Elimination–Addition. Part VIII.[1] Structures of Acetylene–Amine Adducts

By C. H. McMullen and C. J. M. Stirling

Addition of primary and secondary amines to acetylenes activated by the groups PhCO–, $PhCH_2N(Me)\cdot CO–$, $MeO\cdot CO–$, $PhCH_2\cdot SO–$, and $PhCH_2\cdot SO_2–$ has been investigated. In all cases, 1 : 1-adducts are formed and these have the enamine structure.

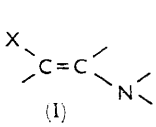
Secondary amines give the thermodynamically more stable *trans*-enamines only; the exceptional behaviour of ethyleneimine, reported by other workers, is discussed.

Primary amines give equilibrium mixtures of *cis*- and *trans*-enamines whose compositions have been determined by proton magnetic resonance spectroscopy. The proportions of *cis*- and *trans*-isomers depend on the solvent used for p.m.r. measurements, and upon the structures both of the activating group and the amine.

Change of solvent from chloroform to dimethyl sulphoxide shifts the equilibrium in favour of the *trans*-isomer; this observation is accounted for in terms of the balance between inter- and intra-molecular hydrogen bonding.

For adducts with benzylamine, the proportion of *cis*-isomer falls along the series of activating groups as follows: $Ph\cdot CO– < PhCH_2\cdot N(Me)CO– < MeO\cdot CO–$ and $PhCH_2\cdot SO– < PhCH_2\cdot SO_2–$. The adducts obtained from the acetylenic ester and ketone with t-butylamine contain a greater proportion of *cis*-isomer than those obtained with benzylamine. By contrast, the *cis–trans* ratios depend little upon either the basicity of the amine or the polarity of the *N*-alkyl group. These observations are discussed.

Reactions of amines with acetylenic sulphones have been described.[2,3] 1 : 1-Adducts between amine and sulphone were always obtained and it was shown that thermodynamic products resulted from equilibration of whatever adduct was initially formed. With secondary amines, *trans**-enamines (cf. I) were the sole products.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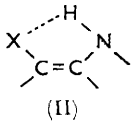
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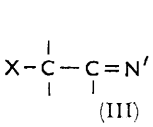
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Primary amines gave *cis–trans* mixtures, in which proton magnetic resonance spectroscopy gave clear evidence for hydrogen bonding in the *cis* isomer (cf. II) between the nitrogen atom and the oxygen atoms of the sulphonyl group. This Paper describes our investigation of the addition of amines to acetylenes bearing a variety of activating groups. We have attempted to discover whether the *cis–trans* equilibration of the products is general and, if so, to investigate the effect of the activating group, the structure of the amine, and the solvent upon the equilibrium.

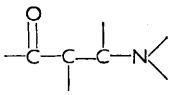
Previous work has considered (usually separately) the stereochemistry of addition of amines to activated acetylenes and the structures of enamines which bear a substituent conjugated to the double bond. Addition of amines to acetylenes has been much studied[4] but differences in behaviour between primary and secondary amines do not appear to have been commented upon. In general, addition occurs smoothly and 1 : 1-adducts with the amino-group β to the activating group are obtained from acetylenic esters[5] and ketones.[6,7] Ultraviolet spectroscopy[6] clearly showed that with primary amines, the adducts have the enamino-structure (I or

* Throughout, *cis* and *trans* refer to the relative dispositions of the activating group and the nitrogen atom.

[1] Part VII, C. J. M. Stirling, *J. Chem. Soc.*, 1964, 5875.
[2] C. J. M. Stirling, *J. Chem. Soc.*, 1964, 5863.
[3] R. C. Pink, R. Spratt, and C. J. M. Stirling, *J. Chem. Soc.*, 1965, 5714.
[4] R. A. Raphael, "Acetylenic Compounds in Organic Synthesis," Butterworths, London, 1955.
[5] E. André, *Ann. Chim.*, 1913, **29**, 569.
[6] K. Bowden, E. A. Braude, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 1946, 45.
[7] K. Bowden, E. A. Braude, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 1946, 945.

