Competition between Acid Catalyzed Interconversion and Solvolysis of Adducts of Dimethyl Azodicarboxylate and 2,5-Dimethyl-3,4-diphenylcyclopentadienone

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Trifluoroacetic acid catalyzes the conversion of each of the isomers, the Diels–Alder adduct **1***a*, the 1,3,4-oxadiazine **2***a*, and the 1,2-diazetidine **3***a* into the others, with the exception of **3***a* → **1***a*. The isomerizations compete with solvolysis to the common end products, the 1,3,4-oxidiazinone **4***a* and methyl trifluoroacetate, directly in the case of **1***a* and **2***a*, but perhaps only by way of **2***a* in the case of **3***a*. The isomerization and solvolysis rates increase with acid concentration in dilute acid but in concentrated acid there is evidence that all the isomers are converted into a (probably) multi-protonated form of **2***a*, which is stable to isomerization and whose solvolysis rate decreases with increasing acid concentration.

A l'exception de la transformation **3***a* vers **1***a*, l'acide trifluoroacétique catalyse la conversion de chacun des isomères soit le produit d'addition de Diels–Alder **1***a*, l'oxadiazine-1,3,4 **2***a* et la diazétidine-1,2 **3***a* dans tous les autres. Les isomérisations sont en compétition avec la solvolyse vers des produits finals identique, dans tous les cas l'oxydiazinone-1,3,4 **4***a* et le trifluoroacétate de méthyle qui se produiraient directement dans le cas de **1***a* et de **2***a* mais peut être seulement par l'intermédiaire de **2***a* dans le cas de **3***a*. Les vitesses d'isomérisation et de solvolyse augmentent avec la concentration d'acide en milieu dilué mais en milieu concentré il semble que tous les isomères sont transformés en une forme multi-protonée de **2***a* qui est stable vis à vis de l'isomérisation et dont la vitesse de solvolyse diminue avec une augmentation de la concentration de l'acide. [Traduit par le journal]

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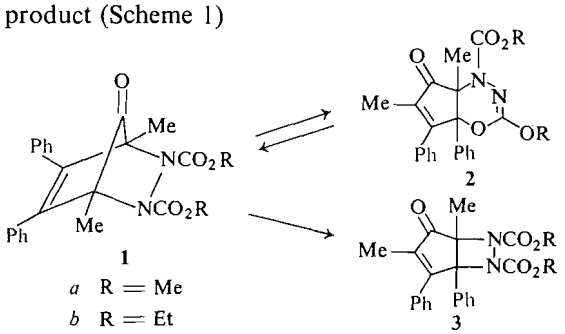
Previous work has established that the thermal isomerization of the adducts of azodiacyls and cyclic 1,3-dienes to 1,3,4-oxadiazine derivatives is a reaction of some generality (1–3) and that the isomerization is extremely sensitive to catalysis by strong protic acids or Lewis acids (4). More recently (5) we have shown that the analogous adducts **1** of azo esters and 2,5-dimethyl-3,4-diphenylcyclopentadienone could also be thermally isomerized to the corresponding oxadiazines **2** but that the isomerization was reversible, and furthermore that a competing, apparently irreversible, isomerization of **1** to the diazetidines **3** made the latter in fact the final thermal end product (Scheme 1)



SCHEME 1

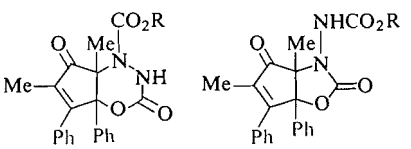
The present work shows that the processes of Scheme 1 are also sensitive to catalysis by acid but that the isomerizations compete with a solvolytic dealkylation which probably occurs by more than one pathway.

Our early attempts to obtain structural information on the stable thermal isomers, which showed some puzzling spectroscopic features (5), included hydrolysis with aqueous ethanolic hydrochloric acid. Refluxing **3***a* with 2*N* acid gave a 93% yield of a compound with m.p. 232.5–234°; a simpler synthesis involved keeping a solution of **3***a* in trifluoroacetic acid (TFA) at room temperature for several hours, in which case the yield was quantitative. The elemental analysis and mass spectrum (M^+ 392) required the formula $C_{22}H_{20}N_2O_5$, corresponding to the loss of CH_2, and along with spectroscopic evidence showed the product to be the 1,3,4-oxadiazin-2-one **4***a*, a relatively uncommon heterocyclic type (6, 7).

The i.r. spectrum ($CHCl_3$) had NH absorption at 3400 and three carbonyl peaks at 1780, 1750, and 1712 cm^{-1}. The u.v. absorption maximum at 281 nm was indicative of survival of the β-phenyl-α-methyl enone chromophore present in

the parent compound and its isomer **2***a* (8). The n.m.r. spectrum ($CDCl_3$) contained an absorption for one easily exchangeable proton at 3.1 and vinylic and *tert*-methyl singlets at 7.86 and 9.06 τ, respectively, but only one methoxy singlet, at 6.25 τ. In particular the anomalously high field methoxy absorption found in **3***a* (5) was absent. Since the reaction had not involved simple *N*-ester hydrolysis, which would have been accompanied by decarboxylation, a more profound structural alteration must have occurred in which the diazetidine ring had been destroyed. The presence of an amide, rather than an amine, NH was indicated by the chemical shift of the exchangeable proton in the n.m.r. spectrum and by the fact that the compound could be dissolved in aqueous sodium hydroxide and reprecipitated unchanged with acid; there was no salt formation with strong acids.

