Isoxazoline Derivatives. Part VII.[1] Behaviour of 5-Acyl-Δ^2-isoxazolines with Bases. Ring–Chain Tautomerism of 5-Hydroxy-Δ^2-pyrrolin-4-ones

By **Giorgio Bianchi,* Anna Gamba-Invernizzi,** and **Remo Gandolfi,** Istituto di Chimica Organica dell'Università, Vial Taramelli, 10, 27100 Pavia, Italy

Reaction with bases of 5-acyl-Δ^2-isoxazolines gave nitriles, α-diketones, and Δ^2-pyrrolin-4-ones. N.m.r. studies revealed that Δ^2-pyrrolin-4-ones exhibited ring–chain tautomerism under a large range of solvent polarities. Possible mechanisms for this base-promoted reaction are suggested. N.m.r., i.r., and u.v. data are reported.

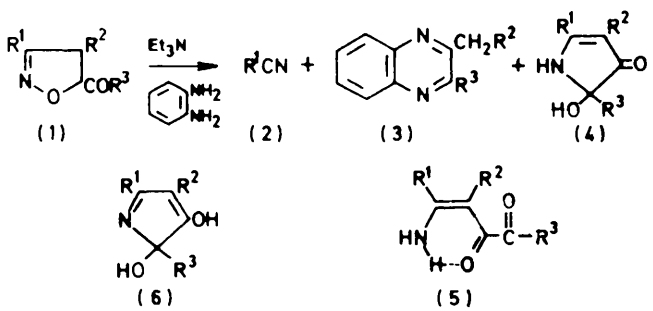
In a previous paper we reported that the reaction with bases of Δ^2-isoxazolines substituted with electron withdrawing groups at position 5 gave rise to nitriles and α-diketones as the main products.[2] The isoxazoline ring bonds C(3)–C(4) and N–O underwent fragmentation during removal of the 5-proton by base. This mechanism was supported by the fact that 5,5-disubstituted-Δ^2-isoxazolines are quite stable towards bases. In this paper, the structure of 5-hydroxy-5-methyl-3-phenyl-Δ^2-pyrrolin-4-one (4e) (Scheme 1 and Table 1) has been assigned to a by-product reported previously.[2] This finding prompted us to reinvestigate the behaviour of 5-acyl-Δ^2-isoxazolines with bases.

TABLE 1

Reaction of (1) with Et_3N

Compound	R^1	R^2	R^3	In methanol Yields (%) (3)	(4)	Ratio (3) : (4)	In benzene Yields (%) (3)	(4)	Ratio (3) : (4)
a	Me	H	Me	90					
b	Me	H	*p*-MeC_6H_4	85			47		
c	Me	H	*p*-$MeOC_6H_4$	90					
d	Ph	H	H	60					
e	Ph	H	Me	77	17	4·53	26 *	23	1·13
f	*p*-BrC_6H_4	H	Me	49	⩽10	4·9	33 *	19	1·74
g	*p*-$NO_2C_6H_4$	H	Me	63	34	1·85	67	23	2·91
h	*p*-$NO_2C_6H_4$	Ph	Me	60	24	2·50	87	*ca.* 5	17·40
i	*p*-$MeOC_6H_4$	H	Me	74	18	4·11			
j	Ph	H	Ph	67	26	2·58	43	48	0·90
k	Ph	Me	Ph	60	20	3·00	57	26·5	2·15
l	Ph	Ph	Ph	60	18	3·33	66	24	2·75
m	Ph	*p*-$NO_2C_6H_4$	Ph	55	4	13·75	82	10	8·2
n	*p*-BrC_6H_4	H	Ph	64	24	2·67	55	37·5	1·47
o	*p*-$NO_2C_6H_4$	H	Ph	62	37	1·68	65	30	2·17
p	Ph	H	*p*-BrC_6H_4	70	25	2·80	45	43	1·05
q	Ph	H	*p*-MeC_6H_4	60	25	2·40	32	58	0·55
r	Ph	H	*p*-$MeOC_6H_4$	69	25	2·76	45	50	0·90
s	Ph	$-CH_2-[CH_2]_2-CH_2-$		58			57		

* The low yields for the reactions of (1e and f) in benzene merit comment. Reactions of (1e and f) with *o*-phenylenediamine and without Et_3N gave different compounds, which were not further studied. Since the reaction of acyl-Δ^2-isoxazolines with Et_3N in benzene is quite slow (*cf.* ref. 2) the competitive reaction with *o*-phenylenediamine explains the poor yields of pyrrolines (4e and f) and quinoxolines (3e and f) respectively. Similar experiments carried out on 5-aroyl-Δ^2-isoxazolines showed that they hardly react with *o*-phenylenediamine.



SCHEME 1

METHODS AND RESULTS

A 0·1M solution of a 5-acyl-Δ^2-isoxazoline in either methanol or benzene containing Et_3N (10%, w/v) and *o*-phenylenediamine was heated under reflux. The α-diketone was characterised as a quinoxaline derivative by reaction with *o*-phenylenediamine. For reactions in benzene the water produced was distilled off azeotropically. The reaction went to completion faster in methanol (*ca.* 1 h) than in benzene (⩾2 h). In both solvents the reaction gave nitriles, quinoxalines and, except for compounds (1a—d) and (1s), 5-hydroxy-Δ^2-pyrrolin-4-ones. Under the same reaction conditions, the 5-hydroxy-Δ^2-pyrrolin-4-ones and *o*-phenylenediamine did not give quinoxalines. Unidentified products were detected (t.l.c.) after longer reaction times.