II) and not the imino-structure (III), although the latter has recently been implicated in the *cis–trans* isomerisation of enamines.[8] In earlier work, tentative assignments of configuration were based[6] upon equivocal ultraviolet spectroscopic results and in some cases assignments were made[9] on the basis of subsequent reaction between *cis*-oriented groups, notwithstanding the earlier observation of the ready interconversion of enamine isomers.[6]

β-Ketoenamines are also obtained from β-dicarbonyl compounds and amines.[10–13] Dudek and Volpp,[13] using proton magnetic resonance spectroscopy, have examined the isomerism of ethyl β-benzylaminocrotonate and found that only *cis*- and *trans*-enamine forms were present. These were readily interconverted in solution and the equilibrium position was solvent-dependent. In chloroform, the chelated *cis*-form (cf. II) was overwhelmingly favoured but in pyridine more of the *trans*-form was present at equilibrium. These workers also confirmed Dabrowski's conclusions,[12] based on infrared studies, that the chelated *cis*-isomer is the preferred form of 4-aminobut-3-en-2-one in chloroform. A view contrary to this general picture has been taken by Russian workers[14] who favour equilibrium between a keto-enamine (IV) and a hydroxy-imine (V). The re-examination and correction of this work is presented elsewhere.[15]



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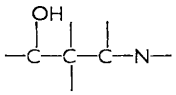

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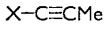
We have examined reactions in two types of system: the terminal acetylenes (VI) in which X = PhCO–, MeOCO–, and PhN(Me)CO–, and the propynes (VII) in

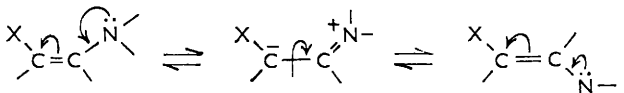
(VI)



(VII)

which X = $PhCH_2SO_2$–, $PhSO_2$–, Bu^tSO_2–, and $PhCH_2SO$–. The general procedure was to allow the amine and acetylene to react in methanol at 20° and, after removal of the solvent (at 40°), to examine both the crude and purified products by p.m.r. spectroscopy in appropriate solvents. High yields of mono-adducts were always obtained so side reactions can be excluded. The proton arrangement always confirmed the enamine structure and the configurations of adducts from terminal acetylenes were assigned from the coupling constants of the vinyl protons.[16] Products from non-terminal acetylenes were assigned configurations on the basis of the τ-values of the *C*-methyl groups according to arguments developed[2] previously.

Secondary Amines.—Details of adducts obtained are in Table 1. In every case, one isomer only is present in deuteriochloroform and except for the sulphoxide adduct where assignment is only tentative, this is a *trans*-enamine. Formation of *trans*-isomers from sulphones has been discussed[2] and whatever the configuration of the kinetic product (usually *cis*[3,17]), equilibration according to the Scheme results in a thermodynamic product. This Scheme accords with the well known carbon nucleophilicity of enamines. The *trans*-isomer is favoured by opposition of the dipoles of the activating



(IX)

Scheme

group and the C–N bond and by the absence of non-bonded interaction between the activating group and the dialkylamino-group. Replacement of dibenzylamine by the less bulky dimethylamine or by the more polar sarcosine ethyl ester does not affect the situation.

Our observations are confirmed by the recent work of Winterfeldt and Preuss[18] who have also found that addition of secondary amines to acetylenic esters gives products which result from *cis*-addition (*trans*-products

TABLE 1

Adducts from acetylenes and secondary amines

Acetylene	Amine	Yield (%)	Basis of assignment	M. p.	Crystd. from	Found (%) C	H	N	Formula	Reqd. (%) C	H	N
Ph·CO·C:CH	$(PhCH_2)_2NH$	99	12 [a]	112—113·5°	PhH–Pet.	84·4	6·7	4·2	$C_{23}H_{21}NO$	84·4	6·5	4·3
Ph·CO·C:CH	Me_2NH	94	12 [a]	91—92 [b]	Pr^i_2O	75·4	7·3	—	$C_{11}H_{13}NO$	75·5	7·4	—
MeO·CO·C:CH	$(PhCH_2)_2NH$	95	13 [a]	68—69	PhH–Pet.	76·6	6·6	4·8	$C_{18}H_{19}NO_4$	76·8	6·8	5·0
Ph·N(Me)·CO·C:CH	$(PhCH_2)_2NH$	93	12·5 [a]	110—111	PhH–Pet.	81·0	6·9	—	$C_{24}H_{24}N_2O$	80·9	6·75	—
$PhCH_2$·SO·C:C·Me	$(PhCH_2)_2NH$	99	8·05 [c,d]	152—153·5	PhH	76·9	6·9	3·6	$C_{24}H_{25}NOS$	76·8	7·0	3·7
Ph·SO_2·C:C·Me	$(PhCH_2)_2NH$	*e*	7·65 [c]	—	—	—	—	—	—	—	—	—
Ph·SO_2·C:C·Me	$MeNH·CH_2·CO_2Et$	*f*	7·88 [c]	—	—	—	—	—	—	—	—	—

[a] *J* (vinyl protons) in c./sec. [b] E. Benary (*Ber.*, 1930, **63**, 1573) gives m. p. 90—92°. [c] *C*-Me group in p.p.m., cf. ref. 2. [d] In monobenzylamine adducts: *trans*-Me, 7·93; *cis*-Me, 8·13. [e] Experimental details in ref. 2. [f] Experimental details in ref. 3.