The chemical and spectroscopic evidence was accommodated reasonably only by the bicyclic structures **4***a* or **5***a*. The carbonyl bands at 1712 and 1750 cm^{-1} are readily identified with the enone and exocyclic urethane carbonyl groups respectively. The absorption at 1780 cm^{-1} does not unambiguously distinguish between the 5- or 6-membered ring forms (9).



4 5

a R = Me
b R = Et

A decision between **4***a* and **5***a* by chemical means was reached by conversion of the amide into its *N*-methoxycarbonyl derivative. No reaction occurred on treatment with methyl chloroformate in pyridine, even after long reflux. However, conversion of the amide into the anion with sodium hydride in dimethoxyethane, followed by addition of methyl chloroformate at room temperature gave a nearly quantitative yield of the urethane. It resisted crystallization but could be purified as an amorphous solid of satisfactory elemental analysis by letting a solution of it slowly evaporate. Its n.m.r. spectrum had two sharp methoxy singlets at 6.19 and 6.28 τ (CCl_4) and was therefore that of the derivative of **4***a*, in which chemical shift difference in the methoxy groups is expected. The analogous derivative of **5***a* would have isochronous methoxy groups, as a result of combinations of rotation and inversion at nitrogen.

The diazetidine **3***b* likewise gave the oxadiazinone **4***b*, m.p. 166–167°, on treatment with aqueous hydrochloric acid or with TFA. The ethoxycarbonyl derivative of **4***b* was a glass, whose n.m.r. spectrum showed chemical shift difference in its ethoxy groups, both in the methylene quartets and the methyl triplets.

Since the solvolysis product of **3***a* had the same basic ring structure as the oxadiazine **2***a*, isomeric with **3***a*, we examined the reaction of **2***a* and the other isomer **1***a* with TFA at room temperature. Again **4***a* was formed quantitatively in each case. We accordingly decided to investigate systematically the competition between isomerization and solvolysis of all the isomers **1***a*–**3***a* with TFA. Analysis by n.m.r. was especially suitable since the aliphatic portion of the spectrum of mixtures of all the isomers and the product **4***a* contained only methyl singlets, no two of which were coincident in chloroform-*d* except the methoxy peaks of **2***a*. The high-field (tertiary) methyl peaks were routinely used in the analysis, peak heights being used as a measure of concentration.

The reactions were run in chloroform-*d*, using 0.25 *M* solutions of each of the isomers, in the presence of increasing amounts of TFA, from 0.2% (v/v; 0.11 equiv.) up to 100%. The extent of the reaction with limited amounts of TFA in commercial chloroform-*d* was found to depend on the trace amounts of water present in the solvent. The reactions with 0.2 and 1% TFA were therefore run in dry[1] chloroform and with chloroform-*d* saturated with D_2O.

The % molar compositions of the reaction mixtures are shown in each case for various times up to completion of the reaction (Tables 1 and 2). Clearly the ratio of total isomerization to solvolysis for both **1***a* and **2***a* is always at a maximum at the beginning of the reaction (since the isomerization products themselves solvolyze). To obtain this maximum the ratios were plotted against time for the early stages of the reaction and extrapolated to zero time. These

[1]This is a difficult solvent to dry rigorously. An easier choice in this regard is benzene, but the methyl peaks of the mixtures of products in benzene were not as well separated as in chloroform, making a quantitative analysis difficult. Furthermore the amide **4***a* was rather insoluble in benzene and began to separate out in the n.m.r. tube at any early stage in the reaction.

TABLE 1. Product composition (%) with limited amounts of TFA in dry (wet) chloroform

