2, completes the construction of the side chain, and we now turn to the introduction of the unsaturated ester function.

Protection of the side-chain carbonyl of 6 by reaction with ethylene glycol (refluxing benzene, 30 hr) followed by chromic acid–pyridine oxidation of the ring hydroxyl led in 80% yield to the ketodioxolane 7a: bp 130–131° (0.3 mm); ir (film) 1710 cm^{-1}; nmr (C$_6$D$_6$) δ 3.65 ppm (s, 4).

In that substance, the ring carbonyl is adjacent to, rather than at, the position eventually occupied by the carbomethoxy function of juvabione, thus preserving the chirality of the asymmetric center in the ring, as well as avoiding obvious problems of regiospecificity in the introduction of the double bond. This approach requires, however, that introduction of a suitable function (cf. R in formula 7) take place selectively on the less hindered methylene of 7a. We expected this to be the case of carbomethoxylation. Indeed, the acylation of 7a (excess dimethyl carbonate, benzene, 2 equiv of sodium hydride, 60°, under nitrogen) led to the expected β keto ester 7b: ir (film) 1745, 1710, 1660, and 1610 cm^{-1}; nmr (C$_6$D$_6$) δ 3.5 (s, 3) and 3.65 (s, 4) ppm.

7a, R = H
b, R = CO$_2$Me

8a, R = H
b, R = Ts
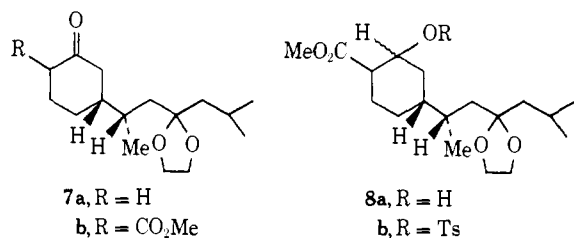
Introduction of the required double bond was then achieved by initial reduction of 7b (sodium borohydride, dimethylformamide–methanol, 1 hr, −10°) to give the hydroxy ester 8a as a mixture of cyclohexanol epimers (ir (film) 3450 (broad) and 1735 cm^{-1}) obtained in 60% overall yield from 7a, after purification by chromatography on neutral silica gel (95:5 benzene–ethyl acetate). There was also formed about 20% of the diols corresponding to the reduction of the ester function of 7b.

Formation of the double bond is carried out by treatment of the crude tosylate 8b (ir (film) 1735 cm^{-1}) with sodium methoxide in refluxing methanol containing 10% dimethyl sulfoxide. Acid hydrolysis of the dioxolane in the side chain then gave (55% from 8a) dl-juvabione (1) (bp 122° (0.01 mm); n^{24}D 1.4823; uv$_{max}$ (EtOH) 219 nm (ϵ 10,400); ir (film) 1710, 1650 cm^{-1}; mass spectrum[8] m/e 266 (M$^+$), 134 (base peak); nmr[9] (CDCl$_3$) δ 0.88 (d, 3), 0.92 (d, 6), 3.72 (s, 3) and 6.93 (s broad, 1)) in agreement with published values.[2b,d] Further confirmation of the structure of our synthetic dl-juvabione[10] was obtained by hydrolysis which gave dl-todomatuic acid (mp 66–67° (pentane), ir (Nujol) 1710, 1690, 1650 cm^{-1}; uv$_{max}$ (EtOH) 216 nm (ϵ 9700); nmr[9] (CCl$_4$) 0.87 (d, 3), 0.90 (d, 6), 7.02 (s, broad, 1)) in agreement with published values.[2b,d]

The stereospecific synthesis which we have described leads in 11 steps to dl-juvabione in a overall yield of

(8) The mass spectrum was recorded on a A.E.I. (MS 30) instrument (70 eV) by Madame Besseyre, Laboratoire de spectroscopie, Paris.

(9) The nmr spectra of dl-juvabione and todomatuic acid were recorded on a Varian XL 100 (100 MHz) instrument (internal TMS) by Madame Platzer, Laboratoire de spectroscopie, Paris.

(10) dl-Juvabione, todomatuic acid, and the intermediates have correct elemental analysis.