[8] J. Dabrowski and J. Terpinski, *Tetrahedron Letters*, 1965, 1363.

[9] E. R. H. Jones and M. C. Whiting, *J. Chem. Soc.*, 1949, 1423.

[10] E. Thielepape, *Ber.*, 1922, **29**, 127.

[11] H. P. Schad, *Helv. Chim. Acta*, 1955, **38**, 1117.

[12] J. Dabrowski, *Spectrochim. Acta*, 1963, **19**, 475.

[13] G. O. Dudek and G. P. Volpp, *J. Amer. Chem. Soc.*, 1963, **85**, 2697.

[14] V. M. Potapov, F. A. Trofimov, and A. P. Terent'ev, *Zhur. obschei Khim.*, 1963, **33**, 853.

[15] C. M. McMullen and C. J. M. Stirling, *J. Chem. Soc.* (*B*), following Paper.

[16] N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, 1964, Section 3—4A (i).

[17] C. J. M. Stirling, *J. Chem. Soc.*, 1964, 5856, and references there cited.

[18] E. Winterfeldt and H. Preuss, *Chem. Ber.*, 1966, **99**, 450.

according to our designation). They offer a different explanation for their results and do not appear to have considered the possibility that the kinetic product rapidly equilibrates.

The sole exceptions to this general observation concern ethyleneimine. This reacts [19] with tolyl-*p*-sulphonylacetylene to give the *cis*-product only, and in reactions with ethyl propiolate [19,20] and 1-ethylsulphonylpropyne,[19] *cis–trans* mixtures are obtained whose compositions depend on the *reaction* solvent. These mixtures are sulphonylacetylenes [2,3] this is so, and considerable proportions of *cis*-isomers appear in the mixtures. Stabilisation of the *cis*-isomer in these instances was ascribed to hydrogen-bonding between the amino-nitrogen atom and the sulphonyl group. Details of the products obtained from primary amines and acetylenes are in Table 2. The results show the interplay of three main factors: (i) the structure of the activating group, (ii) the solvent, (iii) the structure of the amine.

With benzylamine, the proportion of *cis*-isomer falls

TABLE 2

Adducts from acetylenes and primary amines

	Acetylene	Amine	Yield (%)	P.m.r. solvent	*cis* [a] (%)	*trans* [a] (%)
1.	Ph·CO·C:CH	$PhCH_2·NH_2$	98	$CDCl_3$	100	0
				DMSO [e] 10 min.	100	0
				DMSO [e] 330 min.	50	50
2.	Ph·CO·C:CH	$Me_3C·NH_2$	94	$CDCl_3$	100	0
				DMSO 5 min.	50	50
				DMSO 5 hr.	75	25
				DMSO 72 hr.	80	20
3.	Ph·CO·C:CH	$Ph·NH_2$	88	DMSO 10 min.	90	10
				DMSO 30 min.	75	25
				DMSO 24 hr.	55	45
4.	MeO·CO·C:CH	$PhCH_2·NH_2$	99	$CDCl_3$	70	30
				DMSO 20 min.	100	0
				DMSO 24 hr.	20	80
5.	MeO·CO·C:CH	$Me_3C·NH_2$	64	$CDCl_3$	100	0
6.	Ph·N(Me)·CO·C:CH	$PhCH_2NH_2$	86	$CDCl_3$	85	15
				DMSO 10 min.		
				DMSO 24 hr.	45	55
7.	$PhCH_2·SO·CH_2·C:CH$ [b]	$PhCH_2·NH_2$	99	$CDCl_3$	80	20
8.	$PhCH_2SO_2CH_2·C:CH$ [b]	$PhCH_2·NH_2$	99	$CDCl_3$	35	65
9.	$PhSO_2C:C·Me$	$PhCH_2·NH_2$	*c*	$CDCl_3$	65	35
10.	$Ph·SO_2·CH_2·C:CH$ [b]	$NH_2·CH_2·CO_2Et$	*c*	$CDCl_3$	60	40
11.	$Ph·SO_2·C:C·Me$	$Me_3C·NH_2$	67	$CDCl_3$	45	55
12.	$Ph·SO_2·CH_2·C:CH$ [b]	$NH_2·[CH_2]_3OMe$	*d*	$CDCl_3$	65	35
13.	$Me_3C·SO_2·CH_2·C:CH$ [b]	$NH_2·[CH_2]_3OMe$	*d*	$CDCl_3$	80	20

