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TAUTOMERISM IN SIDE-CHAIN DERIVATIVES OF N-HETEROCYCLES

NMR AND UV SPECTRA—I*

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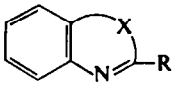
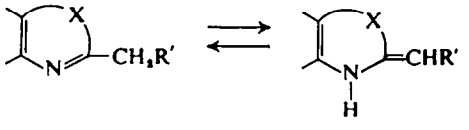
Abstract—NMR and UV spectra of some α (or γ) cyano-, carbethoxy-, and acylmethyl derivatives of 2-oxo-1,2-dihydroquinoxaline, 2-oxo-1,2-dihydro-6,7-benzoquinoxaline, 3,4-dihydro-1,4,2H-benzoxazone, quinoxaline, and quinoline, were recorded in chloroform, dimethyl sulfoxide, and trifluoroacetic acid. The results indicate the existence of tautomeric equilibria, with noticeable contribution of the enaminic structures B or D, depending on the solvent and the nature of the heterocycle. Relationships between some NMR parameters and tautomeric structures were observed.

N-HETEROCYCLIC derivatives in which the proton moves between the annular nitrogen and the atom adjacent to the ring[1,2] have been investigated by NMR spectroscopy. The results obtained in xanthopterin derivatives[3,4] have led to the examination of other similar systems (I) e.g. 2-oxo-1,2-dihydroquinoxaline, 2-oxo-1,2-dihydro-6,7-benzoquinoxaline, 3,4-dihydro-1,4,2H-benzoxazone, 2-quinoxaline, 2-quinoline and 4-quinoline derivatives.



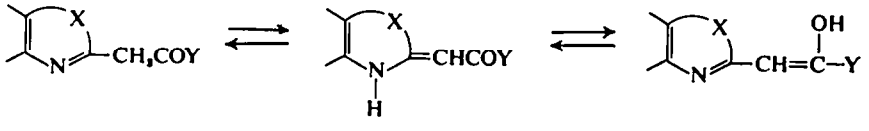
I

When R′ = H, CN, COOAlk only two tautomeric structures A and B are possible:



A B

There are three (C, D, E) when R′ = COY (Y = CH_3, COOAlk):



C D E

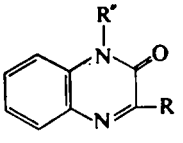
* Presented in part at the symposium *NMR in Chemistry* Cagliari-Sassari, Italy, September (1964).

[1] A. R. Katritzky and J. M. Lagowski, *Advances in Heterocyclic Chemistry* Vol. 1; p. 311. Academic Press, New York (1963).
[2] R. Alan Jones and A. R. Katritzky, *Austral. J. Chem.* **17**, 455 (1964).
[3] W. von Philipsborn, H. Stierlin and W. Traber, *Helv. Chim. Acta* **46**, 2592 (1963).
[4] L. Merlini, W. von Philipsborn, M. Viscontini, *Helv. Chim. Acta* **46**, 2597 (1963).

The literature reports some isolated assignments of structure B to ethyl acetate derivatives[5,6] and of structure D to ethyl pyruvate derivatives.[7-9] The tautomerism of many aromatic and heterocyclic pyruvate esters was discussed by Stock *et al.*,[10] mainly on the basis of the enol bromine titration and of the UV spectra in ethanol, but no clear-cut distinction between structures D and E could be made. The long wavelength absorption in the UV spectrum has been invoked to support the enolic formula E for some compounds,[11,12]

In our experiments NMR spectra were measured in deuterochloroform ($CDCl_3$), dimethyl sulfoxide (DMSO) and trifluoroacetic acid (TFA). To allow a suitable comparison, the UV spectra were taken in the same solvents.[13]

The 2-oxo-1,2-dihydroquinoxaline (II) series (Tables 1, 2) will be discussed first since the general considerations may be extended to the other series. It is well established[14] that these compounds exist in the cyclic amide form.



II

2-Oxo-3-methyl-1,2-dihydroquinoxaline (IIb), where no unsaturated group is present in the side-chain, always appears in the form A. There is no evidence for the methylene-dihydro form B nor in the corresponding derivatives of the other nuclei. In IIe,f,g,h (R = CH_2COOMe or Et) the position of the tautomeric equilibrium is strongly affected by the solvent: it shifts from structure B toward structure A from $CDCl_3$ to DMSO to TFA. Such a shift can be easily followed by NMR, also by addition of TFA to $CDCl_3$ solutions (Fig. 1a,b,c). The two structures are immediately identified by the methylene and methine chemical shifts, and by the presence of the NH absorption at low field in structure B. The methylene and methine protons undergo a more rapid exchange in acid solution, as is shown by the broadening of the CH_2 signal in TFA, and by its disappearance, due to deuteration, in CF_3COOD (Fig. 1c). The shift of the tautomeric equilibrium is accompanied by strong changes in absorption maxima and ε values in the UV spectra (Fig. 2). The UV spectrum of IIe,f,g,h in TFA are superimposable on those of the parent compound 2-oxo-1,2-dihydroquinoxaline (IIa) and of IIb, whereas the high λ and ε values of the three-maxima

[5] Ethyl (2-oxo-1,2-dihydroquinoxalyl-3)-acetate, ethyl 2-oxo-3,4-dihydro-1,4,2-H-benzoxazinyl-3)-acetate, ethyl 2-oxo-3,4-dihydro-1,4,2H-benzothiazinyl-3)-acetate, ethyl (2-oxo-1,2-dihydro-6,7-benzoquinoxalyl-3)-acetate (IR data): Y. Iwanami, *Nippon Kagaku Zasshi* **83**, 593, 597 (1962).

[6] Ethyl (6,7-dimethoxy-3,4-dihydroisoquinolyl-1)-acetate (IR and NMR data): W. Schneider and K. Schilken, *Arch. Pharm.* **296**, 389 (1963).

[7] Ethyl 1-isoquinolylpyruvate (no data): R. Huisgen and H. Seidl, *Tetrahedron Letters* 2023 (1963),

[8] Ethyl 2-methylquinoxalyl-3-piruvate (NMR and UV data): E. C. Taylor and E. Smakula (Hand.) *J. Amer. Chem. Soc.* **85**, 770 (1963).

[9] A. L. Blorror and A. F. Haeberer, *J. Org. Chem.* **30**, 243 (1965).

[10] A. M. Stock, W. E. Donahue and E. D. Amstutz, *J. Org. Chem.* **23**, 1840 (1958).

[11] W. Pfleiderer, *Chem. Ber.* **95**, 2195 (1962).

[12] T. Okamoto and H. Takayama, *Chem. Pharm. Bull.* **11**, 514 (1963).

[13] It is assumed that the position of the tautomeric equilibrium is not strongly affected by the concentration.

[14] G. W. H. Cheeseman, Ref. 1, Vol. 2, p. 229.