Starting isomer	TFA (%)	Products	Time (min) 0.5	1	1.5	2	3	5	8	12	17	25	40	70	∞		$r^0_{1/5}$
1*a*	0.2	**1***a*				91(94)	89(94)	87(90)	83(86)	81(80)	78(75)	76(69)	73(62)	71(66)	71(44)	[b]	2.8±0.4
		2*a*				3 (2)	4 (2)	4 (3)	5 (4)	6 (5)	7 (6)	7 (6)	8 (6)	8 (7)	8 (8)		(2.4±0.4)
		3*a*				3 (2)	3 (2)	4 (3)	6 (4)	6 (6)	7 (7)	7 (9)	8(12)	8(14)	8(17)		
		4*a*				3 (2)	4 (2)	5 (4)	6 (6)	7 (9)	8(12)	10(16)	11(20)	13(23)	13(31)		
	1	**1***a*	71(78)	58(65)	50(48)	44(43)	37(35)	29(26)	23(18)	20(12)	16 (8)	13 (6)	11 (6)	9 (1)		[a c]	1.4±0.3
		2*a*	4 (4)	4 (4)	4 (4)	4 (4)	4 (3)	3 (2)	1 (0)								(1.4±0.3)
		3*a*	11 (6)	15(13)	18(18)	20(20)	23(22)	26(26)	28(30)	30(32)	31(33)	32(34)	32(34)	32(34)	35		
		4*a*	14(12)	23(18)	28(30)	32(33)	36(40)	42(46)	48(52)	50(56)	53(59)	55(60)	57(60)	59(65)	65		
2*a*	0.2	**1***a*				1 (1)	1 (2)	1 (2)	1 (3)	1 (3)	1 (3)	(3)	(3)	(3)	1 (4)	[d]	1.0±0.2
		2*a*				84(95)	82(88)	80(83)	80(78)	80(74)	80(71)	(69)	(65)	(62)	80(59)		(0.9±0.2)
		3*a*				6 (1)	6 (2)	6 (3)	5 (3)	5 (4)	5 (4)	(4)	(4)	(4)	5 (5)		
		4*a*				9 (3)	11 (8)	13(12)	14(16)	14(19)	14(22)	(24)	(28)	(31)	14(32)		
	1	**1***a*	1 (2)	2 (2)	2 (2)	2 (2)	2 (2)	2 (2)	3 (2)	3 (2)	3 (2)	3 (2)	(2)	(2)	3	[a e]	0.5±0.1
		2*a*	63(55)	50(33)	46(28)	43(25)	38(22)	35(18)	33(16)	32(13)	32(12)	31(11)	(10)	(9)	31		(0.6±0.1)
		3*a*	9(10)	9(11)	9(11)	9(11)	9(11)	9(11)	9(10)	9(11)	9(11)	9(11)	(11)	(11)	9		
		4*a*	27(33)	39(54)	43(59)	46(52)	51(65)	54(69)	55(72)	56(74)	56(75)	57(76)	(77)	(78)	57		

[a]Separation of solid 4*a* occurred.
[b]Final ester to methanol mol ratio = 0.54.
[c]Final ester to methanol mol ratio = 2.0.
[d]Final ester to methanol mol ratio = 0.45.
[e]Final ester to methanol mol ratio = 0.20.

maximum values, $r^0_{i/s}$, are also shown in the Tables.[2]

In the presence of 0.2% TFA in dry chloroform solvolysis occurred at about the same rate as isomerization for **1***a* as starting material, but solvolysis was much more rapid than isomerization in the case of **2***a*. In both experiments reaction ceased near the point where the theoretical amount of **4***a* (11%) had been formed. The formation of methyl trifluoroacetate was indicated by a peak at 6.03 τ, authentic ester being prepared for comparison in the n.m.r. tube, from methanol and trifluoroacetic anhydride in chloroform.

The presence of water had little effect on the partitioning of either **1***a* or **2***a* between isomerization and solvolysis in the early stages of the reaction. However, hydrolysis could evidently compete with trifluoroacetolysis, so that consumption of acid was not as fast as in the dry reaction, thus allowing more starting material to react by isomerization. The occurrence of hydrolysis was confirmed by the presence of a methanol CH_3 peak at 6.51 τ. The amount of solvolysis at the end of each reaction in conjunction with the ester to methanol peak ratio (Table 1) was indicative of complete consumption of the acid.

In dry chloroform containing 1% TFA both **1***a* and **2***a* reacted rapidly. **1***a* was completely converted into **3***a* and **4***a*, but solvolysis of **2***a* greatly exceeded isomerization, the resulting consumption of acid thus stopping reaction before isomerization was complete.[3]

Water had little effect on the reaction of **1***a* in 1% acid, **3***a* being stable to isomerization or solvolysis at low acid concentration, but as expected it caused extensive hydrolysis of **2***a*.

Even at a starting concentration of 1% TFA the diazetidine was only slowly solvolyzed (33% in 2 days, after which reaction ceased); there was no detectable isomerization.

At acid levels higher than 1% there was an increase in both the $r^0_{i/s}$ (contrast the trend in dilute acid) and the overall rate of reaction of **1***a*, which was undetectable in acid of 4% strength or greater after the time taken (~30 s) for addition of the acid and rapid scanning of the spectrum. The isomerization to **2***a* and **3***a* went increasingly in favor of the former and with 8–100% acid, only **2***a* and the solvolysis product **4***a* were observable when the spectrum was first run. The solvolyses thereafter were first order but the rates *decreased* markedly with increasing acid concentration.

With the oxadiazine **2***a* as starting material isomerization to **3***a*, but not to **1***a*, was noted in 2 or 4% TFA. In 8–100% acid only solvolysis occurred, the behavior being just that noted for **1***a*.

