Action of Hydroxylamine on Chromone and Khellin. Oxime vs. Isoxazoles Structures

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Received September 21, 1976

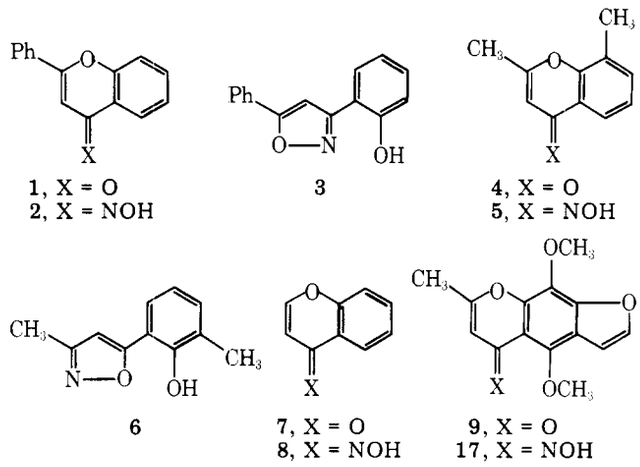
When treated by hydroxylamine under standard conditions, chromone (**7**) does not yield the oxime **8**, but rather two isoxazoles **10** and **11**. The khellin derived isoxazole **14** (mp 120 °C) is the main product formed under similar standard conditions, and its structure has been reassigned. Another isoxazole, having the structure **15**, has also been isolated. On the other hand, the chromone oxime (**8**) and khellin oxime (**17**) are obtained under new oximation conditions (anhydrous methanol, $NH_2OH{\cdot}HCl$). Their structures are unambiguously established by a ^{13}C NMR study.

Nucleophilic attack of hydroxylamine on the γ-pyrone system usually proceeds through opening of the ring and recyclization to yield various nitrogen-containing heterocycles (4-pyridones, isoxazoles). However, scattered examples of oxime formation have been reported.[2,3]

Owing to the difficulty in differentiating γ-pyrone oximes from their isomeric isoxazoles, there has been some confusion in the literature. For example, the compound isolated from the reaction of flavone (**1**) under classical conditions was at first assigned structure **2**.[4] It was much later shown that **3** was actually the correct structure.[5] Similarly, the oxime **5** was thought to be the product isolated by Wittig and Bangert,[6] after treatment of chromone (**4**) with hydroxylamine, but the structure was then revised to **6** by Basinski and Jerzmanowska.[7]

We have applied a one-step oximation method to chromone (**7**) and to khellin (**9**)[8] and we have thus obtained the oximes **8** and **17**. In connection with the structure elucidation, we repeated the previously reported reactions of **7** and **9** (Scheme I).

Scheme I

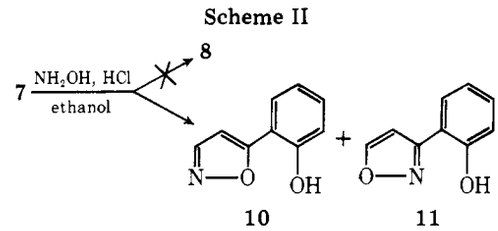


I. Under Standard Conditions. A. Chromone (7) has been recently reported in a patent application[9a] to react with hydroxylamine in ethanol to give chromone oxime (**8**).[9b] We have repeated the experiment and two products **10** and **11** were obtained, both different from the oxime **8** which we have prepared independently by our method (vide infra) (Scheme II).

As no physical data are given in the patent literature it was not possible to tell which product has been obtained by the authors.

Structural data presented in Table I show that neither IR nor NMR allows one to differentiate between **8**, **10**, and **11**. However, the UV spectra of **10** and **11** agree with an isoxazole

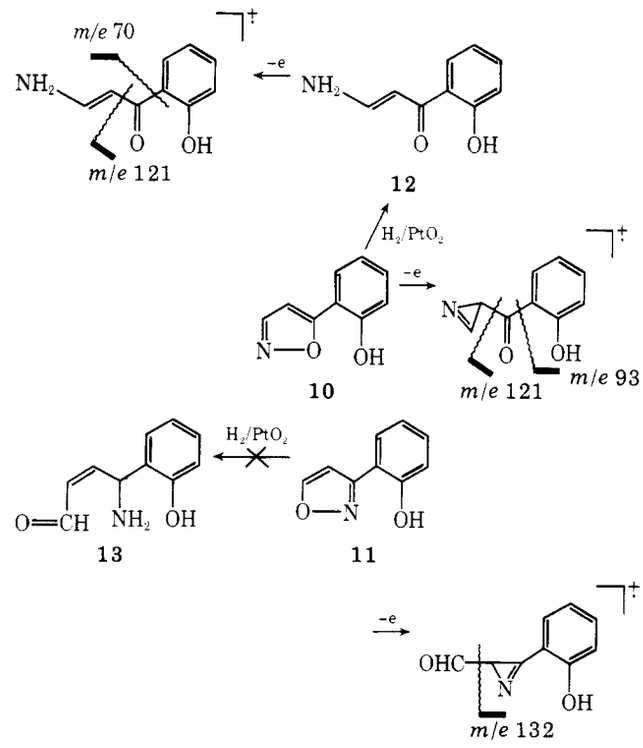
Scheme II



structure[10] and exhibit respectively four bands for the 5-substituted isoxazole and three bands at lower wavelength for the 3-substituted isoxazole in agreement with Crabbé's results.[11]