TABLE 1. CHEMICAL SHIFTS (δ-VALUES) OF 2-OXO-1,2-DIHYDROQUINOXALINES

			TFA		DMSO				$CDCl_3$			
	R″	R	CH_3	=CH	CH_3	=CH	NHCO	NH	CH_3	=CH	NHCO	NH
IIb	H	CH_3	3·10[h]	—	2·43[h]	—	12·28	—	—			
IIc	CH_3	CH_3	3·10[h]	—	2·42[h]	—	—	—	2·58[h]	—	—	—
IId	H	CH_2CN	—	6·20	4·25[e]	5·03		11·5[c]				
							11·60[d]					
							11·9[e]	10·95				
IIe	H	CH_2COOMe	4·55[f]	—	3·83	5·52	11·85[c]	11·00				
							11·68[d]					
							12·41[e]					
IIf	CH_3	CH_2COOMe	4·55[f]	—	3·84	5·54	—	11·00	—	5·83	—	11·15
IIg	H	CH_2COOEt	4·5[f]	—	3·84	5·52	11·8[e]	11·05	—	5·72[e]	11·48	11·15
							11·68[d]					
							12·44[e]					
IIh	CH_3	CH_2COOEt	4·6[f]	—					—	5·82	—	11·20
IIi	H	CH_2COMe	—	6·52[f]	—	6·01	11·82	13·0				
IIl	CH_3	CH_2COMe	—	6·5[f]	—	6·10	—	13·0	—	6·25	—	13·30
IIm	CH_3	$CH_2COCOOEt$	—	7·42	—	6·70	—	13·4[f]	—	7·04	—	14·0[f]
IIn	CH_3	$CH_2COCOOH$	—	7·45								
IIo	H	CH_β=$CH_\alpha COOEt$		7·5–8·3	H_β	7·85	12·6		H_β	8·08	12·6	
					H_α	7·30			H_α	7·40		

Concentrations are in the range 40–50 mg in 0·4–0·5 ml of soln. [a] ca. 25%; [b] ca. 35%; [c] broad signal, which is resolved with a trace of TFA in the underlying signals; [d] tautomer B; [e] tautomer A; [f] broad; [g] measured in solution containing a little DMSO; [h] CH_3 signal.

TABLE 2. UV SPECTRA OF 2-OXO-1,2-DIHYDROQUINOXALINES

	R′	R	TFA		DMSO		$CHCl_3$	
IIa	H	H	259	17800	280	2770		
			284	21000	~339	~4600		
			~330	~8000	348	4650		
IIb	H	CH_3	326	6800	278	8270	278	5760
			379	4900	330	9600	327	6150
					340	9680	338	6150
IIc	CH_3	CH_3	324	7060	279	6750	279	6470
			380	5150	330	7070	330	7330
					340	7200	340	7580
IId	H	CH_2CN	~380	~12950	355	13850		
			390	14850	372	14300		
			401	14850	391	7980		
			~410	~12900				
			~425	~7550				
IIe	H	CH_2COOMe	331	5460	288	3350	262	8300
			381	3190	359	18200	~285	~6200
					377	21900	359	14200
					396	12400	377	15800
							396	9850
IIf	CH_3	CH_2COOMe	328	5900	360	8950	260	8250
			390	3930	377	8460	292	5750
					400	5150	360	17400
							379	20200
							400	12700
IIg	H	CH_2COOEt	330	6050	359	9100	262	7100
			381	3530	376	9850	285	5350
					~396	~6200	360	13250
							377	15250
							398	9250
IIh	CH_3	CH_2COOEt	328	6870	360	17850	260	9400
			390	4650	379	20200	293	6750
					399	12500	361	19650
							378	22900
							400	14100
IIi	H	CH_2COMe	392	9570	374	14500	266	7150
			413	14800	394	20100	375	15800
			438	14200	416	14200	395	21800
							417	15800
III	CH_3	CH_2COMe	~390	~11500	377	12800	266	6760
			415	19350	396	17350	298	3400
			437	18300	418	12700	377	16250
							397	23000
							420	16920
IIm	CH_3	$CH_2COCOOEt$	≈410		278	6870	270	5850
			437	16750	≈410		~405	~13500
			457	18300	428	17150	429	19550
					453	14500	456	17750
IIn	CH_3	$CH_2COCOOH$	415	11300	~405	~17000	272	5500
			440	14600	425	23100	282	5500
			462	13700	450	19050	410	13200
							433	21800
							459	20300
IIo	H	$CH{=}CHCOOEt$	378	17000	323	9500	319	9350
			~425	~6600	380	6500	380	6400

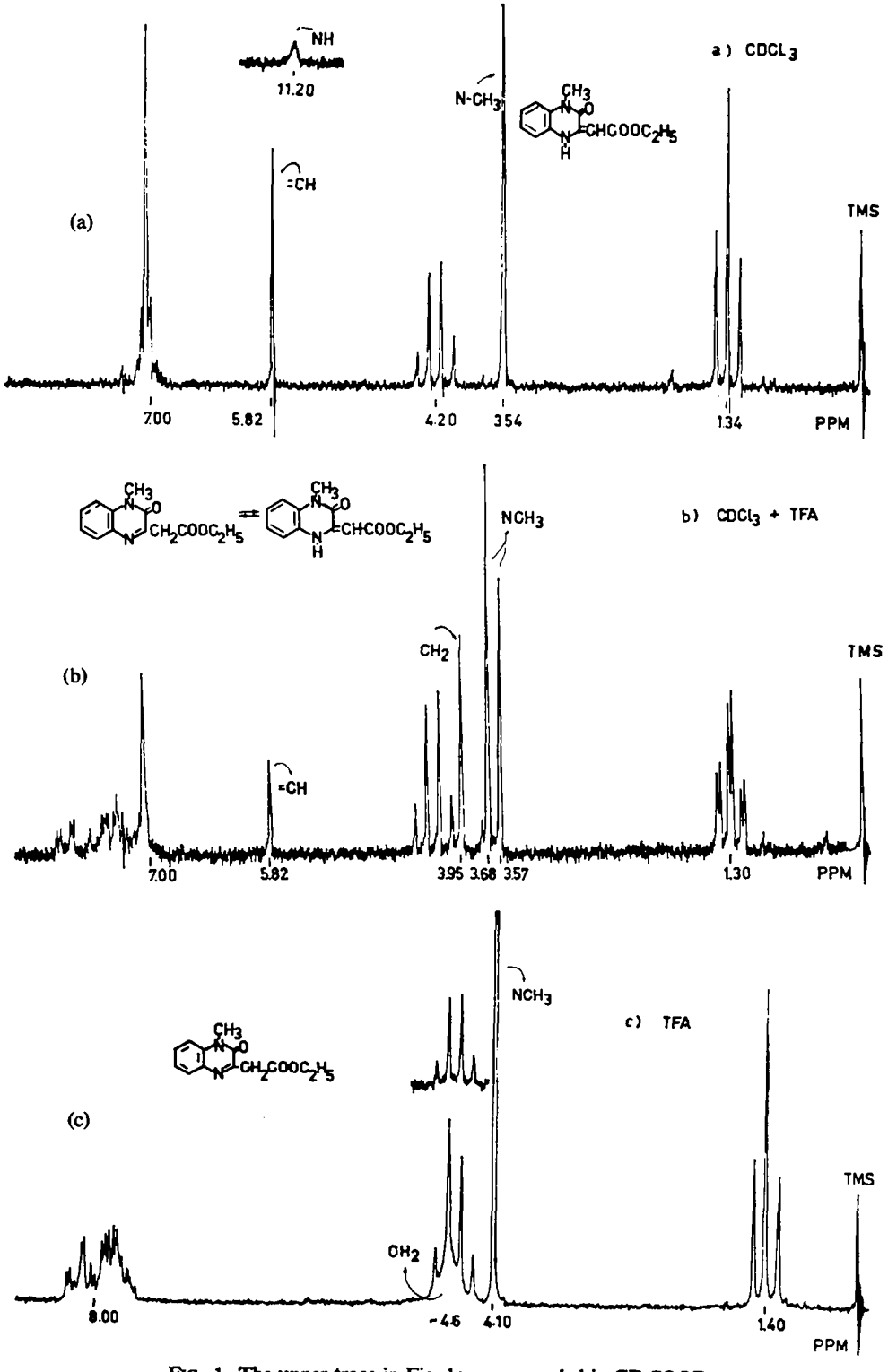


FIG. 1. The upper trace in Fig. 1c was recorded in CF_3COOD.

peak at longer wavelength in chloroform solution are consistent only with the extended conjugated system of the enaminic structure B. In DMSO, in agreement with NMR data, the presence of a mixture can be inferred. A similar behaviour is shown by the acetonitrile derivative IId.