The stability to acid of the diazetidine **3***a*, compared with **1***a* or **2***a*, still persisted in 2% TFA ($t_{\frac{1}{2}}$ ~ 70 m), solvolysis but no isomerization being observed. At acid levels >4% TFA, isomerization, to **2***a* only, became the dominant process, followed by solvolysis, increasingly retarded by acid as before.

The reactions of **1***a*, **2***a*, and **3***a* in concentrated acid, after initial rapid isomerization in the case of **1***a* and **3***a*, followed a common solvolytic pathway. We have described the precursor to **4***a* in each case as **2***a* but the spectra of the solutions suggested that the latter is not present in the free unprotonated form. While all absorptions in **2***a* and **4***a* showed the expected downfield shift in neat TFA, their relative positions remained unchanged,[4] except that one of the methoxy peaks derived from **2***a*, coincident in the absence of acid or in dilute acid, was shifted 0.71 p.p.m. from the other, down to 5.26 τ. It seems most reasonable that this signal was due to the methoxy group on the protonated imidate function of the oxadiazine.

The rapid formation of protonated **2***a* in the reactions of either **1***a* or **3***a* with TFA suggested an alternative synthesis of **2***a* from either of these starting materials, which can each be easily made in one step from the cyclone and dimethyl azodicarboxylate (5). However, attempts to

[2]The ratio in the early stages was of course subject to the largest errors since the composition of the mixture was changing rapidly, but the trends in the limiting value at zero time for both **1***a* and **2***a* in the presence of different amounts of acid and water were both clear and informative.

[3]The theoretical amount of **4***a* is 54%. The value for the reaction of **1***a* is high. The acid was introduced into the n.m.r. tubes using a microsyringe and errors of 2 or 3% are to be expected. However, the discrepancy here was due to inadvertent inclusion of moisture; a small methanol peak was observed in the spectrum.

[4]The *tert*-methyl peaks in **2***a* and **4***a* used in the kinetic analysis not only had the same relative line positions but had exactly the same chemical shift difference in neat TFA as in chloroform. This superimposability was also found in the vinyl and the ester methyls.

TABLE 2. Product composition (%) with excess of TFA in chloroform

Starting isomer	%TFA	Products	Time (min) 0.5	1	1.5	2	3	4	5	7	9	13	$r^0_{i/s}$
1*a*	2	**1***a*	20	5									1.8±0.3
		2*a*	16	10	3								
		3*a*	27	30	30	30	30	29	29	28	28		
		4*a*	37	55	67	70	70	71	71	72	72		
2*a*	2	**2***a*	22	6	3	1							0.6±0.3
		3*a*	17	13	12	12	12	11	11				
		4*a*	61	81	85	87	88	89	89				
3*a*	2	**3***a*		99	97	96	94	91	89	86	83	78[a]	
		4*a*		1	3	4	6	9	11	14	17	22	
1*a*	4	**2***a*	33	25	19	13	7	4	2				2.0±0.3
		3*a*	27	23	20	17	13	12	9	6	2		
		4*a*	40	52	61	70	80	84	89	94	98	100	
2*a*	4	**2***a*	45	18	10	3							0.7±0.3
		3*a*	13	13	12	11	9	8	7	5	4	3	
		4*a*	42	69	78	86	81	92	93	95	96	97	
3*a*	4	**2***a*	6	10	12	13	10	9	7	3	1		1.1±0.2
		3*a*	88	79	72	65	58	51	45	38	32	24	
		4*a*	6	11	16	22	32	40	48	59	67	76	
3*a*	8	**2***a*	43	48	46	41	28	19	10				11±3
		3*a*	50	37	26	16	6						
		4*a*	7	15	28	43	66	81	90	100			
1*a*	8	**2***a*	→	**4***a*	First-order $t_{\frac{1}{2}}$ = 1.2 m								
2*a*	8	**2***a*	→	**4***a*	First-order $t_{\frac{1}{2}}$ = 1.1 m								
	20	**2***a*	→	**4***a*	First-order $t_{\frac{1}{2}}$ = 8.8 m								
1*a*	100	**2***a*	→	**4***a*	First-order $t_{\frac{1}{2}}$ = 30 m								
2*a*	100	**2***a*	→	**4***a*	First-order $t_{\frac{1}{2}}$ = 31 m								
3*a*	100	**2***a*	→	**4***a*	First-order $t_{\frac{1}{2}}$ = 28 m								

[a]Reaction not run to completion.

quench the solutions obtained by adding TFA to **3***a* with excess of aqueous base (sodium hydrogen carbonate) or organic bases (triethylamine or pyridine) lead only to the isolation of **4***a*. Demethylation to the stable amide linkage is thus faster than deprotonation.

Control reactions showed that acid was necessary for hydrolysis, **2***a* being stable to chloroform saturated with water or to 0.001 *M* TFA over 3 days. Methyl trifluoroacetate was also stable to water under the reaction conditions but the rate of esterification of TFA by methanol was significant. The above reactions in the presence of water are thus slightly retarded due to loss of acid by esterification. Finally the solvolysis reactions were irreversible: **4***a* did not react with either methyl trifluoroacetate or methanol in the presence of TFA.