13%, starting from the keto acid 2 (6% starting from cyclohexenone). The general scheme presented here can, of course, be used for the synthesis of natural or modified sesquiterpenes structurally related to juvabione

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Equilibrium Acidities of Carbon Acids. II.[1] Hydrocarbon Indicators, Phenylacetylene, and Other Carbon Acids in the 20–27 pK Region

Sir:

There has been general appreciation in recent years of the merits of dimethyl sulfoxide (DMSO) as a solvent for measuring equilibrium acidities. For acids in the 10–20 pK range measurements have been made potentiometrically,[2,3] spectrophotometrically,[4] and by H_ techniques with H$_2$O–DMSO, MeOH–DMSO, and EtOH–DMSO using nitroaniline and nitrodiphenylamine indicators.[5] The latter method has been extended into the 20–30 pK range by Steiner, using hydrocarbon indicators.[6] During the past 6 years we have extended the investigation of the acidity of sulfones in pure DMSO[1] to a variety of other carbon acids including nitroalkanes, ketones, nitriles, sulfoxides, and hydrocarbons.[7] The Steiner method, which utilizes CH$_3$SOCH$_2$K at low concentrations (10^{-3}–10^{-4} M), has been modified in several ways in order to shorten the time required for each measurement and to increase the accuracy.[8] Standard deviations in a given titration are now routinely less than ±0.05 pK unit, and the reproducibility is generally within ±0.1 pK unit over the 10–27 pK range.

Steiner assigned pK's to his indicators by extrapolating H_ measurements into pure DMSO. We have checked the relative pK's of these indicator standards by measuring acidities of each indicator pair against at least three carbon acids of intermediate acidity and found that only small adjustments need be made (Table I).

The data in Table I show that carbon acids of widely differing structure can be related by the same hydrocarbon indicators. Note, for example, that DDH and XH-9-Ph can be used for both phenyl methyl sulfone, where the negative charge on the carbanion is largely localized on carbon, and for benzyl methyl sulfoxide, where the negative charge is strongly delocalized to the benzene ring. Similarly, TPH and FH can be used for both acetophenone, where the charge is localized to

(1) For paper I in this series see F. G. Bordwell, R. H. Imes, and E. C. Steiner, J. Amer. Chem. Soc., 89, 3905 (1967).

(2) C. D. Ritchie and R. E. Uschold, J. Amer. Chem. Soc., 89, 1721 (1967).

(3) I. M. Kolthoff, M. K. Chantooni, Jr., and S. Bhowmik, J. Amer. Chem. Soc., 90, 23 (1968).

(4) R. Kuhn and D. Rewicki, Justus Liebigs Ann. Chem., 704, 79 (1967); 706, 250 (1969).

(5) K. Bowden and R. Stewart, Tetrahedron, 21, 261 (1965).

(6) (a) E. C. Steiner and J. M. Gilbert, J. Amer. Chem. Soc., 87, 382 (1965); (b) E. C. Steiner and J. D. Starkey, ibid., 89, 2751 (1967).

(7) We are greatly indebted to E. C. Steiner for providing us with the details of his method for measuring acidities in the 20–30 pK range.

(8) A description of the original Steiner titration method is given in the Ph.D. dissertation of R. H. Imes, Northwestern University, 1969. The modified method will be described in a later publication.

Table I. Standardizations of Indicators by Overlap with Carbon Acids of Intermediate Acidity

Indicator	pK (adj)[a]	Carbon acid	pK (obsd)[b]	pK (adj)[c]
Diphenylyldiphenylmethane (DDH)	27.1	$PhSO_2CH_3$	26.96 ± 0.01	
		$PhC{\equiv}CH$	26.67 ± 0.01	
		$PhCH_2SOCH_3$	26.96 ± 0.01	
9-Phenylxanthene (XH-9-Ph)	25.6	$PhSO_2CH_3$	26.66 ± 0.03	26.7_5
		$PhC{\equiv}CH$	26.40 ± 0.04	26.5
		$PhCH_2SOCH_3$	26.60 ± 0.04	26.7
		$Et_2C{=}O$	24.70 ± 0.03	
		$i\text{-}PrCOPh$	23.85 ± 0.05	
1,1,3-Triphenylpropene (TPH)	23.3	$Et_2C{=}O$	24.61 ± 0.03	24.8
		$i\text{-}PrCOPh$	23.77 ± 0.02	24.0
		$MeCOPh$	22.50 ± 0.05	
		$EtCOPh$	22.28 ± 0.01	
		$(PhCH_2)_2SO_2$	21.86 ± 0.04	
Fluorene (FH)	(20.5)	$MeCOPh$	22.30 ± 0.02	22.5
		$EtCOPh$	22.00 ± 0.02	22.2
		$(PhCH_2)_2SO_2$	21.64 ± 0.02	21.8_5