	M.p.	Crystd. from	Found (%) C	H	N	Formula	Reqd. (%) C	H	N
1.	81·5—83°	PhH–Pet. [f]	80·7	6·45	5·8	$C_{16}H_{15}NO$	81·0	6·4	5·9
2.	44—45	MeOH–H_2O	76·8	8·4	—	$C_{13}H_{17}NO$	76·8	8·4	—
3.	140—141 [g]	MeOH	—	—	—	—	—	—	—
4.	65—72 [h]	$(i\text{-}Pr)_2O$	68·6	6·7	—	$C_{11}H_{13}NO_2$	69·1	6·8	—
5.	90/14 mm. [j]	1·4850 [k]	61·0	9·4	—	$C_8H_{15}NO_2$	61·1	9·55	—
6.	93—94	PhH–Pet.	76·4	6·7	—	$C_{17}H_{18}N_2O$	76·6	6·8	—
7.	*l*	—	—	—	—	—	—	—	—
8.	117—118	PhH–Pet.	68·0	6·3	—	$C_{17}H_{19}NO_2S$	67·7	6·3	—
11.	115—116	PhH–$(i\text{-}Pr)_2O$	61·8	7·8	—	$C_{13}H_{19}NO_2S$	61·6	7·5	—

[a] Calculated from integrals of vinyl (or for benzylamine adducts, methylene) protons in *cis*- and *trans*-isomers. [b] Propargyl sulphones give same adducts as prop-1-ynyl sulphones. [c] Ref. 2. [d] Ref. 3. [e] $CD_3·SO·CD_3$. [f] Light petroleum (b. p. 40—60°). [g] Lit.,[6] 140—141°. [h] Separated from crude adduct mixture; p.m.r. spectra of this and crude material identical. [j] B. p. [k] n_D^{19}. [l] Undistillable liquid; p.m.r. spectrum in accord with *cis–trans* enamine mixture.

configurationally stable and it appears possible that isomerisation of the initial adduct *via* an intermediate such as (IX) is inhibited in the special case of ethyleneimine because of the angle strain involved. Professor W. E. Truce shares [21] this view. We find that change of the solvent for the methyl propiolate–benzylamine reaction from methanol to benzene does not affect the product.

Primary Amines.—According to the above principles addition of primary amines to acetylenes should also give equilibrium mixtures of enamines. In the case of

in the series $PhCO- > PhN(Me)CO- > MeOCO$ and $PhCH_2SO > PhSO_2 > PhCH_2SO_2$. It has been suggested that hydrogen-bonding stabilises the *cis*-isomer but, in simple systems, hydrogen-bonding to the carbonyl groups of amides is stronger [22] than to those of ketones. Evidently other factors operate in these equilibria, and possibly the bulky amido-group, required for practical reasons, tends to depress the amount of *cis*-isomer obtained with this activating group. It must also be pointed out that the hydrogen-bonding capabilities of enamino-ketones and amides do not necessarily match

[19] W. E. Truce and D. G. Brady, Abs. American Chemical Society Meetings, Pittsburgh, March 1966, K88.
[20] J. E. Dolfini, *J. Org. Chem.*, 1965, **30**, 1298.
[21] W. E. Truce, personal communication.
[22] E. D. Becker, *Spectrochim. Acta*, 1961, **17**, 436.

those of their simple analogues. The much greater tendency towards hydrogen-bond formation in sulphoxides [23] than sulphones is reflected by the greater proportion of *cis*-isomer obtained in the former system.

For an individual activating group, change of solvent has a marked effect on the *cis–trans* ratio. In chloroform, little hydrogen-bonding to the solvent can occur and the intramolecularly hydrogen-bonded *cis*-forms are thus favoured. Dimethyl sulphoxide, by contrast, forms strong hydrogen bonds and in this solvent a greater degree of intermolecular bonding is expected. In all systems we examined, displacement of the equilibrium in favour of the *trans*-isomer occurs when chloroform is replaced by dimethyl sulphoxide. Equilibrium between the isomers in this solvent is often rather slowly attained even at the concentrations used for p.m.r. determinations. A similar effect was noted by Dudek and Volpp [13] using pyridine, and Table 1 shows that equilibrium is approached from different sides in, for example, the products from propiolophenone with aniline and t-butylamine, respectively. This suggests that the initial solid adducts have opposite configurations. The higher *cis–trans* ratio for the ketone than for the amide is maintained when dimethyl sulphoxide is the solvent.