The figures in the tables and the above discussion are reconcilable with the following qualitative facts.

(*i*) **1***a*, **2***a*, and **3***a* can each isomerize directly to either of the others, except for **3***a* → **1***a*; isomerization of **2***a* → **1***a* is slight in dilute acid but detectable. These results contrast markedly with the thermal isomerizations, in which the process **2***a* → **3***a* could not be confirmed and to which **3***a* was inert (5).

(*ii*) The overall isomerization rates of **1***a*, **2***a*, and **3***a* and, in particular, the isomerization rates of **1***a* and **3***a* to **2***a* increase with TFA concentration; the isomerization of **3***a* is, however, only significant at high acid levels.

(*iii*) The trifluoroacetolysis rates of the isomers show the trend **2***a* > **1***a* ≫ **3***a*; hydrolysis of **2***a* is also much more efficient than that of the others.

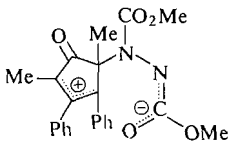
(*iv*) In dilute acid the trifluoroacetolysis rates of **1***a* and **2***a* increase with concentration and more rapidly than the isomerization rates; $r^0_{i/s}$ thus decreases.

(*v*) In concentrated acid **2***a* undergoes pro-

tonation close to the solvolysis site. The species formed resists isomerization, and its solvolysis rate *decreases* with increasing acid concentration. The combined effects of this and *iv* cause $r^0_{i/s}$ for **1***a* to pass through a minimum.

(*vi*) Solvolysis of **1***a* and **2***a* to **4***a* occurs directly;[5] solvolysis of **3***a* to **4***a* probably occurs only through **2***a*.

In the thermal interconversions of **1***a*, **2***a*, and **3***a* we proposed as a common intermediate the dipolar species **6** (5). In the present series of acid catalyzed reactions it seems reasonable to suggest an analogous protonated intermediate either **7** or **8**, the tautomeric forms of a bisurethane which



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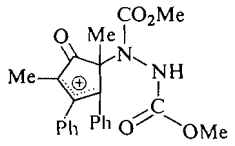

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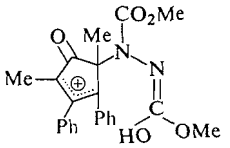
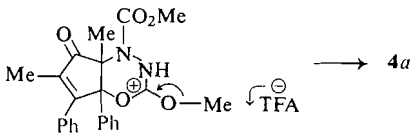


8

could arise formally by protonation of the isomers on nitrogen or oxygen followed by ring opening. A decision between nitrogen and oxygen as the site of protonation is clear only in the case of **2***a* which has a recognizably basic nitrogen. In **1***a* and **3***a* protonation on an amide carbonyl oxygen leading to **8** may be preferred.[6] Either **7** or **8** can isomerize to the protonated isomers, **1***a*–H^+ (by cyclization of Me—C^+ to N), **2***a*–H^+ (Ph—C^+ to O), or **3***a*–H^+ (Ph—C^+ to N) or give **4***a* by solvolytic demethylation with the appropriate nucleophile (the counter-ion TFA^-, TFA itself, or water) at the ester function together with cyclization.

Alternatively **4***a* might be obtained by direct solvolysis of **9**, the protonated oxadiazine (Scheme 2), a pathway consistent with the rapid formation of **4***a* in dilute acid by TFA or water, since it does not involve ring opening and could thus occur in one step.



9

SCHEME 2

Indeed solvolysis of all the isomers could proceed through **9**, this in no way conflicting with our earlier conclusion (point *vi* above) that **1***a* solvolyzes directly to **4***a*. The sequence **1***a* → **8** → **9** → **4***a* does not involve the free oxadiazine.

The low-field methoxy absorption in the spectra from solution of **2***a* in concentrated acid belongs to a species protonated on an imidate nitrogen but it is unlikely that this is the monoprotonated form **9**, which we have judged to be very labile. At high acid levels multiprotonation may become important since there are a number of potential sites available in the isomers or their ring-opened intermediates, both in the enone and the azo derived portions.

The increase in catalytic efficiency of TFA with its concentration in the isomerization reactions was expected (4) but there is no clear reason for the negative effect in solvolysis of the oxadiazine.[7]

A comment on the stereochemistry of the ring junction in the oxadiazines **2** and their solvolysis products **4** is in order. We have tacitly assumed (5) that the thermal reaction of **1** gave the *cis*-oxadiazines, by analogy with the isomerization of the adduct of azodibenzoyl and cyclopentadiene to an oxadiazine in which the *cis* stereochemistry was established by chemical degradation and which the concerted nature of the isomerization in any event dictated (1). No such structural proof has been provided for the oxadiazines **2**.

