was in fact a mixture of the *cis*-form with the previously uncharacterised *trans*-form. Such a possibility is supported by previous observations that stereoisomeric acids of the type $R{\cdot}C(CH_3){:}CH{\cdot}CO_2H$ form molecular complexes or mixed crystals.[17,18] Such complexes have been converted into the *trans*-form by ultraviolet irradiation in the presence of iodine and, when this technique was applied to the acid of m. p. 115°, a new form, m. p. 140°, was obtained. The methyl ester of the new acid exhibited bands at 7·80, 6·935, 6·36 (OMe), and 4·27, and must therefore be the pure methyl *trans*-β-glutaconate.

Experimental

Microanalyses and light absorption measurements were carried out in the microanalytical (Miss J. Cuckney) and spectrographic (Mrs. A. I. Boston and Dr. R. L. Erskine) laboratories of this Department.

Nuclear Magnetic Spectra.—Unless otherwise stated above, all spectra were measured on 5—7% solutions in carbon tetrachloride. For further details see the preceding paper.

Materials.—Commercial samples of methyl methacrylate, n_D^{22} 1·4155, dimethyl maleate, n_D^{23} 1·4420, and dimethyl fumarate, m. p. 101—103°, were used.

Commercial samples of the corresponding acids were esterified with diazomethane at 0—5° in ether to give the following esters: methyl senecioate, b. p. 124—125°, n_D^{21} 1·4388 (lit.,[19] n_D^{20} 1·4382); dimethyl citraconate, b. p. 97—96°/12 mm., n_D^{24} 1·4470 (lit.,[20] n_D^{17} 1·4510); dimethyl mesaconate, b. p. 80°/10 mm., n_D^{25} 1·4538 (lit.,[21] n_D^{20} 1·4557); methyl crotonate (*trans*), b. p. 108—109° n_D^{21} 1·4255 (lit.,[22] n_D^{20} 1·4250); methyl tiglate, b. p. 127—127·5°/21 mm., n_D^{21} 1·4365 (lit.,[23] n_D^{20} 1·4371).

Dimethyl dimethylmaleate, b. p. 107—110°/22 mm., n_D^{23} 1·4565 (lit.,[24] b. p. 106°/17 mm.), was prepared from the anhydride and methanol. The anhydride, m. p. 95°, was prepared by the hydrolysis and dehydration of the cyanohydrin of methyl methylacetoacetate, the procedure used with acetosuccinic ester [25] being followed. Dimethyl dimethylfumarate, m. p. 41—42° (lit.,[25] 41—42°), was prepared from diazomethane and the acid, m. p. 246—248° (lit.,[26] m. p. 239—240°), which was obtained by isomerisation of dimethylmaleic acid by alkali.[27] This acid was separated, in comparable yields, from the more soluble dimethylmaleic acid and β-methylitaconic acid as the insoluble residue left on washing the crude hydrolysis product with hot benzene rather than by the involved procedure given previously.[27]

Methyl *cis*-crotonate was provided by Dr. L. Crombie. Infrared analysis showed it to contain 92·5% of *cis*- and 7·5% of the *trans*-form.

Methyl angelate, b. p. 112—113°/22 mm., n_D^{22} 1·4310 (lit.,[20] 1·4330), was prepared by the diazomethane esterification of angelic acid, prepared as previously described.[20]

Dimethyl *cis*-β-methylglutaconate, b. p. 68—69°/2 mm., n_D^{19} 1·4582, $\lambda_{max.}$ 215 mμ (ε 13,090), was prepared by the esterification of the *cis*-acid of m. p. 148—148·5° with diazomethane. The *cis*-acid was prepared by isomerisation,[10] with hydrochloric acid, of the crude β-methylglutaconic acid resulting from the alkaline hydrolysis of ethyl isodehydroacetate (we are indebted to the Tennessee Eastman Company for generous samples of this ester).[8]