Inspection of Table 1 shows: (*a*) 3-methylisoxazolines (1a—c) and compounds (1d) and (1s) give only fragmentation products; (*b*) the ratio quinoxaline (3) : Δ^2-pyrroline (4) is solvent dependent; (*c*) as a general trend the (3) : (4) ratio is >1; (*d*) the 4-substituted isoxazolines (1k—m) are fragmented to a larger extent than (1j); and (*e*) 5-acetyl

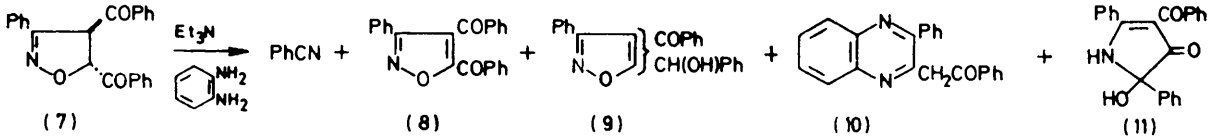
[1] Part VI, G. Bianchi, C. DeMicheli, R. Gandolfi, P. Grünanger, P. Vita Finzi, and O. Vajna de Pava, *J.C.S. Perkin I*, 1973, 1148.

[2] G. Bianchi, R. Gandolfi, and P. Grünanger, *J. Heterocyclic Chem.*, 1968, **5**, 49.

compounds show a (3) : (4) ratio larger than that of the corresponding 5-aroylisoxazolines.

4,5-*trans*-Dibenzoyl-3-phenyl-Δ^2-isoxazoline (7) showed somewhat different behaviour when treated with bases (Scheme 2). In addition to the normal products from fragmentation and cleavage, the isoxazoles (8) and (9) were obtained. Isolation of isoxazole (8) can be explained as an oxidation reaction, whilst formation of (9) should arise from an internal redox reaction.*

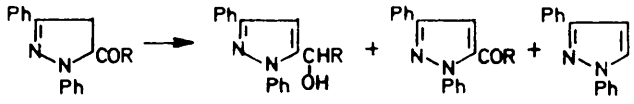
The yields of products (8)—(11) are clearly solvent dependent (Scheme 2). Similar results were found for the 5-acyl-1,3-diphenyl-Δ^2-pyrazoline (12). Compound



(7) (8) (9) (10) (11)

Yields (%) of compounds

Solvent	(8)	(9)	(10)	(11)
Methanol	Traces	8	72	8
Benzene	10	61	21	4



(12) (13) (14) (15)

a, R = Me; b, R = Ph

(12a) —NaOH–EtOH→ (13) (0%) + (14 (30%) + (15) (27%)

(12b) —MeONa–MeOH→ (13) (70%) + (14) (4%) + (15) (Traces)

SCHEME 2

(12a) when treated in ethanol with NaOH solution gave the two pyrazoles (14a) and (15a); compound (12b) in methanol with MeONa gave pyrazole (13b) in good yield and small amounts of (14b) and (15b).

DISCUSSION

Structures of Products.—T.l.c. analysis of the products obtained from Δ^2-isoxazolines (1) on treatment with bases, which can exist in the potential tautomeric forms (4)—(6), showed that they were homogeneous with the exception of those from (1r); also the compound obtained by catalytic reduction of (16b) was not homogeneous (see later). In their i.r. spectra (Nujol) a strong band at 1620—1665 cm^{-1} characteristic of the carbonyl group of a β-enamine [3] and peaks at 3500—3100 cm^{-1} of varying intensities attributed to N–H and O–H stretching, were present (see Table 2).

U.v. experiments were of little value in the study of the tautomeric equilibrium (4) ⇌ (5) ⇌ (6). The only suitable models for comparison were 5-hydroxy-2,5-dimethyl-1-phenyl-Δ^2-pyrrolin-4-one [4a] [$\lambda_{max.}$ 336 nm (log ε 4·11)] and 1-ethyl-5-hydroxy-3,5-diphenyl-Δ^2-pyrrolin-4-one [4b] [$\lambda_{max.}$ 281 (log ε 4·27) and 385 nm (3·78)]. Their u.v. data are in good agreement with those of (4b) and (4e—r) (see Table 2) respectively; on the other hand there is little agreement on comparing data of Table 2 with those of systems similar to the alternative structure (6), which have maxima at *ca.* 225 and 288 nm (log ε *ca.* 4·08 and 4·25).[3b].

The n.m.r. spectra of all the compounds (see Table 3) in $(CD_3)_2SO$ were consistent with structure (4) and did not change with time with the exception of the compounds from (1b) and (1r). From the foregoing data (i.r., u.v., and n.m.r.) we propose structure (4) for all the compounds in the solid state and in $(CD_3)_2SO$ solutions.

The following chemical transformations have been carried out in order to corroborate structure (4): on catalytic hydrogenation absorption of 1 mole of hydrogen by compound (16q) (see Scheme 3) gave a mixture of (18q), (4q), starting material, and (5q) (t.l.c.). Compound (5q) was transformed into (4q) on isolation. Compounds (4b) (which had not been obtained by base induced cleavage), (4l), and (11) have been similarly synthesised.

When catalytic hydrogenation was allowed to proceed with absorption of 2 moles of hydrogen, the main product isolated was (18q) with some (4q). Structure (18) was confirmed by the synthesis of (18q) and (18r) by prior $NaBH_4$ reduction of (16) followed by catalytic reduction.

Compound (4q) under the same conditions was not transformed into (18q).†

The open chain tautomer (5) has been detected for the compounds (b) and (r) also in $(CD_3)_2SO$.

The n.m.r. spectra of compounds from (1b) and (1r)

* Several 4-acyl-Δ^2-isoxazolines gave the corresponding 4-acylisoxazoles in good yields when treated with bases (unpublished results from this laboratory).

† The n.m.r. spectrum of (4q) in CD_3OD did not reveal a detectable amount of (5q) even after 8 h.

[3] (*a*) N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Frank, and D. J. Wallace, *J. Amer. Chem. Soc.*, 1949, **71**, 3337; (*b*) R. Fuks and H. G. Viehe, *Tetrahedron*, 1969, **25**, 5721.