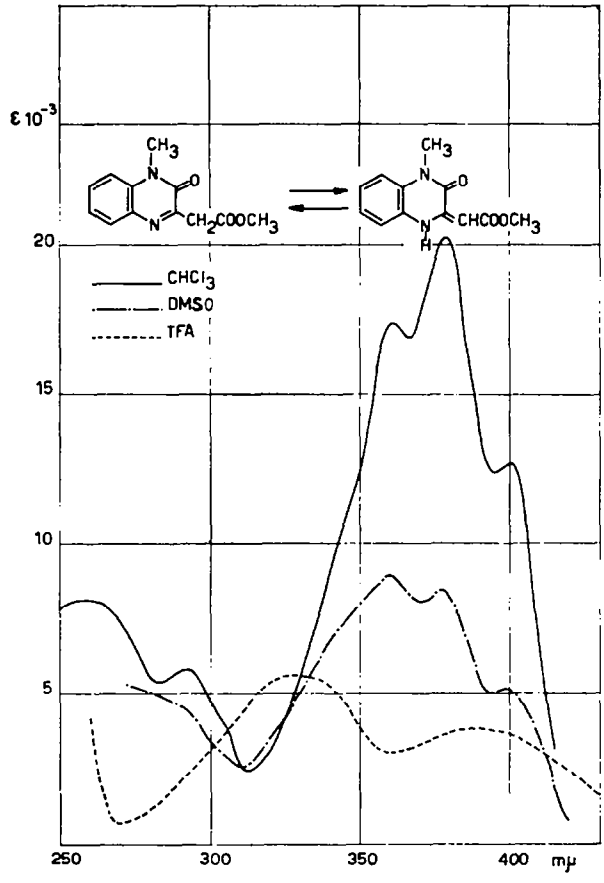
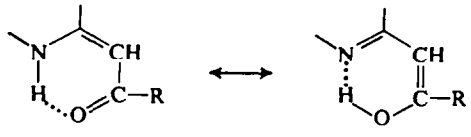


FIG. 2

In IIi,l,m,n (R = CH_2COMe, $CH_2COCOOEt$, $CH_2COCOOH$) no appreciable amount of the ketoform C appears in any solvent. Of the two remaining structures D and E, D is favoured on the basis of the lack of the expected allylic coupling between $—CH_3$ and =CH groups in IIi (which should be present in the enol form E[15]) and of

[15] The tautomeric process D ⇄ E could also be described in terms of resonance



depending on the magnitude of the potential barrier between the two forms.[16] We assume that this barrier is sufficiently high in the compounds examined, and the process will be described as a tautomeric equilibrium. Then the observation in 2-pyridylacetone of an allylic coupling (see later) between the groups $—CH_3$ and =CH, together with the UV spectra, becomes evidence in favour of the predominance in this series of the enol tautomer E with respect to the enamine D.

[16] A. A. Bothner-By and R. K. Harris, *J. Org. Chem.* 30, 254 (1965).

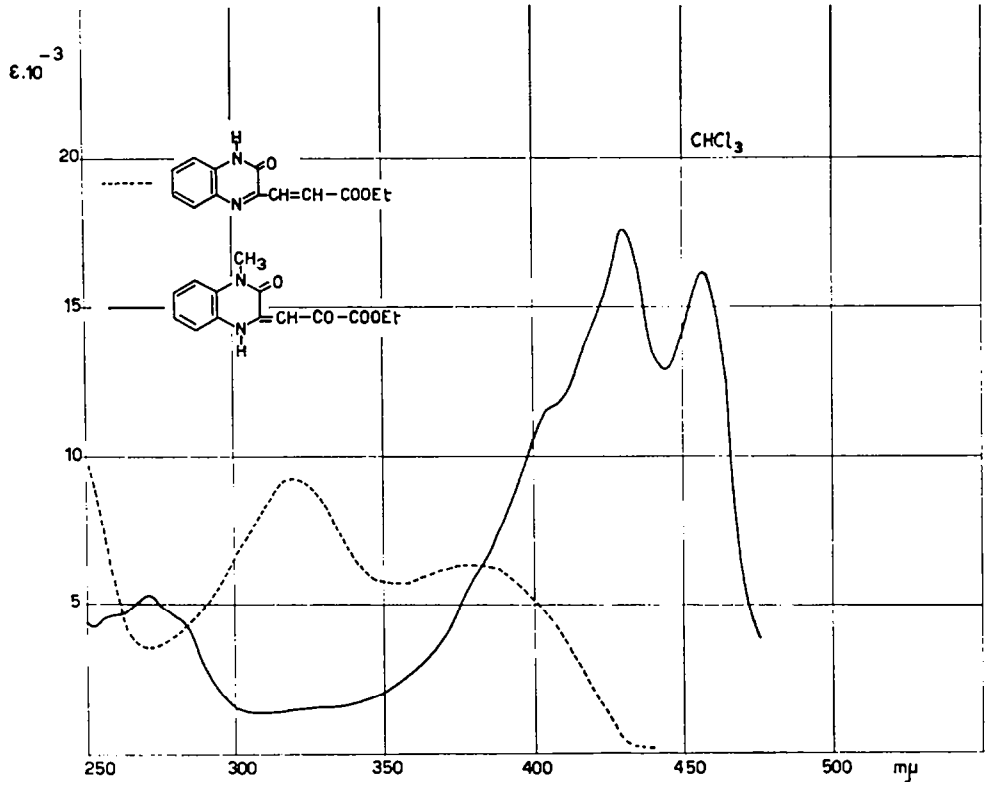


FIG. 3

the similarity of their UV spectra in $CHCl_3$ with that of the acetate IIh in the same solvent. This pattern shows no change in DMSO, EtOH, TFA and in 40% H_2SO_4, and differs strongly from that of the acrylic ester IIc (R = CH=CHCOOEt), which is assumed to have a cromophore comparable with the enol structure E[17] (Fig. 3). Consequently, protonation by the acid solvent, even if it occurs, does not affect the cromophore; the other compounds of this series undergo protonation in TFA, as is shown by the similarity of the UV spectra with those of IIb,c cations.[18]

In the NMR spectra in TFA, separate signals of COOH and NH^+ were not detected, due to the rapid exchange because of the very weak basic character of these heterocycles (the parent compound 2-oxo-1,2-dihydroquinoxaline has $pK_a = -1{\cdot}38$).

In the NMR spectra in $CDCl_3$ of IIf,g,h,l,m the aromatic pattern is simplified to one line, whereas IIc and IIo show in the same solvent a quite complex multiplet, spread between 7·0 and 8·0 δ (Fig. 4). This fits well with the localization of the two exocyclic double bonds at C-2 and C-3 in the former compounds, which give more symmetry to the molecules, and makes the four aromatic protons nearly equivalent. In DMSO and TFA, no singlet is observed, probably because of the interaction between the solute and the more polar solvent.

[17] This assumption is substantiated by the comparison of the spectra in $CHCl_3$ of cinnamic acid (λ_{max} 278 mμ, ε 21,600) with phenylpyruvic acid enol (λ_{max} 293 mμ, ε 22100), and of ethyl *p*-nitrocinnamate (λ_{max} 304 mμ, ε 21,400) with methyl *p*-nitrophenylpyruvate enol (λ_{max} 334 mμ, ε 19,100).

[18] G. W. H. Cheeseman, *J. Chem. Soc.* 108 (1958).