The formation of the *trans* isomer of **2***a* merely requires that the lifetime of the open structure **6** be long enough to allow free conformational rotation. Our belief in the *cis* stereochemistry of both **2** and **4** rests entirely, and we feel con-

[5]The build-up of **4***a* from **1***a* seems too rapid to be explicable on the basis of the sequence **1***a* → **2***a* → **4***a* exclusively.

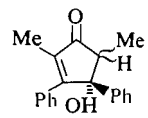
[6]While protonation of simple amides is now well established as occurring on oxygen (10), the general question of oxygen *vs.* nitrogen protonation is not a fully resolved one in complex systems like these. Though we are showing **7** and **8** as the free protonated forms it is possible that in a medium such as dry chloroform only coordination of the amide group to the acid hydrogen occurs and that the acid OH bond is never broken.

[7]A referee has pointed out that if the solvolysis requires TFA^- the nucleophilic activity of the latter would be reduced in excess of TFA by acid to anion hydrogen bonding. The occurrence of free TFA^- in dry chloroform, however, is not certain.

vincingly, on the chemical shift values of their *tert*-methyl groups.

The absorptions of the *tert*-methyl groups in the diazetidine **3***a*, in **2***a*, and in **4***a* occur very close together, at 8.86, 8.96, and 9.06 τ. Since all three methyl groups are attached to carbon atoms with identical nearest neighbor atoms they must also all have the same stereochemistry with respect to the nearest phenyl group, that is, **2***a* and **4***a*, like **3***a*, must have a *cis* ring junction.

A *cis*-phenyl group is expected to have a strong shielding effect on the adjacent methyl. The methyl groups in the *trans* isomers of **2***a* and **4***a* would resonate at much lower fields than in the *cis* isomers. The magnitude of the effect can be gauged from the spectra of the *cis* and *trans* alcohols **10**, both of which are formed when diethyl ketone and benzil are condensed with Triton B as catalyst (5). Separation by fractional crystallization gave the *cis* and *trans* epimers with m.p. 129–129.5° and 153–154° respectively, and *tert*-methyl doublets at 9.28 and 8.78 τ, a shift too large to be reconcilable with any stereochemical difference in the ring junctions of compounds **1***a*–**4***a*.[8]



10

Experimental

The i.r. spectra were obtained on a Beckman IR10 and the u.v. spectra on a Coleman EPS-3T Hitachi spectrometer. All n.m.r. routine and kinetic analyses were done on a Varian T60 spectrometer against tetramethylsilane as internal standard (abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet). For mass spectra a Perkin Elmer RM-U6E Hitachi spectrometer was used.

Anhydrous magnesium sulfate was used as drying agent for solutions in organic solvents. Melting points are uncorrected.

cis-4-Carbomethoxy-4a,6-dimethyl-7,7a-diphenyl-2,3,4,4a,5,7a-hexahydrocyclopenta-1,3,4-oxadiazin-2,5-dione (4a)

From Diazetidine 3a

A solution of **3***a* (122 mg, 0.30 mmol) in 12 *N* hydrochloric acid and methanol (1:5, 3 ml) was refluxed for 2 h and evaporated to near dryness. Water was added and the product (93%) collected. Its i.r. spectrum was identical with that of material obtained as almost colorless prisms, m.p. 232.5–234°, from methanol or aqueous methanol.

Alternatively, a solution of **3***a* (100 mg) was kept in TFA (1 ml) at room temperature for 6 h and then evaporated. Addition of a few drops of methanol induced crystallization and the precipitate was collected and washed with very dilute ammonia, the yield being essentially quantitative.

The *oxadiazinone* had ν ($CHCl_3$) 3400 (NH), 1780, 1750, and 1712 cm^{-1} (endocyclic and exocyclic urethane and enone C=O, respectively); λ_{max} (EtOH) 282 nm; τ ($CDCl_3$) 2.3–3.0 (10 phenyl H), 3.25 (broad, NH), 6.23 (s, OMe), 7.86 (s, vinyl Me), 9.06 p.p.m. (s, *tert*-Me); *m/e* 392 (P^+, 16%), 348 ($C_{21}H_{20}N_2O_3^+$, 100%).

Anal. Calcd. for $C_{22}H_{20}N_2O_5$: C, 67.33; H, 5.15; N, 7.14. Found: C, 67.09; H, 5.28; N, 6.82.

A sample of the product was dissolved by warming it in 1 *N* aqueous sodium hydroxide – methanol (1:1). Most of the methanol was removed by evaporation. Addition of dilute hydrochloric acid reprecipitated **4***a* in pure form.

From Isomers 1a or 2a

The TFA method was used on the same scale and with the same work-up procedure; the yields were quantitative. The identity of the product as **4***a* was confirmed in each case by its spectra and its mixed m.p. with the product from **3***a*.