Two opposing factors are likely to be important in determining the effect of the structure of the amino-group upon the *cis-trans* equilibrium. Non-bonded interaction between the amino-group and the activating group will reduce the stability of the *cis*-isomer.[24] On the other hand, intermolecular hydrogen bonding to a bulky alkylamino-group in the *trans*-configuration is likely to be less favoured than intramolecular bonding in the *cis*-arrangement. Table 2 shows that replacement of the *N*-benzyl group by a t-butyl group in the adducts from the ketone and the ester, stabilises the *cis*-isomer in each case. This suggests that the second factor is dominant. This change of *N*-alkyl groups causes a change in the opposite direction with the acetylenic sulphone. There is an additional *C*-methyl group in this system and space-filling models reveal somewhat more restriction in the *cis*- than in the *trans*-isomer. It is notable that the basicity of the amine appears to have little effect on the equilibrium. Aniline and benzylamine adducts of the ketone have comparable *cis–trans* ratios. Further, the adducts formed from benzylamine and from glycine ethyl ester with 1-phenylsulphonylpropyne also have similar ratios. This observation suggests that the polarity of the *N*-alkyl group is of little consequence in in this system.

The adducts with acetylenic sulphones show quite marked sensitivity of their *cis–trans* ratios to the *S*-alkyl or -aryl group. At present we offer no explanation.

The conclusions drawn refer to structures of adducts in *solution*. Previous assignments of configuration to solid products are of doubtful value.

[23] R. S. Drago, B. Wayland, and R. L. Carlson, *J. Amer. Chem. Soc.*, 1963, **85**, 3125.
[24] K. Mackenzie in "The Chemistry of Alkenes," ed. S. Patai, Interscience, 1964, p. 387.
[25] D. S. James and P. E. Fanta, *J. Org. Chem.*, 1962, **27**, 3346.

EXPERIMENTAL

Extracts were dried over Na_2SO_4. Light petroleum had b. p. 40—60°.

Reagents.—Ethynyl phenyl ketone had [6] m. p. 50—51°. Methyl propiolate [25] had b. p. 101°, and propiolic anhydride [26] had b. p. 60°/15 mm., n_D^{20} 1·4473. Amines were purified by distillation from zinc dust under nitrogen.

3-Benzylsulphinylpropyne.— 3-Benzylthiopropyne [3] (1·682 g.) in methanol (15 ml.) was added during 30 min. with vigorous stirring to sodium periodate [27] (2·219 g., 1 mol.) in water (25 ml.) at 0°. After being stirred at 0° for 15 hr., the mixture was filtered and extracted with chloroform. Evaporation of the extracts gave the *sulphoxide* (1·833 g., 99%), m. p. 54—55° raised to 57—58° (from isopropyl ether) (Found: C, 67·6; H, 6·0. $C_{10}H_{10}OS$ requires C, 67·4; H, 5·7%).

N-Methylpropiolanilide.—Propiolic anhydride (1·15 g.) in ether (10 ml.) was treated with *N*-methylaniline (2·02 g., 2 mol.). After 16 hr., the mixture was washed with N-hydrochloric acid (2 × 50 ml.), aqueous sodium hydrogen carbonate, and water. Evaporation of the ether solution gave the *amide* (1·2 g., 80%), m. p. 74—76° raised to 78—79° (from isopropyl ether) (Found: C, 75·4; H, 5·8. $C_{10}H_9NO$ requires C, 75·5; H, 5·7%).

General Procedure for the Preparation of Amine Adducts.—The following description is typical. Ethynyl phenyl ketone (501 mg.), in dry methanol (10 ml.) under nitrogen, was treated with dibenzylamine (759 mg., 1 mol.). After 20 hr., solvent was removed at 40°/10 mm. and the residue washed with light petroleum (3 ml.). The crude product (1·248 g., 99%) had m. p. 111·5—112·5°, raised to 112—113·5° (from benzene–light petroleum). The p.m.r. spectra of the crude and purified products were identical.

Proton Magnetic Resonance Spectra.—Spectra were obtained on a Varian HR-100 spectrometer operating at 100 Mc./sec. Solutions containing 5% w/v of solute were used at *ca.* 31°. Tetramethylsilane was used as internal standard and assignments were verified when necessary by spin-coupling.

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[6/672 *Received, May* 31*st*, 1966]

[26] F. Strauss and W. Voss, *Ber.*, 1926, **59**, 1681.
[27] Cf. N. J. Leonard and C. R. Johnston, *J. Org. Chem.*, 1962, **27**, 282.