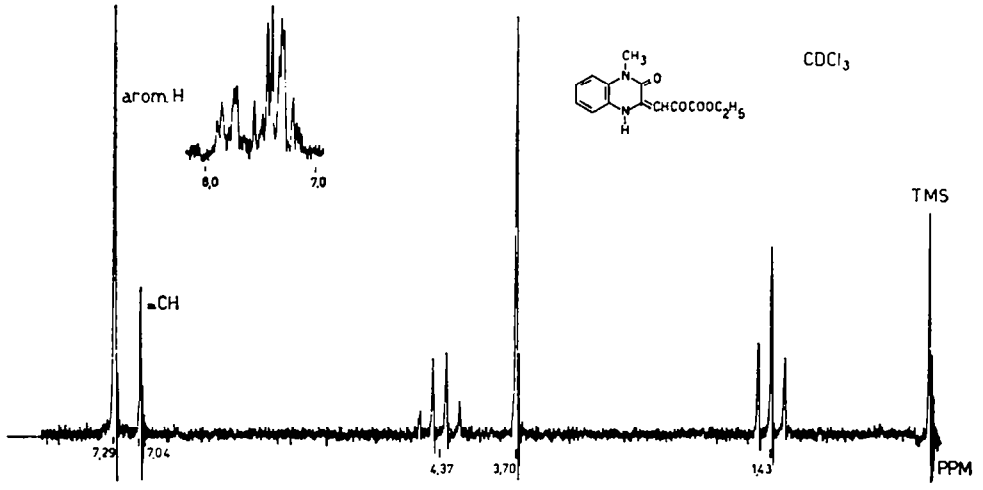
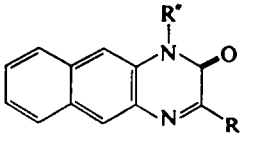


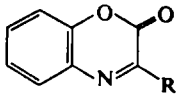
FIG. 4. The upper trace shows the aromatic protons pattern of 1,3-dimethyl-2-oxo-1,2-dihydroquinoxaline (IIc).

From Table 1 it appears that δ values of vinylic protons increase in the order $=CHCOOAlk < =CHCOCH_3 < =CHCOCOOAlk$. This occurs in all the series examined (Tables) and in xanthopterin derivatives (5·58–6·13–6·70 in DMSO).[3,4] Such effects are normal (e.g. between methyl 2-methylcrotonate and 2-methylpent-2-en-4-one there is a shift difference of 0·35 ppm[19]) and may be attributed to the different electronegativity of the substituent groups.

In order to find a possible relationship between the aromaticity of the systems and the position of the tautomeric equilibria, the 2-oxo-1,2-dihydro-6,7-benzoquinoxaline (III) and 3,4-dihydro-1,4,2H-benzoxazone (IV) derivatives were examined and are reported in Tables 3, 4, 5, 6.



III



IV

TABLE 3. CHEMICAL SHIFTS (δ-VALUES) OF 2-OXO-1,2-DIHYDRO-6,7-BENZOQUINOXALINES

			TFA		DMSO				DMSO		TFA	
	R'	R	CH_3	=CH	CH_3	=CH	NHCO	NH	H_5	H_8	H_5	H_8
IIIa	H	CH_3	3·14[a]	—	2·45[a]	—	12·24	—	8·29	7·66	8·65	8·16
IIIb	CH_3[g]	CH_3	3·16	—	2·43	—	—	—	8·24	7·80	8·64	8·23
IIIc	H	CH_2COOMe	4·6[b]	—	3·9[f]	5·66	11·92	11·10	7·80[e]	7·50[d]	8·5	e
IIId	H	CH_2COOEt	4·6[b]	—	3·91[f]	5·65	11·95	11·17	7·75[e]	7·50[d]	8·6	e
IIIe	CH_3	CH_2COOEt	4·6	—	3·88[f]	5·60	—	11·07	7·66[e]	7·62[d]	8·73	e
IIIf	H	CH_2COMe	—	6.50	—	6·16	12·0	12·90	7·75[e]	7·50[d]	7·97[e]	7·70[d]

Concentrations are in the range 40–50 mg in 0·4–0·5 ml of soln. [a] CH_3 signals; [b] the integrated area of these broad signals is less than 2 protons; some percent (10–20) of the other tautomer may be present, but the signals are too broad to be detected; [d] or H_5; [e] or H_8; [e] obscured by other aromatic protons; [f] ca. 10%; [g] containing some O-methyl deriv.

[19] L. M. Jackman, *Applications of NMR Spectroscopy in Organic Chemistry*, p. 61, Pergamon Press, London (1959).

TABLE 4. UV SPECTRA OF 2-OXO-1,2-DIHYDRO-6,7-BENZOQUINOXALINES

			TFA		DMSO		$CHCl_3$	
	R'	R	λ	ε	λ	ε	λ	ε
IIIa	H	CH_3	284	38900	263	31900	264	26300
			375	16450	276	42100	274	35500
			387	16450	284	35700	285	35500
					326	11750	324	12300
					337	11500	341	12200
					~370	~3250	~370	~2630
IIIc	H	CH_2COOMe	289	17000	292	14950	263	14750
			380	13150	305	15300	280	10100
			394	13650	319	20200	293	8680
					~365	~20200	305	6850
					384	28300	319	8470
					~400	~20200	385	9700
IIId	H	CH_2COOEt			305	19100	264	26400
					319	21500	280	18730
					≈365		293	15000
					383	26200	305	12430
					≈405		319	16200
							385	24100
IIIe	CH_3	CH_2COOEt	287	20500	305	15050	295	12950
			~378	~15400	319	18100	305	11400
			392	16550	≈374		319	14300
					386	21600	≈375	
					≈405		388	18500
							≈405	
IIIf	H	CH_2COMe	317	8420	295	11400	294	9950
			≈397		309	13450	308	10900
			419	14200	322	15650	322	16550
			445	14750	380		≈380	
					400	23300	403	26800
					418	17950	≈425	

TABLE 5. CHEMICAL SHIFTS (δ-VALUES) OF 3,4-DIHYDRO-1,4-2H-BENZOXAZONES

		TFA		DMSO			$CDCl_3$		
	R	CH_3	=CH	CH_3	=CH	NH	CH_3	=CH	NH
IVa	CH_3	2·99[a]	—	2·42[a]	—	—	2·56[a]	—	—
IVb	CH_2COOEt	4·4[b]	6·0[c]	—	5·6	10·70	—	5·94	10·70
IVc	CG_2COMe	—	6·57	—	6·15	12·18	—	6·25	12·40

Concentrations are in the range 50–70 mg in 0·3–0·4 cc soln. [a] CH_3 signal; [b] ca. 50%, broad; [c] broad.

TABLE 6. UV SPECTRA OF 3,4-DIHYDRO-1,4-2H-BENZOXAZONES

		TFA		DMSO		$CHCl_3$	
IVa	CH_3	285	19000	285	6600	288	8200
		~330	~9500				
IVb	CH_2COOEt	326	5000	368	13750	257	12300
						363	13700
IVc	CH_2COMe	~405	~8600	395	13700	262	12200
		420	9400			≈386	
		445	6100			398	19600

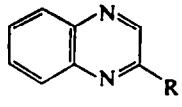
The behaviour of IIId,f and IVb,c is similar to that of IIg,i. The slight trend toward the stabilization of the enaminic structure (like in xanthopterins[3,4]) is shown

(i) In the benzoquinoxaline acetate (IIId) only by the higher equilibrium concentration (~90%) of the enaminic form B with respect to IIg (~65%) in DMSO

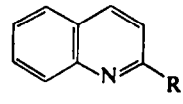
(ii) In the benzoxazone acetate (IVb) by the presence of the tautomer D alone in DMSO, and of the mixture of both C and D (~50%) in TFA. Here again the UV data are related to the NMR results.

In the NMR spectra of compounds III the singlets due to the H_5 and H_8 protons are easily picked out of the complex A_2B_2 pattern of the other aromatic protons (Table 3). In DMSO the H_8 signal appears at higher field in IIIc,d,e,f with respect to IIIa,b. The similar environment (*peri* to NH) experienced by H_8 and H_5 protons in the enaminic tautomers can account for this effect. In TFA this behaviour is shown only by IIIf, which alone exists in the enaminic form in this solvent.