The 4-Carboethoxy Derivative 4b

Either of the above methods on the same scale gave excellent yields (> 90%) of **4***b* which formed colorless prisms from methanol, m.p. 166–167°; ν (CCl_4) 3420, 1796, 1758, and 1712 cm^{-1} (assignments as for **4***a*); λ_{max} (EtOH) 282 nm (ε 12 600); τ ($CDCl_3$) 2.3–3.2 (10 phenyl H), 3.53 (broad, NH), 5.76 (q, 2 methylene H, J = 7.5 Hz), 7.86 (s, vinyl Me), 8.78 (t, 3 methyl H), 9.05 p.p.m. (s, *tert*-Me); *m/e* 406 (P^+, 16%), 362 ($C_{22}H_{22}N_2O_3^+$, 100%).

Anal. Calcd. for $C_{23}H_{22}N_2O_5$: C, 67.96; H, 5.46; N, 6.89. Found: C, 67.42; H, 5.39; N, 7.13.

cis-3,4-Dicarbomethoxy-4a,6-dimethyl-7,7a-diphenyl-2,3,4,4a,5,7a-hexahydrocyclopenta-1,3,4-oxadiazin-2,5-dione (Carbomethoxy Derivative of 4a)

The compound **4***a* (100 mg) was recovered quantitatively after refluxing for 12 h in pyridine (5 ml) containing methyl chloroformate (0.5 ml), evaporating, and adding water.

Addition of **4***a* (98 mg, 0.25 mmol) to a suspension of 50% sodium hydride – mineral oil (26 mg, 0.55 mmol) in dry dimethoxyethane (2 ml) caused vigorous effervescence of hydrogen and formation of a yellow solution. Methyl chloroformate (29 μl, 0.37 mmol) was injected with a microsyringe, causing the solution to become colorless, and the formation of a precipitate of sodium chloride. After 3 h at room temperature ether and water were added, the ether layer was shaken out several times with water, then dried, and evaporated. The residue was washed with several portions of hexane to remove the mineral oil (it was then of 90–95% purity as estimated by n.m.r. analysis) and then dissolved in ethyl acetate. The solution was filtered, 2-methylheptane was added until a second phase just appeared which was then removed by addition of a drop of ethyl acetate. The clear solution was allowed to evaporate slowly at room temperature. The

[8]Work with related cyclopentene derivatives epimeric at these two carbons indicates that this large shift difference in the methyl groups is quite general: for example 0.57 p.p.m. in 2,5-dimethyl-3,4-diphenylcyclopent-2-enone and 0.40 p.p.m. in 2,5-dimethyl-3,4-diphenyl-1,4-dihydroxycyclopent-2-ene (C_1 stereochemistry not known).

amorphous material which separated slowly became brittle; it was ground up, filtered, washed liberally with 2-methylheptane, and kept for a day in an evacuated desiccator over paraffin wax. It had ν (CCl_4) 1801, 1790 (sh), 1762, and 1724 cm^{-1} (three urethane and enone C=O); λ_{max} (EtOH) 286 nm; τ (CCl_4) 2.3–3.1 (10 phenyl H), 6.19 (s, OMe), 6.28 (s, OMe), 7.94 (s, vinyl Me), 9.16 p.p.m. (s, *tert*-Me).

Anal. Calcd. for $C_{24}H_{22}N_2O_7$: C, 64.00; H, 4.92; N, 6.22. Found: C, 64.21; H, 5.15; N, 6.39.

The Carboethoxy Derivative of 4b

The method and scale were the same as those used for **5***a*. The glassy product had ν (CCl_4) 1804, 1782, 1752, and 1722 cm^{-1} (three urethane and enone C=O); λ_{max} (EtOH) 286 nm; τ (CCl_4) 2.3–3.1 (10 phenyl H), 5.73 (q, 2 methylene H, J = 8.0 Hz), 5.80 (q, 2 methylene H, J = 7.5 Hz), 7.93 (s, vinyl Me), 8.69 (t, 3 methyl H), 8.73 (t, 3 methyl H), 9.16 p.p.m. (s, *tert*-Me).

Kinetic Determinations

Materials

The trifluoroacetic acid used was Baker Reagent grade.

Chloroform was dried by refluxing over phosphorous pentoxide for 2 h, fractionating and then stirring for 2 days over molecular sieves (Type 4A, BDH). "Wet" chloroform-*d* was obtained by shaking with D_2O, removing the chloroform layer after all cloudiness had disappeared, and filtering it through a cotton wool plug.

The purification of the isomers **1***a*, **2***a*, and **3***a* has been described previously (5); **1***a* and **2***a* were recrystallized till each was free of traces of the other.

Nuclear Magnetic Resonance Measurements

Solutions of the isomers (50.0 mg, 0.25 *M*) in dry chloroform or wet chloroform-*d* (500 μl) were allowed to warm to the n.m.r. probe temperature (35°) and the TFA added with a microsyringe. The 2, 4, and 8% solutions were made by injecting 10, 20, and 40 μl, respectively, of neat TFA; for the 20% solution containing **2***a*, 400 μl of chloroform were put in the tube and 100 μl of prewarmed neat TFA added. The 0.2 and 1% solutions were obtained by adding 10 and 50 μl, respectively, of a 10% solution of TFA in the appropriate chloroform.