[a] Statistically uncorrected; the average ΔpK's for each indicator pair, as determined from pK (obsd), were rounded to one significant figure (0.2 for FH vs. TPH; 0.1 for TPH vs. XH-9-Ph; 0.2 for XH-9-Ph vs. DDH) and used to adjust the indicator pK's assigned by Steiner. FH was used as an arbitrary reference standard. [b] Relative to Steiner's values of 27.3 for DDH, 25.5 for XH-9-Ph, 23.1 for TPH, and 20.5 for FH. [c] Statistically uncorrected; the adjusted indicator pK's were used as standards.

oxygen, and for benzyl sulfone, where the charge is delocalized to the benzene ring. Furthermore, it is gratifying to note that the indicators used may be varied considerably with respect to structure. These observations support the conclusion, derived from other studies, that, at low concentrations and with potassium as the cation, salts of carbon acids in DMSO exist essentially as fully dissociated ions.[9] This makes possible a comparison of relative acidities in a single solvent (DMSO) over a wide pK range (0–30) under conditions where substituent effects on the undissociated acid and the related anion can be determined without complications from ion aggregation.

The present work in DMSO, where equilibrium concentrations of dissociated ions are being measured, serves to complement earlier equilibrium studies in solvents, such as ether, benzene, and cyclohexylamine (CHA), where ion aggregates are present. The powerful effect produced on equilibria by ion aggregation is brought out by a comparison of the apparent acidity of phenylacetylene in ether, CHA, and DMSO. Conant and Wheland found that in ether phenylacetylene has an apparent acidity close to that of 9-phenylfluorene (pK = 15.8 on our scale),[10] whereas in CHA Streitwieser found its apparent acidity to be close to that of fluorene (pK = 20.5 on our scale).[11] In DMSO we find the apparent acidity of phenylacetylene to be close to that of 9-phenylxanthene and assign it a pK of 26.5 (Table I).[12] This change of almost 10^{11} in apparent acidity must be associated, as Streitwieser has pointed out,[11] with the extent of ion pairing in the various solvents. In essence the apparent pK is determined by the position of the equilibrium between the

indicator acid (HIn), the unknown acid (HA), and its potassium salt, i.e.

$$K^+In^- + HA \rightleftharpoons HIn + K^+A^-$$
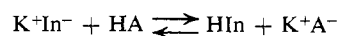
The equilibrium shifts to the right for $PhC{\equiv}CH$ in going from CHA to Et_2O because the stability of the ion pair, $PhC{\equiv}C^-K^+$, or the ion aggregate, $(PhC{\equiv}C^-K^+)_n$, becomes greater. It is clear, then, that the apparent acidities in a solvent where ion aggregation occurs may vary markedly depending on the solvent, the cation, and the reference indicator. On the other hand, in dilute DMSO both the K^+A^- and the K^+In^- salts are highly dissociated, and the equilibrium position is close to being indicative of a true pK.

The marked difference in the apparent acidity in CHA and DMSO for phenylacetylene contrasts sharply with the behavior of a series of hydrocarbon indicators containing two or three benzene rings. For these the apparent pK's in CHA and DMSO give very good agreement when adjusted to a common reference standard.[13] It now appears that the latter agreement is fortuitous. It must be a consequence of the similarity in the stability of ion pairs of closely related structural types in CHA. In contrast, the extent of ion pairing in $PhC{\equiv}C^-K^+$, where the negative charge on the carbanion is localized, differs greatly from that in salts such as those derived from fluorene, 9-phenylxanthene, etc., where the charge is highly delocalized; the apparent acidity of phenylacetylene relative to these indicators differs greatly, therefore, in CHA and DMSO. We can anticipate that apparent relative acidities in benzene, Et_2O, CHA, and DMSO will also differ for many other types of compounds. Another striking example is provided by comparison of the relative acidities of acetophenone and fluorene in benzene and DMSO. In benzene (or ether[10]) acetophenone is a stronger acid than fluorene by about 6 pK units,[14] whereas in DMSO fluorene is the stronger acid by ca. 2 pK units (Table I).

(9) (a) T. E. Hogen-Esch and J. Smid, J. Amer. Chem. Soc., 88, 307 (1966); (b) J. I. Brauman, J. A. Bryson, D. C. Kahl, and N. J. Nelson, ibid., 92, 6678 (1970); (c) J. Smid, "Ions and Ion Pairs in Organic Reactions," M. Szwarc, Ed., Wiley, New York, N. Y., 1972, Chapter 3; (d) A. Streitwieser, Jr., C. J. Chang, and D. M. E. Reuben, J. Amer. Chem. Soc., 94, 5730 (1972); (e) E. M. Arnett, T. C. Moriarity, L. E. Small, J. P. Rudolph, and R. P. Quirk, ibid., 95, 1492 (1973).