The fragmentation patterns of isoxazoles in the mass spectrometer are well known[12-15] and ions at *m/e* 121 and 93 are expected and indeed observed for **10**, whereas an ion at *m/e* 132 is similarly predicted and observed for **11** (Scheme III).

Scheme III



The catalytic hydrogenation of **10** yields **12** after absorption of 1 mol of hydrogen. The disappearance of the IR band at ν 1130 cm^{-1} (O–N) and the two units increase of the molecular ion in the mass spectrum of **12** suggest the hydrogenolysis of the N–O bond, and the formation of the vinylogous amide **12**

Table I. Physical Data of Isoxazoles 10 and 11 and Oxime 8

	Isoxazoles		Oxime
	10	11	8
Mp, °C	181 (benzene) (lit. 184[9b])	Liquid	127 (benzene)
IR, ν, cm^{-1} (OH)	3260	3260	3580, 3270
(C=N)	1620	1630	1650
(C=C)	1580	1595	1625
(O–N)	1130	1130	1135
NMR, δ, ppm	6.9 d J = 1.5 Hz	6.7 d J = 2 Hz	6.65 d J = 5 Hz
	8.4 d J = 1.5 Hz	8.4 d J = 2 Hz	7.2 d J = 5 Hz
	AX system	AX system	AB system
UV, λ_{max}, nm (log ϵ)	219 (4.60)	217 (4.35)	240 (3.98)
	261 (4.61)	249 (4.06)	316 (3.89)
	272 (4.49)	298 (3.56)	
	306 (4.43)		
MS, m/e	161 (M^+), 121, 93	161 (M^+), 132	161 (M^+), 145, 130, 102

Table II. Physical Data of Isoxazoles 14 and 15 and Oxime 17

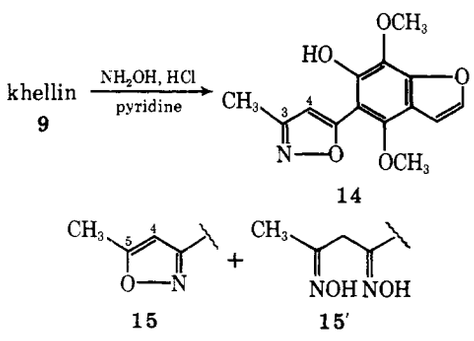
	Isoxazoles		Oxime
	14	15	17
Mp, °C	120 (ethanol–water) (lit. 120–121[23])	124–126 (ether)	224–225 dec (acetone–ether)
IR, ν, cm^{-1} (OH)	3500	3500	3200
(C=N)	1630	1625	1675 br
(C=C)	1590	1605	
(O–N)	1135	1140	1130
NMR, δ, ppm	CH_3 2.35 s $W_{1/2}$ = 1.6 Hz	CH_3 2.4 d J = 0.8 Hz	CH_3 2.3 s
	C_4 H 6.5 s $W_{1/2}$ = 1.4 Hz	C_4 H 6.7 s $W_{1/2}$ = 2 Hz	C=CH 6.75 s
UV, λ_{max}, nm (log ϵ)	221 (4.47)	220 (4.39)	226 (4.63)
	245 (4.58)	244 (4.51)	269 (4.25)
	310 (3.4)	265 shoulder	323 (4.0)
		313 (3.6)	333 (3.98)
MS, m/e	275 (M^+), 205, 177	275 (M^+), 260, 43	275 (M^+), 257

by a well-documented process.[16–19] The presence in the mass spectrum of **12** of an ion at m/e 121 can be explained, as for **10**, by the cleavage α to the carbonyl. The fragment at m/e 70 characterizes **12**. Conversely the α cleavage occurring in the rearranged structure obtained from **11** gives rise to the m/e 132 ion, which does not appear for **10**. The isoxazole **11** failed to hydrogenolyze, as has been reported for other isoxazoles.[20]

All these data completely agree with the proposed isoxazoles structures **10** and **11** and not with the oxime structure.