[4] (*a*) J. Davoll, *J. Chem. Soc.*, 1953, 3802; (*b*) M. Weigele, J. F. Blount, J. P. Tengi, R. C. Czajkowski, and W. Leimgruber, *J. Amer. Chem. Soc.*, 1972, **94**, 4052.

just after dissolution in all solvents used were consistent with the tautomeric structure (4), but spectra recorded later showed the formation of the tautomer (5), revealed by the appearance of a second ethylenic proton. These signals were found at lower fields [δ 5·23 for (5b) and 5·78 for (5r)] than those corresponding to the ethylenic protons in the cyclic structure (4). Furthermore the *ortho* aromatic protons in R^3, giving a doublet, absorbed at δ 7·96 for (5b) and 8·09 for (5r) as opposed to 7·40 and 7·49 for (4b) and (4r) respectively.

One analogous shift towards lower field was recorded for the *para*-methoxy-group of (5r) resonating at δ 3·84 compared with the value of δ 3·72 for the (4r) structure.

The tautomeric equilibria (4b) ⇌ (5b) and (4r) ⇌ (5r) were reached faster in CD_3OD and CD_3CN than in $(CD_3)_2CO$.

The composition of the mixtures of (4) and (5) was greatly dependent on the solvent [5] but could not be correlated with the usual solvent polarities (see Table 4 in which the Dimroth's E_T values are reported). Interestingly enough the solid products recovered from the equilibrated solutions consisted again of the same tautomer (4) (identified by t.l.c. and i.r.) used to make up the solutions for the n.m.r. analysis.

TABLE 2

I.r. and u.v.* spectra of the 5-hydroxy-Δ^2-pyrrolin-4-ones and of compounds (18)

Compound	$\nu_{max.}$(Nujol)/cm^{-1} N–H, O–H	C=O	$\lambda_{max.}$(EtOH)/nm (log ε)
(4b)	3400sh, 3270s	1650s	333 (3·86)
(4e)	3260s, 3125s	1645s	252 (4·21), 364 (3·92)
(4f)	3200s	1628s	266 (4·29), 370 (3·96)
(4g)	3290s	1660s	272 (4·29), 395 (3·83)
(4h)	3360w, 3280s	1625s	264 (4·38), 422 (3·75)
(4i)	3260s	1633s, 1615s	287 (4·23), 363 (4·10)
(4j)	3390m, 3175m	1655s, 1620s	255 (4·26), 372 (3·92)
(4k)	3270s	1652s	251 (4·21), 378 (3·90)
(4l)	3400sh, 3280s	1663s	247 (4·30), 390 (3·82)
(4m)	3390sh, 3280s	1665s	
(4n)	3260s	1650s	268 (4·33), 376 (3·94)
(4o)	3300s	1663s	272 (4·28), 399 (3·82)
(4p)	3190w	1665s, 1645s	256 (4·31), 373 (3·93)
(4q)	3190w	1660s, 1640s	255 (4·17), 372 (3·93)
(4r)	3370w, 3170w	1630s	253 (4·26), 378 (3·82)
(11)	3360s, 3140m	1685s, 1600s	253 (4·30), 345 (3·96)
(18b)	3370s, 3300w, 3230w	1645s, 1615m	307 (4·27)
(18q)	3360s, 3260m, 3200w	1607s	240 (4·00), 333 (4·26)
(18r)	3370s, 3280m, 3200w	1608s	230 (4·02), 333)4·14)

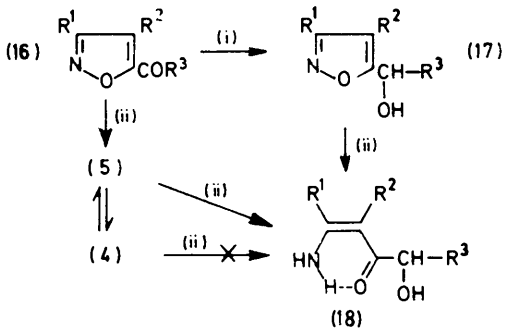
* Spectra were recorded 5 min after dissolving compounds in ethanol. U.v. spectra of compounds (b) and (r) were recorded for solutions made up from samples of pure tautomers (4) (n.m.r. analysis).

TABLE 3

Proton n.m.r. spectra of tautomers (4) and (5)

Compound	Chemical shift [a]/δ CH_3	OH [b]	NH [b]	=C(H [c])	$J_{NH,CH=}$/Hz
(4b)	2·16 s				
	2·27 s	6·55br s	8·52br s	4·60br s	
(4e)	1·33 s	6·11 s	8·43br s	5·41 d	1·3
(4f)	1·31 s	6·14 s	8·44br s	5·46 d	1·2
(4g)	1·36 s	6·27 s	8·61br s	5·62 d	1·2
(4h)	1·42 s	6·40br s	8·60br s		
(4i)	1·31 s	6·03 s	8·33br s	5·34 d	1·2
	3·86 s (CH_3O)				
(4j)		6·88 s	8·98br s	5·41 d	1·2
(4k)	1·76 s	6·72 s	8·32br s		
(4l)		7·07 s	9·04br s		
(4m)			9·77br s		
(4n)		6·90 s	9·01br s	5·46 d	1·4
(4o)		7·05 s	9·19br s	5·62 d	1·1
(4p)		7·04 s	9·07br s	5·46 d	1·2
(4q)	2·27 s	6·81 s	8·95br s	5·41 d	1·4
(4r)	3·72 s	6·77 s	8·91br s	5·39 d	1·2
(5b)	2·00 s			5·23br s	
	2·38 s				
(5r)	3·84 s			5·78br s	

[a] Relative to Me_4Si as internal standard in $(CD_3)_2SO$. [b] The signal disappeared on addition of D_2O. [c] On irradiation at the N–H proton frequency or by addition of D_2O the doublet collapsed to a singlet.