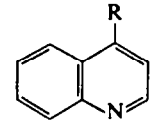
The opposite trend is observed in 2-quinoxaline (V, Tables 7, 8), 2-quinoline



V



VI



VII

(VI, Table 9, 10) and 4-quinoline (VII, Table 11, 12) derivatives. Thus in these series the tautomeric equilibrium in the case of acetate, acetonitrile and acetone derivatives is largely shifted toward the forms A and C, whereas for pyruvates the enaminic structure D predominates again in $CDCl_3$ and DMSO.These statements are supported by the same UV and NMR[20] evidence as above. Compounds forced into the 2(1H)-quinolylidene structure[9] have the same long wavelength UV absorption as the enamines of the series.

Moreover, the values of other NMR parameters, particularly of $J_{2,3}$ and $J_{3,4}$ in the quinoline ring, seem strictly related to the structure of the predominating tautomer. Thus, from the easily identified AB quartets due to C_3—H and C_4—H in 2-quinolines and to C_2—H and C_3—H in 4-quinolines, the values $J_{3,4}$ = 8·0–8·2 c/s and $J_{2,3}$ = 4·0–4·5 c/s (in DMSO, $CDCl_3$, CCl_4) are obtained for all the tautomers

[20] The lack of the allylic coupling between $—CH_3$ and =CH in 2-quinolylacetone and then in the other acetone derivatives cannot be ascribed to poor resolution, because in the former the long-range coupling (0·4–0·5 c/s) between $—CH_3$ and $—CH_2$ through the carbonyl group[21] in the keto form (which is present as about 25% in $CDCl_3$) was observed.

[21] K. Takahashi, *Bull. Chem. Soc. Japan* 37, 963 (1964).

TABLE 7. CHEMICAL SHIFTS (δ-VALUES) OF 2-SUBSTITUTED QUINOXALINES

	R		TFA		DMSO			$CDCl_3$			$CDCl_3$	DMSO	TFA
			CH_3	=CH	CH_3	=CH	NH	CH_3	=CH	NH	H_3	H_3	H_3
Va	CH_3		3·27[a]	—	2·75[a]	—	—	2·76[a]	—	—	8·72	8·89	9·55
Vb	CH_2CN		4·81	—	4·68	—	—	4·21	—	—	8·93	9·06	9·40
Vc	CH_2COOMe		4·68	—	4·23	—		4·10	—	—	8·86	9·00	9·43
Vd	$CH_2COCOOEt$		—	7·22	—	6·73	[b]	—	6·65	13·8[c]	8·67	9·00	9·56
Ve	CH_β=$CH_\alpha COOH$	H_β		8·30		7·85						9·35	9·45
		H_α		7·58		7·20							

Concentrations are in the range 50–80 mg in 0·4–0·5 cc soln. [a] CH_3 signal; [b] not detectable; [c] broad.

TABLE 8. UV SPECTRA OF 2-SUBSTITUTED QUINOXALINES

		TFA		DMSO		$CHCl_3$	
	R	λ	ε	λ	ε	λ	
Va	CH_3	337	6720	309	5400	~309	~5200
				318	6050	318	5900
Vb	CH_2CN	331	7250	~310	~6070	~310	~6000
				318	6820	318	6850
Vc	CH_2COOMe	332	8750	~308	~6700	~308	~6100
				317	6830	317	6550
Vd	$CH_2COCOOEt$	405	14850	290	15200	289	17950
				~310	~11300	320	8480
				370	10100	341	8250
				383	10100	382	12620
				~428	~6800	~430	~7500
				448	8950	450	10070
				474	6850	476	7800
Ve	CH=CHCOOH	361	8200	335	13450	265	33000
						335	11900

with structure A or C, in agreement with the normal values found for the quinoline ring.[22] $J_{3,4}$ increases to 9·0–9·5 c/s and $J_{2,3}$ to 6·5–7·0 c/s in VId,f and resp. VIIb.d, as it could be expected for the methylenedihydro structures, because of the lost ring current contribution. Values of 9·0 c/s for $J_{3,4}$ were found in N-alkyl-2-quinolones,[23] 9·5 c/s in 1-methyl-2-dicarbethoxymethylene-1,2-dihydroquinoline (VIh), and 9·7–10·0 c/s in some 1,2-dihydroquinolines.[24]

The NMR pattern of the four aromatic protons on the benzene ring, although not analysed, appears quite different in the methylenedihydro structures VIf, VIId, with respect to VIa,c and VIIa,c which show an aromatic protons pattern of the simple quinoline type.[22] The same aromatic spectrum as VIf is shown by VIh.

In the particular case of 2-quinolylacetone, the IR spectrum in CCl_4 solution shows the chelated carbonyl band at 1638 cm^{-1} and lacks the characteristic absorption of 2-substituted quinolines in the 1500–1600 cm^{-1} range,[25] especially the strong and sharp peak at 1508 cm^{-1}, and the other bands at 1570, 1588 and 1622 cm^{-1}. This result agrees with the enaminic formulation D. From NMR data, in CCl_4 this compound appears as a mixture with only 15% of the keto form.

In TFA the increase of $J_{2,3}$ (to 6–7 c/s) is observed for all the 4-quinoline derivatives but this is explained by the occurrence of protonation, with a consequent decrease of the aromatic character of the ring. The protonation results in the appearance of the NH^+ signal in the range 13·5–14·5 δ, and of the coupling between the NH^+ and

[22] P. J. Black and M. L. Heffernan, *Austral. J. Chem.* 17, 558 (1964).
[23] Y. Makisumi, *Tetrahedron Letters* 2833 (1964).
[24] R. Bramley and M. D. Johnson, *J. Chem. Soc.* 1372 (1965),
[25] See the spectrum of 2-propylquinoline, in Sadtler Colln. No. 13293.

TABLE 9. CHEMICAL SHIFTS (δ-VALUES) OF 2-SUBSTITUTED QUINOLINES

	R		TFA			DMSO			$CDCl_3$			CCl_4		
			CH_3	CH=	$^cNH^+$	CH_3	CH=	^cNH	CH_3	CH=	^cNH	CH_3	CH=	^cNH
VIa	CH_3		3·13[a,d]	—	13·5	2·69[a]	—	—	2·72[a]	—	—	2·68[a]	—	—
VIb	CH_2CN		4·83	—	[b]	4·50	—	—	4·08	—	—			
VIc	CH_2COOEt		4·57	—	14·2	4·08	—	—	4·03	—	—			
VId	CH_2COMe[h]		4·77	—	14·0	4·20[e]	5·45	14·8	4·12[f]	5·32	15·0	3·98[g]	5·22	14·8
VIe	$CH{=}CMe_2$			6·70	13·0		6·48			6·52	—		6·36	—
VIf	$CH_2COCOOEt$		—	7·00	13·5	—	6·32	[b]	—	6·37	15·7			
VIg	$CH_\beta{=}CH_\alpha COOH$	H_β		8·41	14·5		8·30							
		H_α		7·48			7·34							

Concentrations are in the range 40 mg in 0·3–0·4 ml of solution. [a] CH_3 signal. [b] Not detectable. [c] Broad signals. [d] J_{CH_3,H_3} = ca. 1 c/s. [e] ca 35%. [f] ca. 25%. [g] ca. 15%. [h] The methyl signal shows a long-range coupling through the carbonyl group of 0·4–0·5 c/s (in $CDCl_3$).

