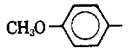
TABLE II

$R_3P^+-CH_2CO_2C_2H_5X^-$

R	X	M.p., °C.	Calcd., % C	H	B	Br	P	Found, % C	H	B	Br	P	Crystn. solvents
n-C_4H_9	Br	99–100	52.00	9.28	..	21.63	8.39	52.01	9.35	..	22.00	8.40	Methylene chloride–ether
n-C_4H_9	$B(C_6H_5)_4$	190–191	79.00	8.95	1.77	...	5.09	78.76	9.33	2.08	...	5.11	Methylene chloride–hexane
	Br	148–150	59.10	9.02	...	17.85	6.92	58.87	8.92	...	17.97	6.81	Methylene chloride–ether
	$B(C_6H_5)_4$	193–194	80.50	8.82	1.58	...	4.51	80.27	8.72	1.59	...	4.45	Ethanol
n-C_6H_{13}	$B(C_6H_5)_4$	124–125	79.80	9.61	1.56	...	4.41	80.05	9.71	1.84	...	4.40	Methylene chloride–hexane
n-C_8H_{17}	$B(C_6H_5)_4$	79–81	80.42	10.12	1.39	...	3.98	80.91	10.31	1.44	...	4.00	Methylene chloride–hexane
n-$C_{10}H_{21}$	$B(C_6H_5)_4$	72–73	81.00	10.53	1.26	...	3.51	81.46	10.35	1.23	...	3.64	Methylene chloride–hexane
	$B(C_6H_5)_4$	148–149	77.65	6.38	1.42	...	4.08	77.68	6.48	1.60	...	4.09	Methylene chloride–hexane

oxy substitution the two effects cancel one another for little change in *cis–trans* olefin ratio is observed.

Experimental[7]

Phosphines.—Triphenylphosphine was purchased from M and T Chemicals and recrystallized from hexane. Tributylphosphine was purchased from K and K Laboratories, Inc., and distilled prior to use. Tricyclohexylphosphine was prepared according to the procedure of Issleib.[8] Trihexylphosphine and trioctylphosphine were prepared as described by Jackson.[9] Tridecylphosphine was prepared from n-decylmagnesium bromide and phosphorus trichloride, and the crude phosphine was used for preparation of the phosphonium salt. Tris-p-anisylphosphine was synthesized as described by Mann and Chapplin.[10]

Phosphonium Salts.—The phosphonium salts were prepared by heating a benzene solution of equivalent amounts of the phosphine and ethyl bromoacetate overnight at reflux. In most cases the phosphonium bromides resisted all attempts at crystallization. The tetraphenylborates are solids and were prepared by dissolving the oily phosphonium bromides in ethanol and adding an equivalent amount of sodium tetraphenylborate in ethanol. The tetraphenylborates, insoluble in cold ethanol, were collected by filtration and recrystallized. The physical constants and analyses data are presented in Table II.

Wittig Reactions.—All experiments were performed in the same manner. The phosphonium salt (0.0045 mole) was suspended (dissolved) in 20 ml. of anhydrous ethanol under nitrogen. The bromides were soluble while the tetraphenylborates were insoluble at room temperature. Five milliliters of 0.895 M sodium ethoxide was added, whereupon the solution became homogeneous. Benzaldehyde (0.0045 mole) in 5 ml. of anhydrous ethanol was then added, and the solution was stirred under nitrogen for 16 hr. The solvent was then removed *in vacuo*, and the residue was digested with a small amount of hexane (in which the olefins are soluble) and filtered. The hexane solution was then analyzed by g.l.p.c. using a 6-ft. column of silicone rubber SE-30 on 60-80 Diatoport S and an external standard.

(7) Melting points are uncorrected.

(8) V. K. Issleib and A. Brock, *Z. anorg. allgem. Chem.*, **477**, 258 (1954).

(9) I. K. Jackson, W. C. Davies, and W. J. Jones, *J. Chem. Soc.*, 2109 (1931).

(10) F. G. Mann and E. J. Chapplin, *ibid.*, 527 (1937).