SCHEME 3

Reagents: (i) $NaBH_4$; (ii), H_2–Raney Ni

TABLE 4

Composition of tautomer mixtures by n.m.r.[a]

Solvent	Tautomers (%) (4r)	(5r)	(4b)	(5b)	E_T [b]
CD_3CN	31	69	36	64	46·0
$(CD_3)_2CO$	38	62	34	66	42·0
CD_3OD	77	23	85	15	55·5
$(CD_3)_2SO$	⩾95	⩽5	95	5	45·0

[a] The solutions of the compounds were left to equilibrate for 20 days at room temperature. Longer periods brought about some decomposition of the dissolved compound. [b] See E. Reichardt, *Angew. Chem. Internat. Edn.*, 1965, **4**, 29.

From this n.m.r. study it was evident that tautomerism involved structures (4) and (5) while structure (6) was not evident. Consistent with these findings, the catalytic reduction of (4r) with Raney nickel in ethanol gave (18r) in 50% yield. The n.m.r. study of the other compounds [in $(CD_3)_2CO$] showed that tautomer (4) was always predominant.

Solutions of (e), (i), (h), and (k) did not contain detectable amounts of the tautomers (5e), (5i), (5k), and (5h), (j) and (p) contained just a small amount of the tautomers (5), and for (q) the amount of open chain tautomer reached 30%. The correlation of structure

[5] For analogous results on other systems see A. F. McDonagh and H. E. Smith, *J. Org. Chem.*, 1968, **33**, 1, and J. E. Whiting and J. T. Edward, *Canad. J. Chem.*, 1971, **49**, 3799.

with tautomeric equilibrium constant could not be rationalised in terms of resonance stabilisation alone. Thus in the equilibrium (4) ⇌ (5), while it is reasonable to ascribe the larger percentage of (5r) than (5q), which in turn is more favoured than (5e), to better stabilisation by resonance [an R^3CO group is present in tautomer (5)], it is less easy to rationalise the fact that (5b) was more favoured than (5q).[6]

Additional products (8) and (9) were obtained from the base-induced cleavage and fragmentation of (7) (Scheme 2). Their structures were verified *via* alternative synthetic routes. Compound (8) was prepared by the addition of benzonitrile oxide to dibenzoylacetylene and by CrO_3 oxidation of compound (9), whilst sodium borohydride reduction of (8) gave (9) or its regioisomer. Compounds (14) were obtained by dehydrogenation of the Δ^2-pyrazolines (12) with chloranil. Reduction of (14a) by $NaBH_4$ gave (13a).

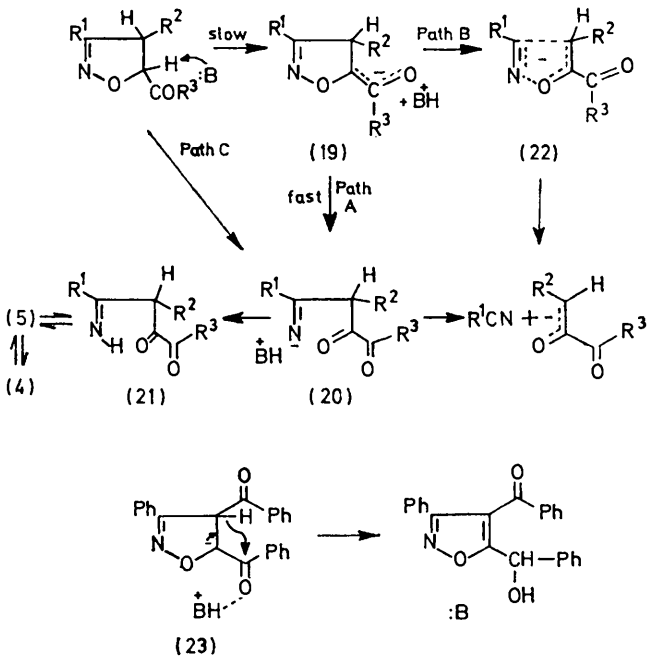
Reaction Mechanisms.—The mechanism for the formation of 5-hydroxy-Δ^2-pyrroline-4-one (4) may be rationalised by the abstraction by base of the 5-proton of the isoxazoline to give (19) (Scheme 4), followed by nitrogen–oxygen bond cleavage to afford the anion (20) which on reprotonation gave the tautomeric mixture (21) ⇌ (5) ⇌ (4).

Also the fragmentation products, nitriles, and α-ketones, can be accounted for by this mechanism.

Path A seems to be favoured over path B, which involves a thermal symmetry-allowed cyclo-reversion [$5^- \longrightarrow 3^- + 2$] through an activated complex (22) possessing an aromatic electron distribution.[7,8]

In path B the driving force of the overall fragmentation is due to the formation of the carbonyl double bond C=O (*ca.* 80 kcal mol^{-1}) and the cleavage of the weak N–O bond (*ca.* 53 kcal mol^{-1}). This energy gain should be found in the first step of path A. A transition state with an N–O bond severely stretched, is more likely than (22) where also the C(3)–C(4) bond is implicated even though the latter state possesses some aromaticity.* Because the n.m.r. spectra of isoxazolines (1) in $CDCl_3$ containing some D_2O showed no changes on addition of Et_3N, we can safely dismiss a prior equilibrium (1) ⇌ (19) and suggest the slowest step to be proton abstraction from the 5-position of the isoxazoline.

This result, while not sufficient evidence for the formation of (19), does not exclude a concerted mechanism (path C). Bordwell [9] has recently concluded that β-eliminations and similar reactions are more likely to occur by a two-step rather than a one-step mechanism. If we assume that compounds (4) and quinoxalines came from routes A and B respectively we would have expected route A, with minor charge dispersion in the transition state, to be greatly favoured in the more polar solvent methanol, in contrast with the experimental results (see Table 1). On the other hand, discarding route B and considering A as the sole route to products, an intimate ion pair between (20) and Et_3NH^+ (Scheme 4) which gives rise to (21) should be more favoured in benzene, a poor dissociating solvent, than in methanol. According to this mechanism the intimate ion pair (23) might be responsible for the high



SCHEME 4

yield of (9) in the reaction of 4,5-dibenzoyl-3-phenyl-Δ^2-isoxazoline with Et_3N in benzene. As regards the behaviour of pyrazolines towards bases it seems likely that the great tendency of these heterocycles to undergo aromatisation plays an important role.