TABLE 10. UV SPECTRA OF 2-SUBSTITUTED QUINOLINES

	R	TFA λ	TFA ε	DMSO λ	DMSO ε	$CHCl_3$ λ	$CHCl_3$ ε
VIa	CH_3	310	5750	270	3580	~272	3300
		317	6340	290	2560	290	2520
				296	2210	296	2060
				303	2660	303	2710
				309	2130	309	2040
				316	3100	316	3300
VIb	CH_2CN	317	8650	285	6350	279	4250
				302	5270	290	4050
				316	4470	296	3500
				405	950	303	3960
						309	2990
						318	4200
VIc	CH_2COOEt	319	8500	290	6730	290	5000
				295	6350	296	4900
				302	6380	303	4680
				316	5350	316	3730
				402	2700	402	2340
VId	CH_2COMe	319	8030	276	7500	276	6970
				~290	~7700	302	9700
				302	8550	319	9400
				317	7600	~400	~8300
				~400	~6250	418	10500
				417	7530	442	7100
				~440	~5100		
VIe	$CH{=}CMe_2$	263	19650	261	23200	254	28100
		272	23900	329	3370	259	28800
		343	19000	343	2300	320	5480
						328	5900
VIf	$CH_2COCOOEt$	280	21850	284	7400	284	7550
		357	27200	302	6700	302	8600
		374	31900	364	5270	~320	~7800
				≈400		≈400	
				425	13150	426	20100
				447	12350	452	20400
VIg	$CH{=}CHCOOH$	337	13800	262	18600	266	21200
				311	7680	338	7750

TABLE 11. CHEMICAL SHIFTS (δ-VALUES) OF 4-SUBSTITUTED QUINOLINES

	R	TFA CH_3	TFA =CH	TFA $^{e}NH^{+}$	DMSO CH_3	DMSO =CH	DMSO NH	$CDCl_3$ CH_3	$CDCl_3$ =CH	$CDCl_3$ NH
VIIa	CH_3	3·17[a,c]	—	13·7	2·68[a,b]	—	—	2·68[a,b]	—	—
VIIb	CH_2CN	4·86[c]	—	14·2	4·65[b,d]	4·97	11·0[e]	4·13[b]	—	—
VIIc	CH_2COOEt	4·67	—	14·1	4·25	—	—	4·06	—	—
VIId	$CH_2COCOOEt$	5·22[c]	7·58	13·5	—	6·76	*f*			
VIIe	$CH_\beta{=}CH_\alpha COOH$	H_β	8·80	14·2		8·35				
		H_α	7·10			6·81				

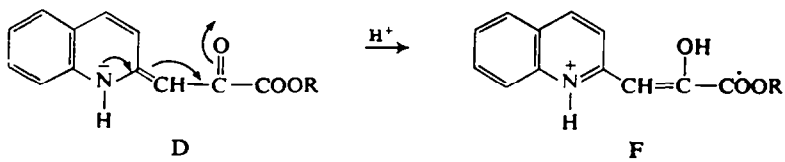
Concentrations are in the range 40–50 mg in 0·4 ml of soln. [a] CH_3 signal. [b] Doublet, J = 1 c/s [c] Doublet, J = 0·7 c/s. [d] ca. 75%. [e] ca. 20%. [f] Not detectable. [g] Broad

TABLE 12. UV SPECTRA OF 4-SUBSTITUTED QUINOLINES

		TFA		DMSO		$CHCl_3$	
	R	λ	ε	λ	ε	λ	ε
VIIa	CH_3	~305	~7400	275	4300	278	4880
		311	9170	301	2300	301	3020
				315	2150	314	2780
VIIb	CH_2CN	316	6150	279	7120	281	5520
				285	6950	303	3480
				302	2830	317	3480
				316	2740		
				~385	~4900		
				400	6570		
				420	5300		
VIIc	CH_2COOEt	314	7480	278	5470	281	4450
				302	3460	303	2850
				316	3260	316	2500
VIId	$CH_2COCOOEt$	~322	~9300	283	9100		
		335	10920	442	23700		
		364	11050	~470	~10500		
VIIe	CH=CHCOOH	269	12600	319	9400		
		324	9100				

the C-2 proton ($J_{1,2}$ = 5·5–7·0 c/s. This coupling disappears in CF_3COOD (Fig. 5)). The protonation occurs also in 2-quinoline derivatives.[26,28]

The pyruvates VIf and VIId show NH^+ absorption at 13·5 δ and the vinylic proton. This can be interpreted with the protonation of the enamine D leading to the cation F,



D F

in agreement with the usual protonation of vinylogous amides at oxygen. This process occurs also in the corresponding derivatives of 4-quinoline and quinoxaline VIId and Vd, and in 2-quinolylacetone (VId). The UV spectra of the cations Vd, VIf VId are indeed the same as in TFA, whereas the anions show a bathochromic shift consistent with the enolate formation (Table 15). These patterns are nevertheless at shorter wavelengths than the neutral molecules, thus supporting the enaminic formulation for the latter ones.

When the cations of type F are not stable, they readily tautomerize to the ketone

[26] We observed separate NH^+ and TFA signals also in quinoline[27] to 300 mg/ml TFA concentration. At 100 mg/ml the triplet structure expected for the coupling with ^{14}N (J = 55–60 c/s) could be detected even in the broad absorption of NH^+.

[27] E. Krakower and L. W. Reeves, *Spectrochim. Acta* **20**, 71 (1964).

[28] The protonation of quinoxaline derivatives, which is suggested by the UV spectra, does not give separate signals of NH^+ and COOH in NMR (TFA), because of the weaker basic character of these heterocycles.

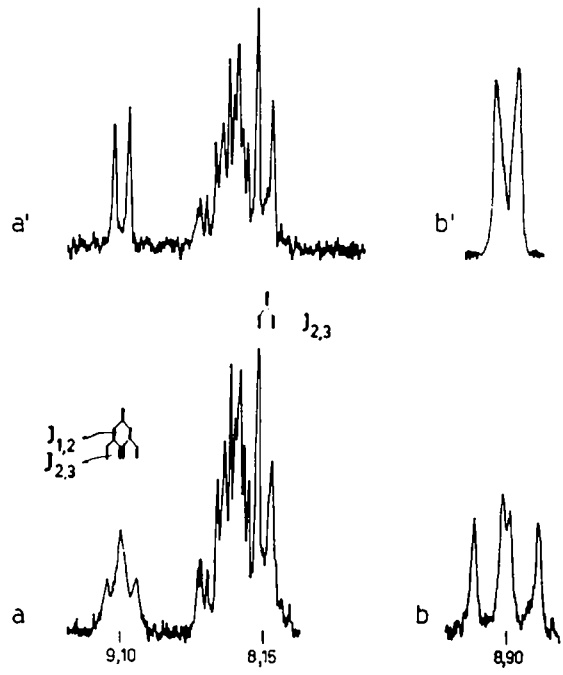
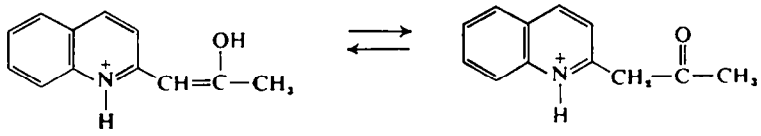


FIG. 5. NMR spectra of ethyl 4-quinolylacetate (VIIc) in CF_3COOH (a), and in CF_3COOD (a'), sweep width 500 c/s; of 4-methylquinoline (VIIa) in CF_3COOH (b) and in CF_3COOD (b'), sweep width 250 c/s.

cation, as in 2-quinolylacetone VId, both in TFA and in aqueous acid. The UV spectra (Table 15) show that this occurs also for VIId only in aqueous acid.