Ethyl *cis*- and *trans*-β-ionylideneacetate were prepared as previously described.[28] The ethyl ester of the *trans*-isomer was prepared by esterification of the acid, m. p. 127·5—128·5°. The *cis*-ester was obtained from a mixture of isomers by chromatography on alumina. The

[17] Stoermer, Grimm, and Laage, *Ber.*, 1917, **50**, 959.
[18] Wiley, *J.*, 1958, 3831.
[19] Wagner and Moore, *J. Amer. Chem. Soc.*, 1950, **72**, 974.
[20] von Auwers and Eisenlohr, *J. prakt. Chem.*, 1911, **84**, 97.
[21] Knops, *Annalen*, 1888, **248**, 197.
[22] Gordon, Miller, and Day, *J. Amer. Chem. Soc.*, 1948, **70**, 1946.
[23] Buckles and Mock, *J. Org. Chem.*, 1950, **15**, 680.
[24] von Auwers and Cauer, *Annalen*, 1929, **470**, 307.
[25] Thiele, *Annalen*, 1899, **306**, 242.
[26] von Auwers and Harries, *Ber.*, 1929, **62**, 1678.
[27] Fittig and Kettner, *Annalen*, 1898, **304**, 158.
[28] Huisman *et al.*, *Rec. Trav. chim.*, 1952, **71**, 899; 1956, **75**, 977.

purity of both esters was established by gas–liquid chromatography (we are indebted to W. Gee for preparing these two esters).

trans-β-*Methylglutaconic acid.* The mixture of isomers of β-methylglutaconic acid, m. p. 115°, was prepared from the crude acids, which have been shown to be mostly *trans*,[10] obtained by alkaline hydrolysis of ethyl isodehydroacetate.[8]

β-Methylglutaconic acid (5 g.), m. p. 115°, was dissolved in dry benzene (50 ml.) and absolute ether (50 ml.). The solution was placed in a quartz flask and a solution (3·5 ml.) of iodine (1·0 g.) in benzene (50 ml.) was added. The flask and its contents were placed within ½″ of a 125 w Crompton Parkinson 3 pin B.C. ultraviolet lamp, from which the shield had been removed, and irradiated for 2 hr. The solution was evaporated to one-third of its volume and cooled to precipitate the acid. The precipitates from five such runs were combined and repeatedly extracted with boiling benzene (25 × 25 ml.). Recrystallisation of the product from ether and from chloroform afforded pure trans-β-*methylglutaconic acid* (3·6 g.), m. p. 139—140° (Found: C, 49·8; H, 5·9. $C_6H_8O_4$ requires C, 50·0; H, 5·6%). The material recovered from the benzene extracts could be isomerised to yield further quantities of the *trans*-acid.

Dimethyl trans-β-*methylglutaconate*, b. p. 65—66°/0·7 mm., n_D^{19} 1·4595, $\lambda_{max.}$ 215 mμ (ε 13,780), was prepared by the esterification of the acid of m. p. 139—140° with diazomethane (Found: C, 55·95; H, 7·1. $C_8H_{12}O_4$ requires C, 55·8; H, 7·0%). A mixture of the methyl esters of *cis*- and *trans*-β-methylglutaconate, b. p. 56—58°/0·5 mm., n_D^{19} 1·4598, was prepared by similar esterification of the acid, m. p. 115°, described above.

cis-β-Methylglutaconic acid, m. p. 150°, shows infrared absorption lines (in Nujol) at 1709, 1684, 1639, 1416, 1355 (sh), 1319, 1282, 1222, 1155, 1050, 1035, 954 (sh), 933, 911, 878, 856, 744, 721, 685, and 672 cm.$^{-1}$. The *trans*-acid, m. p. 140°, shows infrared absorption lines (in Nujol) at 1706, 1645, 1414, 1357 (sh), 1323, 1309 (sh.), 1272, 1238, 1199, 1174, 1046 (w), 1033 (w), 927, 904, 873, 847, 750, 724, 690, and 672 cm.$^{-1}$.

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