(10) J. B. Conant and G. W. Wheland, J. Amer. Chem. Soc., 54, 1212 (1932).

(11) A. Streitwieser, Jr., and D. M. E. Reuben, J. Amer. Chem. Soc., 93, 1794 (1971).

(12) A pK of 26.3 in DMSO is predicted from Arnett's correlation of pK's with heats of dissociation.[9e]

(13) C. D. Ritchie, "Solute-Solvent Interactions," J. F. Coetzee and C. D. Ritchie, Ed., Marcel Dekker, New York, N. Y., 1969, Chapter 4, Table 4-6, p 245.

(14) (a) W. K. McEwen, J. Amer. Chem. Soc., 58, 1124 (1936); (b) see also, D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, Chapter I.

We are in the process of developing an extended version of the McEwen-type pK scale[14] as applied to DMSO solvent. Subsequent papers will report pK values for a variety of parent carbon acids and will show the effect of substituents on their acidities.

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Equilibrium Acidities of Carbon Acids. III.[1] Carbon Acids in the Methane Series

Sir:

In the previous paper[1b] it was shown that the apparent acidities of carbon acids is often highly dependent on solvent. In solvents such as ether, benzene, and cyclohexylamine (CHA), where ion pairing in the salts is important, the apparent acidities of weak acids are usually much greater than in dilute dimethyl sulfoxide (DMSO) solutions, where the salts are highly dissociated. Measurements under the latter conditions allow accurate comparisons of acidities in a single solvent over a wide pK range (0–30) with a minimum of interference from counterion effects. In subsequent papers we will present pK data showing the effects of substituents on the acidities of a variety of carbon acids. In this paper we give pK data on the acidities of a number of parent acids in the methane series, CH_3-EWG, where EWG is one of the electron-withdrawing groups: NO_2, COC_6H_5, $COCH_3$, $SO_2C_6H_5$, SO_2CH_3, or $C\equiv N$ (Table I). This is the first direct comparison of the pK's of these fundamental types of weak organic

Table I. Equilibrium Acidities of Carbon Acids of the Methane Series, CH_3EWG, in Dimethyl Sulfoxide (DMSO)

Carbon acid	pK^a	Indicator	Indicator pK^a
Nitromethane	15.1[b,c]	FH-9-Ph[d]	15.8[d]
Acetophenone	22.5[c]	TPH[e]	23.3
Acetone	24.25[c]	XH-9-Ph[f]	25.6
Methyl phenyl sulfone	26.75[c,g]	DDH[h]	27.1
Dimethyl sulfone	28.8[c,i]	TH[j]	28.3
Acetonitrile	29.1	TH[j]	28.3

[a] Relative to fluorene (FH) at pK 20.5 as a reference standard; values are not statistically corrected. [b] C. D. Ritchie and R. E. Uschold, *J. Amer. Chem. Soc.*, **89**, 1721 (1967), report 15.9 (determined potentiometrically). [c] This measurement agreed within ±0.1 pK unit with that obtained against a second indicator. [d] 9-Phenylfluorene: C. D. Ritchie and R. E. Uschold, *J. Amer. Chem. Soc.*, **89**, 2752 (1967), report pK 16.4 (determined potentiometrically). [e] 1,1,3-Triphenylpropene (the abbreviation TP₂H has also been used). [f] 9-Phenylxanthene. [g] Previously reported as 27.[1a] [h] Diphenylyldiphenylmethane. [i] Previously reported as 28.[1a] [j] Triphenylmethane: E. C. Steiner (private communication), obtained ΔpK for TH vs. DDH of 1.2, which corresponds exactly with our value. Steiner's values relative to FH were, however, 0.2 pK unit higher than ours.

(1) For previous papers in this series see: (a) F. G. Bordwell, R. H. Imes, and E. C. Steiner, *J. Amer. Chem. Soc.*, **89**, 3905 (1967); (b) F. G. Bordwell and W. S. Matthews, *ibid.*, **96**, 1214 (1974).

acids. The measurements allow a new comparison of the effects of NO_2, COC_6H_5, etc., groups and provide a basis for future studies of substituent effects.