Inspection of Table 13 shows that the introduction of the groups CN, COOEt, $COCH_3$ in the side chain of 2-quinolines has a slight downfield effect (ca. 0·1–0·2 ppm) in $CDCl_3$ and DMSO on C_3 and C_4 protons with respect to the methyl derivatives. The presence of the conjugated carboxyl group in VIg results in a more marked effect. In the tautomer D of 2-quinolylacetone, the signals of the two protons are shifted ca. 0·6 ppm upfield with respect to the keto form C. The same upfield $\Delta\delta$ results if VIf ($R = CH_2COCOOEt$, tautomer D) is compared with VId ($R = CH{=}CHCOOH$). This may be explained with the loss of the ring current contribution. Rather similar effects are observed on the protons at C-2 and C-3 in the 4-substituted quinolines (Table 14) and on C-3 hydrogen in 2-quinoxalylpyruvate (Table 7). The other four aromatic hydrogens in Va, Vb and Vc appear in $CDCl_3$ as two separate groups of lines resp. in the range: Va 7·55–7·85 ($H_6 + H_7$), 7·90–8·15 ($H_5 + H_8$); Vb and Vc 7·60–7·95 ($H_6 + H_7$), 8·00–8·25 ($H_5 + H_8$). The presence of the NH in position 1 in Vd (tautomer D) shifts H_8 upfield (7·35–7·85: $H_6 + H_7 + H_8$; 7·80–8·15, multiplet, H_5).

TABLE 13. CHEMICAL SHIFTS (δ-VALUES) AND COUPLING CONSTANTS (c/s) OF 2-SUBSTITUTED QUINOLINES (AROM. PROTONS)

		CCl_4			$CDCl_3$			DMSO			TFA		
	R	H_3	H_4	$J_{3,4}$	H_3	H_4	$J_{3,4}$	H_3	H_4	$J_{3,4}$	H_3	H_4	$J_{3,4}$
VIa	CH_3	7·11	7·87	8–8·5	7·21	7·97	8–8·5	7·42	8·25	8–8·5	7·93	9·00	8·5–9
VIb	CH_2CN				7·45	8·16	8–8·5	7·60	8·44	8–8·5	8·30	9·28	8·5
VIc	CH_2COOEt				7·41	8·10	8–8·5	7·53	8·35	8–8·5	8·00	9·08	8·5–9
VId	CH_2COMe[b]	7·1–7·5[a]	8·00	8–8·5	7·2–7·6[a]	8·10	8–8·5	7·47	8·34	8	7·90	9·07	8·5
	$=CHCOMe$[c]	6·56	7·46	9–9·5	6·61	7·51	9–9·2	6·88	7·84	9	—	—	—
VIe	$CH=CMe_2$	7·13	7·90	8–8·5	7·28	8·02	8·5	7·35	8·20	8·5	8·0–8·1[a]	8·95	8·5–9
VIf	$CH_2COCOOEt$				7·00	7·88	9–9·2	7·5–7·7[a]	8·18	9	8·10	8·96	9
VIg	$CH_\beta=CH_\alpha COOH$							8·4	8·95	8–8·5	8·4	9·25	8·5

Concentrations are in the range 40 mg in 0·3–0·4 ml of solution. [a] Obscured by other aromatic protons. [b] Tautomer C. [c] Tautomer D.

TABLE 14. CHEMICAL SHIFTS (δ-VALUES) AND COUPLING CONSTANTS (c/s) OF 4-SUBSTITUTED QUINOLINES (AROM. PROTONS)

		$CDCl_3$			DMSO			TFA			
	R	H_2	H_3	$J_{2,3}$	H_2	H_3	$J_{2,3}$	H_2	H_3	$J_{2,3}$	$J_{1,2}$
VIIa	CH_3	8·75	7·17	4–4·3	8·80	7·36	4–4·3	8·90[b]	7·95	6·0	7·0
VIIb	CH_2CN[h]	8·80	7·52	4·5	8·98	7·60	4·5	9·22[d]	8·2–8·5[a]	6·0	[e]
	$=CHCN$[i]	—	—	—	7·15–7·35[a]	6·26	7·0	—	—	—	—
VIIc	CH_2COOEt	8·87	7·33	4·5	8·86	7·48	4·5	9·10[c]	8·15	5·5	5·5–6·0
VIId	$CH_2COCOOEt$				8·57	7·4–8·2[a]	6·5				
VIIe	$CH=CHCOOH$				8·95	7·84	4·5	9·15[f]	8·2–8·6[a]	5·5	ca. 6

Concentrations are in the range 40–50 mg in 0·4 ml of soln. [a] Obscured by other aromatic protons. [b] quartet; [c] triplet; [d] broad doublet, which is sharpened in CF_3COOD; [e] not appreciable; [f] broad signal (width = 12 c/s) which becomes a doublet in CF_3COOD; [h] tautomer A; [i] tautomer B.

We have also noted that the chemical shift difference between the side-chain vinylic protons in 2-quinolylacetone and 2-isobutenylquinoline amounts to more than 1 ppm; a more pronounced effect occurs between the β vinylic hydrogens in pyruvate and acrylic derivatives. The observation that $\Delta\delta$ between acetylacetone enol and isobutenylmethylketone[19] is only 0·42 ppm and that shielding caused by an OH or OR on the *ortho* protons in aromatic molecules is around 0·6–0·7 ppm[29], could suggest in our case a differentiation between enamine and enol structures. However, the high value of $\Delta\delta = 1{\cdot}17$ and 1·19 (in DMSO) between cinnamic acid,

TABLE 15. MAIN ABSORPTION BANDS (IN H_2O)

		λ (mμ)		ε	
Vd	neutral	446	468	18400	15600
	cation	404		7850	
	anion	422		17600	
VIf	neutral	418	438	26800	27700
	cation	373		6450	
	anion	393		24100	
VId	neutral[a]	405	315	14650	14600
	cation	318[b]		30600	
	anion	382		26600	
VIId	neutral	435		17100	
	cation	315[b]		8950	
	anion	390		15200	

[a] Most probably a mixture of enamine and ketone; [b] ketone

methyl *p*-nitrocinnamate, and respectively phenylpyruvic acid enol and methyl *p*-nitrophenylpyruvate enol does not allow any assumption on this point.

The predominance of the enaminic structure in a considerable number of the above compounds would suggest that a six-membered chelated ring strongly contributes to its stabilization. Thus the large paramagnetic shift of all the NH absorptions indicates that they are hydrogen bonded. On addition of TFA to DMSO solutions of 2-oxo-1,2-dihydroquinoxalines the enamine NH exchange very slowly, with respect to the amide NH (Fig. 6). The difficulty of exchange with TFA, and the observation that in dilution with CCl_4[30] we did not notice any shift of the enaminic signal is in favour of chelation. The enaminic NH absorptions in all the acetate and acetonitrile derivatives lie in the range 10·7–11·2 δ; those of acetone and pyruvate derivatives are always at lower field, i.e. in the range 12·5–15·7 δ. This downfield shift has to be related to the stronger intramolecular hydrogen bonds, due to the higher donor character of the ketone with respect to the ester carbonyl.[31]

[29] J. N. Shoolery, *Tetrahedron Letters* 285 (1961).

[30] These measures were made on compounds IVb, IVd (200–300 mg/cc of CCl_4 soln), and IVc (230 mg/cc of $CDCl_3$ soln) diluted with CCl_4 to 40 mg/ml. Measures on a large number of compounds or in a broader range of concentrations were inhibited by low solubility.

[31] In methyl salicylate and *o*-hydroxyacetophenone (ca. 10% in DMSO) chelated OH signals lie respectively at 10·5 and 12·0 δ.

The NHCO protons, which are interested only in intermolecular hydrogen bonds, fall in the narrow range 11·5–12·0 δ.