In conclusion we wish to point out that the Δ^2-isoxazolines bearing 5-acyl group are quite unstable in basic solution and that this reaction can be used for their detection.

EXPERIMENTAL

U.v. spectra were obtained as 95% EtOH solutions on a Perkin-Elmer 137 recording instrument and i.r. spectra as Nujol suspensions on a Perkin-Elmer 257 spectrophotometer. N.m.r. spectra (60 MHz) were recorded at 36° on a Perkin-Elmer R12 spectrometer with Me_4Si as internal standard.

T.l.c. was performed on plates precoated with silica gel

* The transition states implicated in routes A and B are both cyclic and with very similar order so that they should possess nearly the same $\Delta S^{\ddagger}$.

[6] A study on the substituent effect on equilibria such as (4) ⇌ (5) has been made by H. Alper and A. E. Alper, *J. Org. Chem.*, 1970, **35**, 835, and H. Alper, E. C. H. Keung, and R. A. Partis *ibid.* 1971 **36**, 1352.

[7] M. J. S. Dewar, *Angew. Chem. Internat. Edn.*, 1971, **10**, 761.

[8] For a review of [$3^- + 2 \longrightarrow 5^-$] cycloaddition see R. R. Schmidt, *Angew. Chem. Internat. Edn.*, 1973, **12**, 212. For examples of [$5^- \longrightarrow 3^- + 2$] cycloreversion see J. N. Hines, M. J. Peagram, G. H. Whitham, and M. Wright, *Chem. Comm.*, 1968 1593; R. B. Bates, L. M. Kroposki, and D. E. Potter, *J. Org. Chem.*, 1972, **37**, 560; D. Seebach, *Angew. Chem. Internat. Edn.*, 1969, **8**, 639; and K. Burger and E. Burgis, *Annalen*, 1970, **741**, 39.

[9] F. G. Bordwell, *Accounts Chem. Res.*, 1972, **5**, 374.

GF_{254} (Merck). In some cases the products were detected on t.l.c. plates with a 3% solution of CrO_3 in sulphuric acid (50%) followed by heating at 120° in an air-bath.

Preparative columns were prepared with silica gel H (Merck). The identity of compounds with authentic material was established by mixed m.p. determination and by comparison of i.r. spectra and R_F values (t.l.c.).

Elemental analysis were performed by Dr. L. Maggi Dacrema.

Preparation of Δ^2*-Isoxazoline Derivatives.*—The Δ^2-isoxazolines (1a),[2] (1f),[2] (1g),[2] (1n),[2] (1r),[2] (7),[2] (1b),[10] (1j),[10] (1p),[10] (1q),[10] (1d),[11] (1e),[12] (1h),[1] (1k),[1] (1l),[1] and (1s) [1] were prepared by literature methods.

The hitherto unknown compounds (1c), (1i), (1m), and (1o) have been synthesised by cycloaddition of nitrile oxides to vinyl ketones.[13] 5-p-*Anisoyl*-3-*methyl*-Δ^2-*isoxazoline* (1c), formed needles from methanol, m.p. 73—74° (Found: C, 65·3; H, 5·7; N, 6·2%). 5-*Acetyl*-3-p-*anisyl*-Δ^2-*isoxazoline* (1i), occurred as prisms from ethanol, m.p. 93—94° (Found: C, 65·3; H, 6·1; N, 6·5. $C_{12}H_{13}NO_3$ requires C, 65·7; H, 6·0; N, 6·4%).

5-*Benzoyl*-4-p-*nitrophenyl*-3-*phenyl*-Δ^2-*isoxazoline* (1m) was obtained along with its regioisomer 4-benzoyl-5-*p*-nitrophenyl-3-phenyl-Δ^2-isoxazoline from which it was separated by fractional crystallisation, as prisms from ethanol, m.p. 157—161° (Found: C, 71·2; H, 4·6; N, 7·6. $C_{22}H_{16}N_2O_4$ requires C, 71·0; H, 4·3; N, 7·5%).

5-*Benzoyl*-3-p-*nitrophenyl*-Δ^2-*isoxazoline* (1o), formed needles from ethanol, m.p. 178—180° (Found: C, 64·6; H, 4·1; N, 9·5. $C_{16}H_{12}N_2O_4$ requires C, 64·9; H, 4·1; N, 9·5%).

Reaction of 5-*Acyl*-Δ^2-*isoxazolines with Triethylamine.*—The 5-acyl-Δ^2-isoxazoline (5·0 mmol) and *o*-phenylenediamine (5·0 mmol) were heated under reflux in methanol or benzene (25 ml) containing Et_3N (2·5 g) until the disappearance of the isoxazoline was indicated by t.l.c. When the reaction was carried out in benzene, the water formed was distilled off azeotropically. Reactions in methanol were complete in 1 h, and in benzene in over 2 h. Some values, of only qualitative significance, were reported previously.[2]

The solvent was evaporated off and the residue, when heated with benzene–cyclohexane, gave on cooling almost all the crystalline Δ^2-pyrrolin-4-one (4) which was separated by filtration.

The mother liquors were combined and chromatographed on a column (benzene–ethyl acetate, 95 : 5) to give the nitrile, the quinoxaline, and some (4). The yields of pyrrolines (4) and quinoxalines (3) are listed in Table 1. Nitriles were obtained in nearly the same yields as (3). Elemental analyses, m.p.s, and solvents of crystallisation are in Table 5. Compound (4m) could not be purified for elemental analysis. Quinoxaline (3m), previously unknown, crystallised from ethanol to afford yellow needles, m.p. 122—123° (Found: C, 73·4; H, 4·4; N, 12·4. $C_{21}H_{15}N_3O_2$ requires C, 73·9; H, 4·4; N, 12·3%).