The Stereospecificity of Amine Additions to Acetylenic Esters

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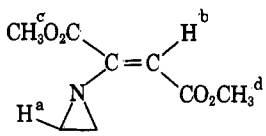
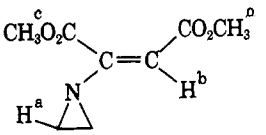
Nucleophilic addition to triple bonds has been studied from a variety of synthetic viewpoints.[1-3] The stereochemistry of additions of thiolic nucleophiles has been carefully studied by Truce who has evolved a "Rule of *trans*-Nucleophilic Addition" in such cases.[4] However, it has been previously suggested by some that the reaction of amines with acetylenic materials may involve cisoid additions[2,5] while others have favored transoid mechanisms.[3] We have been able to establish that indeed *both* types of additions are possible depending upon the nature of the solvent.

In conjunction with certain synthetic efforts we studied the reaction of aziridine with dimethyl acetylenedicarboxylate and with ethyl propiolate. Reaction of equimolar ratios of aziridine and dimethyl acetylenedicarboxylate in methanol at room temperature provides a 76% yield of a semisolid, b.p. 80–85° (0.20 mm.). Analysis of the product mixture was expedited by examination of the p.m.r. spectrum which revealed that the *trans* ester I comprised 67% of the product and the *cis* ester II, 33%.



I



II

However the reaction course in dimethyl sulfoxide under the same conditions proved to be dramatically different. The reaction product obtained in this solvent consisted of 95% *cis* ester II and only 5% of the *trans* ester I; the product mixture was obtained in 75% yield.

The pure fumarate ester I was a solid, white needles from hexane–benzene, m.p. 67–70°; the pure maleate ester II was a mobile liquid, b.p. 80–82° (0.20 mm.). We have established that neither of the esters in question isomerize to the other under the conditions of the respective reactions.

The difference in physical properties parallels the classic differences of maleates and fumarates. How-

(1) A. W. Johnson, "Chemistry of the Acetylenic Compounds," Vol. II, Longmans, Green and Co., New York, N. Y., 1950, pp. 199–266; W. E. Truce and R. B. Kruse, *J. Am. Chem. Soc.*, **81**, 5372 (1959); E. I. Grinblat and I. Y. Postovsky, *Dokl. Akad. Nauk SSSR*, **133**, 847 (1960); H. J. Backer and A. E. Beute, *Rec. trav. chim.*, **54**, 200, 523 (1936); S. Ruhemann and A. V. Cunnington, *J. Chem. Soc.*, **75**, 954 (1899); J. B. Hendrickson, *J. Am. Chem. Soc.*, **82**, 653 (1962); G. Stork and M. Tomasz, *ibid.*, **86**, 471 (1964).

(2) E. R. H. Jones and M. C. Whiting, *J. Chem. Soc.*, 1423 (1949).

(3) J. B. Hendrickson, R. Rees, and J. F. Templeton, *J. Am. Chem. Soc.*, **86**, 107 (1964).

(4) W. E. Truce, H. G. Klein, and R. B. Kruse, *ibid.*, **83**, 4636 (1961), and previous papers.

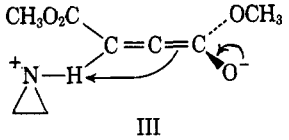
(5) W. E. Truce and B. F. Heine, *ibid.*, **79**, 5311 (1957), footnote 2.

ever, a more certain indication of structure was accessible from the different chemical shifts in the respective p.m.r. spectra. It would be expected that the significant diamagnetic anisotropy of ester carbonyls[6] would lead to a greater deshielding of the vinyl and aziridino protons in the fumarate ester I than in the maleate ester II; in the former case both types of protons are flanked by two carbonyl fields, whereas in the latter case each type of proton is flanked by a single carbonyl field. This reasoning is in accord with predicted and observed shifts for the corresponding protons in mesaconic and citraconic acid esters.[7] Thus the chemical shifts from tetramethylsilane in p.p.m. characteristic of the esters I and II are assigned as shown in Table I.