Previously we reported values for the indicators TPH, XH-9-Ph, and DDH relative to FH as a standard, obtained by overlap experiments using carbon acids in the 20–27 pK range.[1b] We now add the indicators triphenylmethane (TH; pK 28.3) and 9-phenylfluorene (FH-9-Ph; pK 15.8) to this list. It is noteworthy that we find FH-9-Ph to be *ca.* 5 pK units more acidic than fluorene (FH) in DMSO,[2] whereas the difference as determined by H_- techniques is only *ca.* 2.4 pK units in DMSO-EtOH (0–95%) and *ca.* 3.5 units in DMSO-HOH (40–90%).[3] These results emphasize the point that relative acidities of carbon acids will often differ depending on solvent.[1b] In the present instance, however, the differences are not due to ion pairing effects. The salts are presumably highly dissociated in all of these solutions, and the differences arise from the differences in solvating ability of pure DMSO *vs.* DMSO diluted with a protic solvent.[5]

The range of acidities from CH_3NO_2 to CH_3CN is 14 pK units (Table I) corresponding to about 19 kcal/mol in ΔG°. Since preliminary indications are that ΔpK's in DMSO can be correlated with carbanion stabilization energies in DMSO,[6] these differences in acidity are probably due primarily to differences in carbanion stabilization by EWG. In Table II ΔpK's for the CH_3-

Table II. Effects of Electron-Withdrawing Groups on Equilibrium Acidities in Dimethyl Sulfoxide

EWG	ΔpK	
	p-$HOC_6H_4EWG^{a,b}$	CH_3EWG
H	0.0 (16)[c]	0.0 (50)[c,d]
CN	4.8[e]	21
CH_3SO_2	5.6[e]	21
CH_3CO	6.0[e]	26
NO_2	6.6[e,f]	35

[a] E. M. Arnett, T. C. Moriarity, L. E. Small, J. P. Rudolph, and R. P. Quirk, *J. Amer. Chem. Soc.*, **95**, 1492 (1973). [b] Comparable ΔpK's are expected for the series p-$CH_3SO_2CH_2C_6H_4EWG$ (pK = 23.15 for EWG = H) on the basis of a similar ρ of 5.0 (R. H. Imes and W. S. Matthews, unpublished results). [c] pK of parent acid (EWG = H). [d] Estimated pK; see ref 9; the size of ΔpK is dependent on this estimate, but the relative ΔpK's are *not.* [e] Calculated from σ_R- values (ref 13) with ρ = 5.3 (see Arnett, *et al.*, footnote *a*). [f] I. M. Kolthoff, M. K. Chantooni, and S. Bhownik, *J. Amer. Chem. Soc.*, **90**, 23 (1968), found ΔpK to be 5.4 (pK p-$NO_2C_6H_4OH$ = 11.0); a ΔpK of 6.0 is obtained by using the pK of 10.4 for p-$NO_2C_6H_4OH$ reported by C. D. Ritchie and R. E. Uschold, *J. Amer. Chem. Soc.*, **89**, 2752 (1967).

(2) This is the statistically corrected difference. The value for FH-9-Ph may be subject to minor uncertainty (perhaps ±0.2 pK) since it has been linked to FH through 4-nitroaniline, which we no longer consider to be completely reliable as an indicator.

(3) K. Bowden and A. F. Cockerill, *J. Chem. Soc. B*, 173 (1970). These ΔpK values do not appear to have been statistically corrected (add 0.3 to ΔpK for statistical correction). The pK in sulfolane-H_2O is 0.1 pK unit higher than that in DMSO-H_2O.[4]

(4) R. L. Burwell, Jr., and C. H. Langford, *J. Amer. Chem. Soc.*, **82**, 1503 (1960).

(5) See C. D. Ritchie, "Solute-Solvent Interactions," J. F. Coetzee and C. D. Ritchie, Ed., Marcel Dekker, New York, N. Y., 1969, Chapter 4, for a discussion of solvent effects in DMSO.

(6) Judging from the reasonable agreement found by Ritchie and Uschold for the pK's of p-nitro- and tris-p-nitrotriphenylmethanes with those calculated from carbanion stabilization energies,[7] as determined by McKeever and Taft.[8]

(7) C. D. Ritchie and R. E. Uschold, *J. Amer. Chem. Soc.*, **89**, 1721 (1967).

(8) L. D. McKeever and R. W. Taft, *J. Amer. Chem. Soc.*, **88**, 4544 (1966).