Reaction of trans-4,5-*Dibenzoyl*-3-*phenyl*-Δ^2-*isoxazoline* (7).—Compound (7) (5·0 mmol) and *o*-phenylenediamine (5·0 mmol) were heated under reflux in methanol or benzene (25 ml) containiug Et_3N (2·5 g) for 0·5 h. When the reaction was carried out in methanol the 2-phenacyl-3-phenylquinoxaline precipitated on cooling and was removed by filtration. The mother liquors, for reactions in methanol and in benzene, were evaporated and the residues were chromatographed separately on columns, the first with benzene–ethyl acetate (95 : 5), and the second with benzene–ethyl acetate (7 : 3) as eluant. The yields of the products are shown in Scheme 2. The compounds were eluted in the following order: 4,5-*dibenzoyl*-3-*phenylisoxazole* (8), prisms from methanol, m.p. 105—106° (Found: C, 77·6; H, 4·6 N, 4·1. $C_{23}H_{15}NO_3$ requires C, 78·2; H, 4·3; N, 4·0%); $\nu_{max.}$ (Nujol) 1680 and 1685 (C=O) cm^{-1}; $\lambda_{max.}$ (EtOH) 257·5 nm (log ε 4·38) [this compound was identical with that obtained by cycloaddition of benzonitrile oxide with dibenzoylacetylene (see below)]; 2-phenacyl-3-phenylquinoxaline (10); [14] 4(or 5)-benzoyl-5(or 4)-(α-hydroxybenzyl)-3-phenylisoxazole (9a or b), needles from benzene, m.p. 109—113° (Found: C, 78·2; H, 5·0; N, 3·8. Calc. for $C_{23}H_{17}NO_3$: C, 77·7; H, 4·8; N, 3·9%); $\nu_{max.}$ 3380 (O–H) and 1640 (C=O) cm^{-1}; $\lambda_{max.}$ 242 nm (log ε 4·29);

TABLE 5

Physical data of 5-hydroxy-Δ^2-pyrrolin-4-ones (4)

Compound	Solvent	M.p. [h] (°C)	Found (%) C	H	N	Formula	Required (%) C	H	N
(4b)	Benzene [a]	112—115	70·8	6·8	7·1	$C_{12}H_{13}NO_2$	70·9	6·5	6·9
(4e)	MeOH [a,d]	197—198	69·9	5·6	7·6	$C_{11}H_{11}NO_2$	69·8	5·9	7·4
(4f)	AcOEt [b,d]	145—148	49·7	3·8	5·6	$C_{11}H_{10}BrNO_2$	49·3	3·7	5·2
(4g)	Dioxan [a,e]	213—216	56·6	4·5	11·8	$C_{11}H_{10}N_2O_4$	56·4	4·3	12·0
(4h)	Benzene–AcOEt [a,f]	197—198	65·9	4·9	9·2	$C_{17}H_{14}N_2O_4$	65·8	4·6	9·0
(4i)	AcOEt [b]	165—166	66·1	6·1	6·6	$C_{12}H_{13}NO_3$	65·7	6·0	6·4
(4j)	Benzene–AcOEt [b,d]	146—148	76·1	5·2	5·7	$C_{16}H_{13}NO_2$	76·5	5·2	5·6
(4k)	Benzene [c,e]	160—165	77·0	5·6	5·4	$C_{17}H_{15}NO_2$	77·0	5·7	5·3
(4l)	EtOH [b,e]	210—213	80·8	5·6	4·1	$C_{22}H_{17}NO_2$	80·7	5·2	4·3
(4n)	AcOEt [b,d]	170—173	58·6	3·8	4·3	$C_{16}H_{12}BrNO_2$	58·2	3·6	4·2
(4o)	EtOH [b,g]	182—184	64·8	4·2	9·6	$C_{16}H_{12}N_2O_4$	64·9	4·1	9·5
(4p)	AcOEt [g,d]	163—164	58·4	3·7	4·2	$C_{16}H_{12}BrNO_2$	58·2	3·6	4·2
(4q)	Benzene–AcOEt [a,d]	161—162	76·6	5·6	5·3	$C_{17}H_{15}NO_2$	77·0	5·7	5·3
(4r)	Benzene [b,d]	143—146	72·2	5·7	5·1	$C_{17}H_{15}NO_3$	72·6	5·4	5·0

[a] Prisms. [b] Needles. [c] Leaflets. [d] Slight yellow. [e] Yellow. [f] Orange. [g] Brown-yellow. [h] All the compounds listed decomposed on heating. M.p.s have therefore been determined by raising the temperature very quickly.

[10] (*a*) G. Bianchi, A. Galli, and R. Gandolfi, *Gazzetta*, 1968, **98**, 331; (*b*) G. Bianchi and P. Grunanger, *Chimica e Industria* (*Milan*), 1964, **46**, 1187.

[11] G. Stagno D'Alcontres and G. De Giacomo, *Att Soc. Peloritana Sci. fis. mat. nat.*, 1958—1959, **3**, 159.

[12] A. Quilico and P. Grünanger, *Rend. Ist. Lombardo Sci. Lettere A*, 1955, **88**, 990.

[13] Ch. Grundman and P. Grünanger, 'The Nitrile Oxides,' Springer-Verlag, Heidelberg, 1971.

[14] R. E. Lutz and A. H. Stuart, *J. Amer. Chem. Soc.*, 1936, **58**, 1885.