TABLE I

trans ester I		*cis* ester II	
Proton	Shift, p.p.m.	Proton	Shift, p.p.m.
H^a	2.27	H^a	2.13
H^b	6.15	H^b	5.31
H^c	3.81	H^c	3.87
H^d	3.71	H^d	3.67

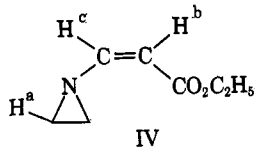
The variation of the course of the amine addition in dimethyl sulfoxide *vs.* methanol may be attributed to the formation of zwitterionic intermediate III. In



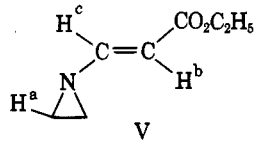
III

the absence of an external proton source, the zwitterion III would be expected to undergo a stereospecific collapse *via* intramolecular protonation, leading to the *cis* disposition of the ester functions. However, in a hydroxylic solvent, solvation of the incipient Michael anion will be an attenuating factor on such cisoid reaction: protonation of the anion by solvent becomes the favored path. Whether this protonation is of a kinetic nature concerted with the addition of the nucleophile or is a product-controlled process is speculation. Either factor would provide a predominance of the fumarate-type ester.

It should be noted that this highly exothermic reaction proceeds readily even in the nonpolar solvent mixture of 1:1 cyclohexane–benzene to give results identical with the reaction in dimethyl sulfoxide. The addition of aziridine to ethyl propiolate was found to proceed analogously to the previous example. Reaction of an equimolar ratio of aziridine and ethyl propiolate in methanol at room temperature gave rise to a 73% yield of a liquid, b.p. 89–95° (12 mm.), which was determined by examination of its p.m.r. spectrum to consist of 58% *cis*-aziridinoacrylic acid ethyl ester (IV) and 42% *trans*-aziridinoacrylic acid



IV



V

ethyl ester (V). However, similar reaction in dimethyl sulfoxide gave rise exclusively to the pure *trans* ester V resulting from *cis* addition of the amine; there was no evidence of the *cis* ester IV as determined by examination of the p.m.r. trace. The larger coupling of *trans* protons than *cis* protons provides a simple determination of structure.[8] The *trans* protons in the *trans* ester V possessed J = 13.5 c.p.s.; the *cis* protons in the *cis* ester IV possessed J = 9.0 c.p.s. The assignment of chemical shifts in p.p.m. from TMS are as shown in Table II. We have ascertained that the esters IV and V do not interconvert under the conditions of their formation.

TABLE II

cis ester IV		*trans* ester V	
Proton	Shift, p.p.m.	Proton	Shift, p.p.m.
H^a	2.13	H^a	1.98
H^b	5.13	H^b	5.31
H^c	6.64	H^c	7.51
$J_{H^bH^c}$ = 9.0 c.p.s.		$J_{H^bH^c}$ = 13.5 c.p.s.	

Our results put to question a recent statement: "..., whenever mobile protons are available, the first product of additions to acetylenedicarboxylic esters is the simple *trans* adduct."[3]

This statement, made to include the ammonium proton in the zwitterionic intermediate as a "mobile" proton is at least an oversimplification of the reaction mode and possibly an erroneous conclusion except in the case where the "mobile" protons are derived from solvent molecules. Although the authors report a *trans* addition obtaining in aprotic medium (hot benzene), it was not demonstrated that the observed product, corresponding to gross *trans* addition, was not the result of an isomerization of an initially formed product, corresponding to *cis* addition.[3] Until further experimental results are garnered, generalizations concerning the addition of amines to acetylenic bonds cannot be made with confidence.[9]

The differentiation of stereochemistry as a function of solvent[10] observed here suggests the capability of the Michael reaction to produce stereoselective results in other cases in which a *neutral* nucleophile is a participant.

Experimental[11]

Reaction of Aziridine with Dimethyl Acetylenedicarboxylate A. In Dimethyl Sulfoxide.—To 30 ml. of dimethyl sulfoxide maintained at 25–30° was simultaneously added a solution of 4.30 g. (0.10 mole) of aziridine in 25 ml. of dimethyl sulfoxide and a solution of 14.2 g. (0.10 mole) of dimethyl acetylenedicarboxylate in 25 ml. of dimethyl sulfoxide with magnetic stirring. The addition lasted 20 min. after which stirring was continued for 1.5 hr. The reaction solution was diluted with 300 ml. of water and extracted with four 50-ml. portions of benzene. The benzene extracts were washed with water, dried (sodium sulfate), filtered, and evaporated *in vacuo*. Distillation of the residual oil at re-

(6) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Inc., New York, N. Y., 1959, pp. 17, 18.

(7) See ref. 6, pp. 121, 122.