On the other hand, the presence of tautomers D in some 4-quinoline derivatives, where chelation is not possible, and the appearance of methylene dihydro forms also in TFA, which is a strong hydrogen-bonding medium, suggest that chelation is

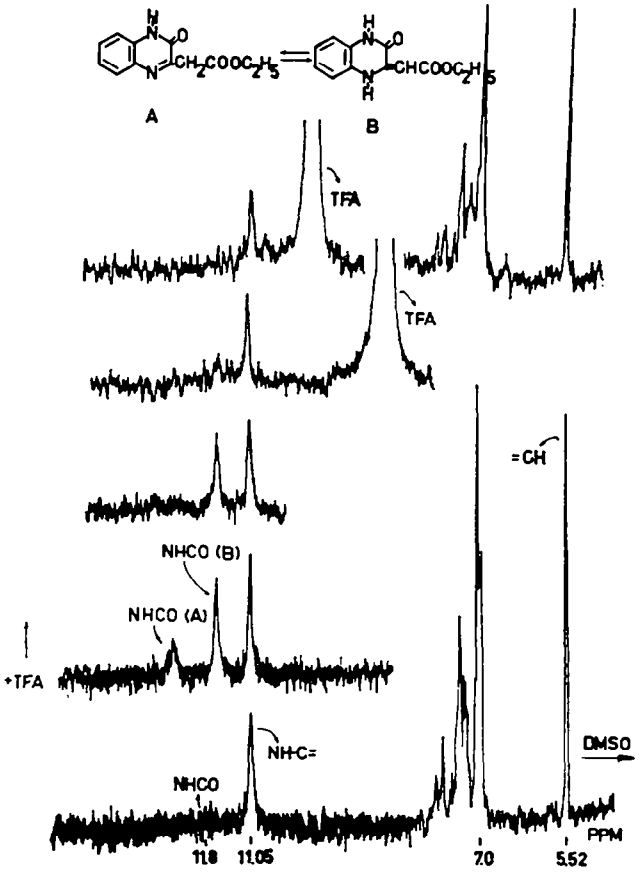


FIG. 6. NMR spectra of IIg in DMSO (lower trace), and with successive addition of minute amounts of TFA (from bottom to top).

not the unique factor of the stabilization of the enaminic structure, whose existence must be probably related also to the aromaticity of the system. Significant is the strong difference between the amount of the enaminic tautomers in II, III and IV, with respect to the more aromatic systems VI and VII.

In order to obtain information on the influence of these different factors, a similar investigation of some monocyclic systems, as well as 4-pyrimidine, 2-pyrazine, and 3-pyridazine derivatives has been undertaken. We can anticipate that in the most aromatic nucleus examined, i.e. pyridine, the enol tautomer predominates (with respect to D), appearing as ca. 100% in the pyruvate derivative, and in ca. 10% amount besides the keto form in the acetone derivative (in CCl_4 solution). This

is supported by the presence of an allylic coupling (0·65–0·75 c/s)[32] between the $-CH_3$ and $=CH$ groups. The magnitude of this interaction rules out the possibility of long-range coupling through the carbonyl (i.e. in the sequence $CH=COCH_3$)[21]. The UV spectrum of ethyl 2-pyridylpyruvate (λ_{max} 274, 318, 402 mμ; ε 9350, 16200, 1350 in $CHCl_3$) is consistent with the presence of the enol tautomer.[37,38]

EXPERIMENTAL

NMR spectra (Varian A-60 spectrometer) at temp 34–36°; shifts in ppm (δ) with TMS as internal standard. Accuracy in chemical shift is within 2–3 c/s. The accuracy of the sweep-width was checked for the 500 and 1000 c/s sweep, using the separation between the singlets due to chf and TMS in CCl_4 soln, which was always within 1 c/s of 436 c/s. Coupling constants were measured with a first order approximation. The concentrations are reported in the Tables; no appreciable variation in chemical shifts was found within the range of concentrations used.

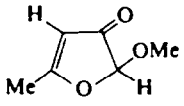
UV spectra (Beckman DK-2). DMSO and TFA Fluka were employed both for NMR and UV spectra. Absence of data in the Tables means that the substance was not sufficiently soluble.

All the compounds prepared had physical constants according to the literature. Only the preparation of new compounds is reported. *Ethyl* and *methyl* (1-methyl-2-oxo-1,2-dihydroquinoxalyl-3) acetate[39] were obtained by methylation with CH_2N_2 in ether–MeOH of the corresponding (2-oxo-1,2-dihydroquinoxalyl-3)-acetates.

Ethyl (1-*methyl*-2-*oxo*-1,2-*dihydro*-6,7-*benzoquinoxalyl*-3) *acetate* (IIIe). Ethyl (2-oxo-1.2-dihydro-6,7-benzoquinoxalyl-3) acetate,[5] suspended in ether–MeOH, was treated with excess of diazomethane in ether, and left one day. Evapn. and crystn. from MeOH gave IIIe, m.p. 165–167°. (Found: C, 68·16; H, 5·39. $C_{17}H_{16}N_2O_3$ requires: C, 68·90; H, 5·44%.)

(2-*Oxo*-1,2-*dihydro*-6,7-*benzoquinoxalyl*-3) *acetone* (IIIf). To 0·9 g of 2,3-diaminonaphthalene in 60 ml hot EtOH were added 1·2 g of ethyl acetonoxalate, and the mixture left one day at room temp.

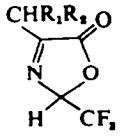
[33] This relatively low value of the allylic J has to be related both to the electronegativity of the oxygen of the OH substituent and to the partial delocalization of the double bond. Although relationships in this sense between electronegativity of substituents and ethylenic protons couplings are known,[33] the influence of substituents on the allylic coupling is not fully understood.[34,35] That the delocalization of the double bond tends to diminish the magnitude of the allylic coupling has been recently emphasized.[34] See

e.g.  where J = 0·8 c/s[34]

[33] T. Schaefer, *Canad. J. Chem.* **40**, 1 (1962).

[34] H. Rottendorf and S. Sternhell, *Austral. J. Chem.* **17**, 1315 (1964).

[35] The dependence of the *homo*allylic coupling constant from the electronegativity of the substituents has been observed in a series of pseudoxazolones VIII, where $J_{H,H}$ assumes the values 2·3, 1·8, 1·4, 0·85 c/s, respectively for R_1, R_2 = H,H; H, C_6H_5; H,Br; Br,Br; F. Weygand, W. Steglich, D. Mayer and W. von Philipsborn, *Chem. Ber.* **97**, 2023 (1964).



VIII

[36] D. Gagnaire and E. Payo Subiza, *Bull. Soc. Chim. Fr.* in the press, quoted in Ref. 34.

[37] An absorption at much longer wavelength (425 mμ) appears already in 1-methyl-2-pyridonemethide: L. C. Anderson and N. V. Seeger, *J. Amer. Chem. Soc.* **71**, 343 (1949).

[38] The existence of some 2-acylmethylpyridines in the enol form E has been recently reported on the basis of chemical shifts: G. Klose, E. Uhlemann, H. Muller, Communication at the symposium *NMR in Chemistry*. Cagliari-Sassari (1964).

[39] J. K. Landquist, *J. Chem. Soc.* 2850 (1953).

Filtration, and crystallization from dioxan gave 0·4 g IIIf, m.p. 315° (dec). (Found: C, 72·05; H, 4·82; N, 11·35 $C_{16}H_{12}N_2O_2$ requires: C, 71·41; H, 4·80; N, 11·11%.)

Methyl 2-quinoxalylacetate (Vc). A solution of 80 mg 2-quinoxalylacetonitrile in 10 ml MeOH was saturated with dry HCl, refluxed 15 min, and evaporated under red. press. The residue was taken up in Na_2CO_3aq and extracted with ether. Evaporation of the extract and distillation gave 55 mg Vc, yellow oil, b.p. 120°/0·4 mm (kugelrohr).

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