Spectra of the *tert*-methyl region were recorded immediately and repeatedly after injection of the acid and mixing, first at rapid (10 Hz s^{-1}) and later at slow (2 Hz s^{-1}) scan. Other regions of the spectrum were also examined as necessary. Radio frequency values were optimized to prevent saturation.

Calculation of Composition of Mixture

Analysis of suitable mixtures of **1***a*, **2***a*, **3***a*, and **4***a* showed that the *tert*-methyl peak heights (times a factor of one half for the symmetrical adduct **1***a*) could be used as a measure of concentration (±3%) except in the case of **4***a* whose peak was consistently less intense by about 10%. This was corrected for when necessary. The peak positions for the compounds **1***a*–**4***a* in chloroform-*d* were respectively 8.18, 8.96, 8.86, and 9.06 τ.

The percentage of each compound in a given run, as determined by peak heights, was plotted against time and a smooth curve drawn through the points. The % composition of the mixture at representative times, as shown in Tables 1 and 2, was read off the curves by interpolation.

The results for the reactions in concentrated or neat TFA involving only the process **2***a*–$H^+ \rightarrow$ **4***a* gave a first-order rate plot.

Control Reactions

Stability of 2a to Water or Very Dilute Acid. A solution of **2***a* (50 mg) in chloroform (0.50 ml) containing 1.2 μl D_2O (0.13 *M*) showed no change in its spectrum over 12 days. Similarly addition of 1.5 μl of aqueous TFA (40:1 v/v) to a solution of **2***a* (50 mg) in chloroform (0.50 ml; hence 0.001 *M* in acid) was without effect over 3 days).

Esterification of Methanol by Aqueous TFA. A solution 0.13 *M* in each reagent was made by adding TFA (5 μl, 1%), water (1.2 μl), and methanol (2.7 μl) to chloroform (0.50 ml) in the n.m.r. sample tube. The extent of esterification was 24% in 2.5 h and 70% in 24 h.

Stability of Methyl Trifluoroacetate to Aqueous TFA. A solution 0.13 *M* in each reagent was made by adding trifluoroacetic anhydride (9.5 μl) and methanol (2.7 μl) to chloroform (0.05 ml) in the n.m.r. tube. Esterification was complete in 20 h (90% in 5 h). Water (1.2 μl, 0.13 *M*) was then added; over a period of 30 h no methanol could be detected.

Irreversibility of Solvolysis. A solution of **4***a* (50 mg) in chloroform (0.50 ml) was made 0.13 *M* in TFA, water and methanol (as in *b*). Over a 24-h period only esterification, and no reaction of **4***a*, was observed. Enough trifluoroacetic anhydride to destroy the water, and generate fresh acid and more ester, was then added. No trace of the isomers **1***a*, **2***a*, **3***a* could be detected after 15 h.

Attempted Synthesis of 2a from 3a with TFA

Samples of **3***a* (about 30 mg) were dissolved in TFA (0.2 ml) and treated as follows.

(*i*) Methylene chloride and a large excess of aqueous sodium hydrogen carbonate were added and the organic layer was separated.

(*ii*) Methylene chloride containing an excess of pyridine was added, followed by a large volume of water, and the organic layer was separated.

(*iii*) An excess of pyridine was added directly, with cooling and the salt which precipitated was filtered off from the pyridine solution.

In each case the n.m.r. spectrum of the organic solution showed the presence only of **4***a*.

2,5-Dimethyl-3,4-diphenyl-4-hydroxycyclopent-2-enone (Cis- and Trans-10)

To a solution of benzil (20 g, 0.095 mol) in diethyl ketone (20 ml) was added 10 ml of a 40% solution in methanol of benzyltrimethylammonium hydroxide (Triton B). There was an exothermic reaction and the whole was then refluxed for 0.5 h and poured into an excess of cold dilute hydrochloric acid. The product crystallized (>95%) but its n.m.r. spectrum indicated the presence of both epimers in about equal amounts. Crystallization from aqueous ethanol gave the *trans*-alcohol, m.p. 153–154°, as prisms (lit. (11) m.p. 150°). Repeated crystallization of the soluble fraction, with working-up of the mother liquors in each case, gave the *cis*-alcohol, which formed prisms, m.p. 129–129.5°, from benzene–hexane.

The *trans*-alcohol had τ ($CDCl_3$) 2.3–3.2 (10 phenyl H), 7.35 (q, *tert*-H, J = 11 Hz), 7.4 (s, OH), 8.02 (s, vinyl Me), 8.78 p.p.m. (d, *tert*-Me).

The *cis*-alcohol had τ ($CDCl_3$) 2.3–3.2 (10 phenyl H), 7.07 (q, *tert*-H, J = 11 Hz), 7.5 (s, OH), 8.00 (s, vinyl Me), 9.28 p.p.m. (d, *tert*-Me).

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