δ ($CDCl_3$) 6·20br (1H, s, OH) and 6·10br (1H, s, >C–H) [compound (9) was also synthesised by reduction with sodium borohydride (10 mg) of (8) (280 mg) in methanol (15 ml) in 80% yield]; 3-*benzoyl*-5-*hydroxy*-2,5-*diphenyl*-Δ²-*pyrrolin*-4-*one* (11), prisms from ethanol, m.p. 269—270° (decomp.) (Found: C, 77·3; H, 4·9; N, 4·0. $C_{23}H_{17}NO_3$ requires C, 77·7; H, 4·8; N, 3·9%), identical with the compound obtained by catalytic reduction of (8) (see below).

4,5-*Dibenzoyl*-3-*phenylisoxazole* (8).—To a solution of benzohydroximoyl chloride (200 mg) and dibenzoylacetylene (290 mg) in benzene (6 ml), Et_3N (0·18 ml) in benzene (10 ml) was added dropwise. The precipitated triethylamine hydrochloride was filtered off, and the solution was evaporated to give a residue which soon crystallised. Recrystallisation from ethanol gave pure (8) (305 mg, 70%). Compound (8) was also obtained in 75% yield by chromic anhydride oxidation of (9) in acetone and sulphuric acid (25%).

3-*Benzoyl*-5-*hydroxy*-2,5-*diphenyl*-Δ²-*pyrrolin*-4-*one* (11).—Catalytic hydrogenation (760 mmHg and room temperature) with Raney Ni (1·5 ml) of (8) (300 mg) in ethanol (35 ml) (28 ml of H_2 absorbed) and the usual work-up gave (11) (150 mg, 50%) as an oil which crystallised upon treatment with cyclohexane–ethyl acetate.

5-*Hydroxy*-2,3,5-*triphenyl*-Δ²-*pyrrolin*-4-*one* (4l).—5-Benzoyl-3,4-diphenylisoxazole [15] (325 mg) in ethanol (70 ml) was hydrogenated over Raney Ni (1·0 ml) at atmospheric pressure and room temperature. The hydrogenation was stopped after absorption of 30 ml of H_2. The usual work-up and recrystallisation of the crude material from ethanol gave pure (4l) (300 mg, 92%).

5-*Hydroxy*-3-*methyl*-5-p-*tolyl*-Δ²-*pyrrolin*-4-*one* (4b).—Catalytic hydrogenation of 3-methyl-5-*p*-tolylisoxazole (16b) [10] (300 mg) in ethanol (15 ml) over Raney Ni under normal conditions (38 ml of hydrogen absorbed) gave a residue consisting mainly of (4b) and some (18b) (t.l.c. analysis). Recrystallisation of the residue from benzene gave pure (4b) (200 mg, 66%).

5-*Acetyl*-1,3-*diphenyl*-Δ²-*pyrazoline* (12a).—A solution of *N*-(α-chlorobenzylidene)-*N'*-phenylhydrazine (2·30 g), methyl vinyl ketone (2·10 g), and Et_3N (3·03 g) in anhydrous benzene (25 ml) was heated under reflux for 3 h. The precipitated Et_3N,HCl was separated by filtration and the solvent evaporated off to give a residue which was crystallised from ethanol as yellow *needles* of (12a) (1·87 g, 70%), m.p. 138—144° (Found: C, 77·3; H, 6·1; N, 10·6. $C_{17}H_{16}N_2O$ requires C, 77·3; H, 6·1; N, 10·6%); δ ($CDCl_3$) 2·05 (3H, s, CH_3), 3·35 (2H, m, CH_2), and 4·56 (1H, dd, *J* 8·3 and 12·3 Hz, CH).

Reaction of the Pyrazoline (12a) *with* NaOH *in Ethanol*.—A solution of (12a) (500 mg) in ethanol (20 ml) containing NaOH (100 mg) was heated to reflux for 7 h when the pyrazoline had disappeared (t.l.c.). The solvent was evaporated off and the residue chromatographed (cyclohexane–ethyl acetate, 7 : 3) to give, in order of elution, 1,3-diphenylpyrazole (15) [16] (100 mg, 24%) and 5-*acetyl*-1,3-*diphenylpyrazole* (14a) (50 mg, 30%), as needles from ethanol, m.p. 136—137° (Found: C, 78·0; H, 5·5; N, 10·5. $C_{17}H_{14}N_2O$ requires C, 77·8; H, 5·4; N, 10·7%). The foregoing 5-acetyl-1,3-diphenylpyrazole (14a) was identical with the product obtained from chloranil oxidation of (12a) in boiling xylene for 3 h.

Reaction of the Pyrazoline (12b) [17] *with Sodium Methoxide in Methanol*.—A solution of (12b) (500 mg) and sodium methoxide (250 mg) in methanol (30 ml) was heated under reflux for 11 days. After this time the pyrazoline had disappeared (t.l.c.). The usual work-up and column chromatography (cyclohexane–ethyl acetate, 9 : 1) gave, in order of elution; 1,3-diphenylpyrazole (15) [16] (traces), 5-*benzoyl*-1,3-*diphenylpyrazole* (14b) (20 mg, 4%), prisms from hexane, m.p. 98—100° (Found: C, 81·8; H, 5·2; N, 8·5. $C_{22}H_{16}N_2O$ requires C, 81·5; H, 5·0; N, 8·6%), $\nu_{max.}$ 1660 cm^{-1} (C=O), and 5-(α-*hydroxybenzyl*)-1,3-*diphenylpyrazole* (13b) (350 mg, 70%), needles from cyclohexane, m.p. 120—121° (Found: C, 82·0; H, 5·6; N, 8·6. $C_{22}H_{18}N_2O$ requires C, 81·7; H, 6·0; N, 8·6%), $\nu_{max.}$ 3250 cm^{-1} (OH). Compound (14b) was also prepared by heating (12b) for 4 h in xylene with chloranil or by CrO_3 oxidation of (13b) in acetone containing 25% H_2SO_4. The pyrazole (13b) was obtained in quantitative yield by $NaBH_4$ reduction of (14b) in methanol.