(8) See ref. 6, pp. 85–87.

(9) W. E. Truce and J. S. Pizey (private communication) have observed similar *cis* addition of piperidine to tetrolic acid esters.

(10) Certain *anionic* nucleophilic additions to conjugated systems have been shown to retain the possibility of a thermodynamical isomerization of the Michael anion intermediate when the protonation of the anion is caused to be slower than isomerization. That this may depend on the proton-donating ability of the solvent system has been shown: *cf.* W. E. Truce and R. J. Levy, *J. Am. Chem. Soc.*, **83**, 4641 (1961); *J. Org. Chem.*, **28**, 679 (1963).

(11) Melting points are corrected. Analyses were performed by Dr. C. S. Yeh's laboratory at Purdue University. N.m.r. spectra were obtained on a Varian A-60 instrument.

duced pressure gave 13.0 g. (70.3%) of aziridinomaleic acid dimethyl ester containing 5% aziridinofumaric acid dimethyl ester as determined by p.m.r. absorption intensities, b.p. 80–82° (0.2 mm.).

Anal. Calcd. for $C_8H_{12}NO_4$: C, 51.80; H, 5.99; N, 7.57. Found: C, 52.14; H, 6.23; N, 7.53.

Substitution of 1:1 benzene–cyclohexane solvent in the procedure gave closely similar results.

B. In Methanol.—A procedure identical with method A was employed in which methanol was substituted for dimethyl sulfoxide. The product was distilled at 80–85° (0.2 mm.) and amounted to 14.0 g. (75.7%) of a semisolid mass which proved to be a mixture of 67% aziridinofuramic acid dimethyl ester and of 33% aziridinomaleic acid dimethyl ester by examination of the p.m.r. spectrum.

An analytical sample of the pure fumarate ester, m.p. 67–70°, was obtained by crystallization from benzene–hexane.

Anal. Calcd. for $C_8H_{12}NO_4$: C, 51.80; H, 5.99; N, 7.57. Found: C, 51.92; H, 5.92; N, 7.45.

Reaction of Aziridine with Ethyl Propiolate. Method A. In Dimethyl Sulfoxide.—To 40 ml. of dimethyl sulfoxide maintained at 25–30° was simultaneously added a solution of 9.80 g. (0.10 mole) of ethyl propiolate in 40 ml. of dimethyl sulfoxide and a solution of 4.30 g. (0.10 mole) of aziridine in dimethyl sulfoxide over a 15-min. interval with magnetic stirring. The reaction solution was stirred for 1.5 hr., diluted with 100 ml. of water, and extracted with three 50-ml. portions of benzene. The benzene extracts were washed with 50 ml. of water, dried (sodium sulfate), decanted, and evaporated *in vacuo*. Distillation of the colorless, mobile residue gave 12.0 g. (85%) of *trans*-aziridinoacrylic acid ethyl ester, b.p. 98–103° (12 mm.). The spectrum possessed only maxima attributable to the *trans* ester.

Anal. Calcd. for $C_7H_{11}NO_2$: C, 59.50; H, 7.85; N, 9.93. Found: C, 59.83; H, 7.63; N, 9.82.

Method B. In Methanol.—The procedure followed was identical with that of method A, with the exception of the substitution of methanol for dimethyl sulfoxide. Distillation of the product provided 10.3 g. (73%), b.p. 89–95° (12 mm.), of a mixture of 58% *cis*-aziridinoacrylic acid ethyl ester and 42% *trans*-aziridinoacrylic acid ethyl ester determined by examination of the p.m.r. spectrum.

Anal. Calcd. for $C_6H_{11}NO_2$: C, 59.50; H, 7.85; N, 9.93. Found: C, 59.78; H, 7.95; H, 10.25.

Equilibration Experiments.—It was determined simply that the esters I and II can be quantitatively recovered unchanged from dimethyl sulfoxide and methanol, respectively, after 10 hr. at room temperature even in the presence of added aziridine. The criteria for judgment rested with the identity of the infrared and p.m.r. spectra of the esters, taken before and after the equilibration experiments.

Likewise, it was found that the ester V was unaffected by pure methanol or methanol containing aziridine after 10 hr. at room temperature. The mixture of IV and V proved to be stable to treatment with either dimethyl sulfoxide or methanol for 10 hr. at room temperature even in the presence of added aziridine.