4-*Amino*-1-*hydroxy*-1-p-*tolylpent*-3-*en*-2-*one* (18b).—Sodium borohydride (40 mg) was added to a solution of the isoxazole (16b) [10] (200 mg) in methanol (10 ml) and left for 1 h. The solvent was evaporated off, and the residue was treated with water and extracted with ether to give 5-(α-hydroxy-p-methylbenzyl)-3-methylisoxazole (17b) as an oil. This compound was not characterised further but was converted by catalytic hydrogenation (pressure 760 mmHg, room temperature, Raney Ni in 95% ethanol) into the *ketone* (18b) (130 mg, 65%), needles from cyclohexane–benzene, m.p. 149—151° (Found: C, 70·6; H, 7·5; N, 6·7. $C_{12}H_{15}NO_2$ requircs C, 70·2; H, 7·4; N, 6·8%).

5-p-*Methoxybenzoyl*-3-*phenylisoxazole* (16r).—Compound (1r) (1·50 g) was dissolved in anhydrous CCl_4 (150 ml) with *N*-bromosuccinimide (1·90 g) and α,α'-azodi-isobutyronitrile (0·10 g) and then heated under reflux for 0·5 h. An intense red colour was observed. The resultant succinimide was filtered off, and the solvent evaporated to give (16r) (1·00 g, 67%), *needles* from ethanol, m.p. 95° (Found: C, 73·3; H, 4·7; N, 5·2. $C_{17}H_{13}NO_3$ requires C, 73·1; H, 4·7; N, 5·0%); $\nu_{max.}$ 1640 cm^{-1} (C=O).

4-*Amino*-1-*hydroxy*-1-p-*methoxyphenyl*-4-*phenylbut*-3-*en*-2-*one* (18q) *and* 4-*Amino*-1-*hydroxy*-1-p-*tolyl*-4-*phenylbut*-3-*en*-2-*one* (18r).—Sodium borohydride reduction of (16q) [10b] and (16r) gave (17q) and (17r) respectively in quantitative yields; 5-(α-*hydroxy*-p-*methylbenzyl*)-3-*phenylisoxazole* (17q) was obtained as leaflets from cyclohexane, m.p. 86—88° (Found: C, 77·4; H, 5·9; N, 5·1. $C_{17}H_{15}NO_2$ requires C, 77·0; H, 5·7; N, 5·3%); $\nu_{max.}$ 3300 cm^{-1} (OH); 5-(α-*hydroxy*-p-*methoxybenzyl*)-3-*phenylisoxazole* (17r) was obtained as leaflets from benzene–cyclohexane, m.p. 107—108° (Found: C, 72·3; H, 5·5; N, 5·1. $C_{17}H_{15}NO_3$ requires C, 72·6; H, 5·4; N, 5·0%); $\nu_{max.}$ 3310 cm^{-1} (OH). Compounds (17q) and (17r) on catalytic hydrogenation (pressure 760 mmHg, room temperature, Raney Ni in 95% ethanol) gave quantitative yields of (18q), *needles* from cyclohexane, m.p. 106—107° (Found: C, 76·1; H, 6·4; N, 5·3. $C_{17}H_{17}NO_2$ requires C, 76·4; H, 6·4; N, 5·2%), and (18r), *needles* from cyclohexane–benzene, m.p. 130—133° (Found: C, 71·9; H, 6·3; N, 5·0. $C_{17}H_{17}NO_3$ requires C, 72·1; H, 6·1; N, 4·9%), respectively.

Catalytic Hydrogenation of 3-*Phenyl*-5-p-*toluoylisoxazole* (16q).—(*a*) Compound (16q) (200 mg) was dissolved in ethanol (20 ml) and catalytically reduced with hydrogen

[15] E. P. Kohler, *J. Amer. Chem. Soc.*, 1924, **46**, 1733.
[16] R. Huisgen, M. Seidel, G. Wallbillich, and H. Knupfer, *Tetrahedron*, 1962, **17**, 2.
[17] C. Runti and F. Collino, *Ann. Chim.* (*Italy*), 1964, **54**, 441.

and Raney Ni (0·35 ml) under normal pressure (760 mmHg) and at room temperature. After an uptake of 20 ml of H_2 (2 h) the mixture was analysed by t.l.c. which showed the presence of small amounts of (18q) and (4q) and of a large amount of material possessing a higher R_F, as well as some starting compound. The solution was left aside for 24 h after which the spot with the highest R_F had disappeared and the spot corresponding to (4q) was now the main one. At this point the solution was further hydrogenated, 10 ml of H_2 being absorbed. The solution was filtered, and the solvent evaporated off to give a residue which was treated with benzene–cyclohexane whereupon (4q) (70 mg) precipitated; the precipitate was filtered off, and the filtrate was evaporated and the residue chromatographed (cyclohexane–ethyl acetate, 1 : 1) to give (16q) (traces), (18q) (50 mg, 25%), and more (4q) (40 mg, overall yield 55%).

(*b*) The hydrogenation of (16q) (200 mg) under the same conditions as above was carried out without interruption until no more hydrogen was absorbed (50 ml in 6 h). The usual work-up and column chromatography gave (18q) (130 mg, 65%) and (4q) (30 mg, 15%).

Catalytic Hydrogenation of 5-*hydroxy*-5-p-*methoxyphenyl*-2-*phenyl*-Δ^2-*pyrrolin*-4-*one* (4r).—Compound (4r) (120 mg) was reduced as described above (Raney Ni 0·5 ml,16 ml of H_2, 2 h). The usual work-up and crystallisation of the residue from cyclohexane–benzene gave (18r) (50 mg, 41%). Compound (4q) under the same hydrogenation conditions absorbed a small amount of hydrogen. No traces of (18q) were detected by t.l.c. analysis.

We are grateful to C.N.R. (Rome) for financial aid.

[4/093 *Received*, 21*st January*, 1974]