Acknowledgment.—This work was supported, in part, by Institutional Grant IN-17F from the American Cancer Society to Purdue University.

The Reaction of O^{18}-Labeled Ethanol with Phenols and N,N′-Dicyclohexylcarbodiimide

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In 1962 Vowinkel[1] reported the synthesis of aryl alkyl ethers from phenols and alcohols using N,N′-dicyclohexylcarbodiimide (DCC) as a condensing agent (see eq. 1). The reaction was carried out in a refluxing, inert solvent and afforded satisfactory yields when primary alcohols were used; however, poor yields were afforded using secondary or tertiary alcohols; *ortho*-substituted phenols also caused a marked decrease in ether formation.

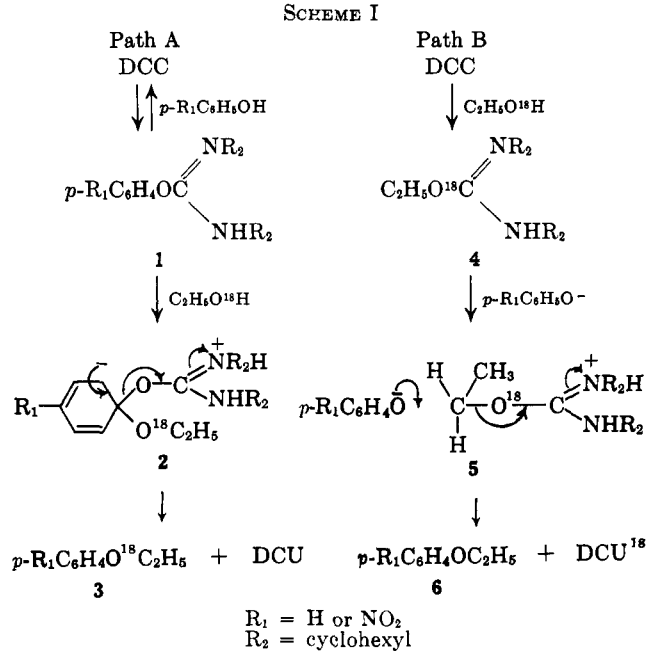
$$\mathrm{ArOH} + \mathrm{ROH} \xrightarrow{\mathrm{DCC}} \mathrm{ArOR} + \mathrm{DCU} \qquad (1)$$

Ar = phenyl or substituted phenyl
R = *n*-alkyls
DCU = N,N′-dicyclohexylurea

In 1963 an improved synthesis of aryl alkyl ethers was described[2] where phenolic substances, primary alcohols, and DCC were heated without solvent in a sealed tube at *ca.* 100° for 24 hr. This modification was repeated in our laboratories and, in every case, excellent yields were afforded (87–92%).

The mechanism proposed by Vowinkel[1] for aryl alkyl ether formation (see path A, Scheme I) in refluxing, inert solvents required the initial formation of a phenol–DCC adduct (1) followed by a primary alcohol attack (see 2). The failure of secondary and tertiary alcohols to participate in this reaction was attributed to nonbonded interaction between the phenyl ring and the attacking branched alcohols. The formation of 2-arylpseudoureas (1) from phenols and carbodiimides has been reported[3] and is not questioned. However, there is little analogy for the final step in path A, *i.e.*, nucleophilic attack by a primary alcohol on an aromatic system.

SCHEME I



R_1 = H or NO_2
R_2 = cyclohexyl

An alternate mechanism is therefore outlined in path B (Scheme I) which requires the intermediacy of a 2-alkylpseudourea (4). Ordinarily, alcohols are unreactive towards carbodiimides at room temperature; however, high yields are afforded[4] when N,N′-diphenylcarbodiimide and ethanol are heated in a sealed tube (the conditions used in this study). There is also no doubt that owing to increased acidity of phenols the

(1) E. Vowinkel, *Chem. Ber.*, **95**, 2997 (1962).

(2) E. Vowinkel, *Angew. Chem., Intern. Ed. Engl.*, [4] **2**, 218 (1963).

(3) M. Busch, G. Blume, and E. Pungs, *J. prakt. Chem.*, [2] **79**, 513 (1909).

(4) F. Lengfeld and J. Stieglitz, *Chem. Ber.*, **27**, 926 (1894).