B. Khellin (9). The isoxazole system had been correctly recognized as being formed under classical conditions but the authors were unable to differentiate between the isomers **14** and **15**, although preference was given to structure **15**.[23] We have repeated the experiment and could isolate **14**, **15**, and the dioxime **15'** (Scheme IV).[21]

Scheme IV



We have observed that the main product, **14**, has the same melting point (120 °C) as the product to which structure **15** had been attributed by Schonberg and Sidky.[23] Our structure assignments rely on physical data reported in Table II.

IR and UV spectra of **14** and **15** agree with the proposed isoxazole structures. The NMR spectra allow differentiation between **14** and **15**. In agreement with other studies[7,24] the methyl of **14** resonates at lower field (2.35 ppm) than the methyl of **15**.

Furthermore, allylic coupling is observed for the methyl borne by **15**, in agreement with the reported observations for 3,5-dimethylisoxazole.[25] The mass spectrum exhibits a fragmentation pattern already observed for **10** (vide supra).

The isoxazole **14**, after absorption of 1 mol of hydrogen, gives the ring-opened vinylogous amide **16** which, when treated with $NaOD/CH_3OD$, incorporates four deuterium atoms to give **16**-d_4.[26] Both **16** and **16**-d_4 give a mass spectrum where the main peaks are m/e 220 and 205, which shows that the fragment m/e 220 has incorporated no deuterium, and has indeed the proposed structure. The ion m/e 205 is common to the spectra of **14**, **16**, and **16**-d_4 and arises from the cleavage α to the carbonyl in all cases (Scheme V).

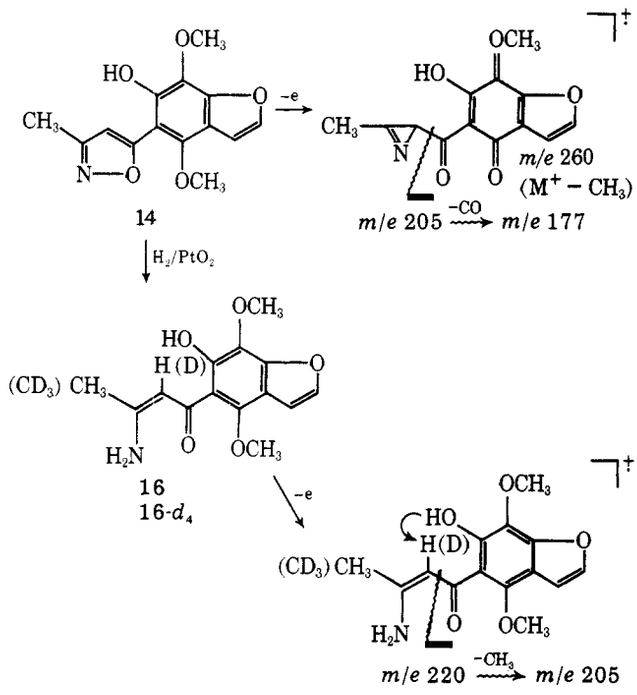
The NMR spectrum of **16** shows at δ 2.02 a signal for a methyl adjacent to a nitrogen atom.[27]

The isomeric isoxazole **15** shows in its mass spectrum an ion at m/e 43 ($CH_3C{\equiv}O^+$) and fails to be hydrogenolyzed as has been similarly observed for the chromone derived isoxazole **11**.

II. Under Anhydrous Acidic Conditions. The compounds **8** and **17** that we have obtained under our conditions[43] (dry, distilled, anhydrous methanol, hydroxylamine hydrochloride)[8] are isomeric with the isoxazoles **10**, **11** and **14**, **15**, respectively. The spectroscopic data of **8** and **17** are in agreement with an oxime structure;[42] but, owing to the confusion we have noted in the literature (see the introduction), a ^{13}C NMR study has been carried out in order to establish unambiguously their structures.

^{13}C NMR Structural Study. A. Calculation of $\Delta\delta^i$ =

Scheme V



$\delta^{i}_{C=O} - \delta^{i}_{C=NOH}$ in the Flavone Series. We took flavone (1) and its oxime **2** as reference compounds since they share with chromone (7) and khellin (9) a common array of carbon atoms α, β, and γ to the carbonyl. Flavone (1) ^{13}C chemical shifts have been assigned by Kingsbury and Cooker[28] whose results are taken here;[29] on the other hand, flavone oxime has been prepared through an indirect method.[5] It is thus possible to determine the induced shifts $\Delta\delta^{i}$ on going from **1** to **2**, that is, replacing a carbonyl by an oxime group in a γ-pyrone system.

The flavone oxime ^{13}C spectrum was recorded and assignments are collected in Table III. They are made from single-frequency off-resonance decoupled (sford) data and by comparison with flavone ^{13}C shifts for atoms which are far remote from the substitution site such as 1′, 2′, 3′, 4′, 3a, 9, and 9a (where little or no variation is expected).

B. Chromone Oxime (8). ^{13}C chromone shifts are known[28,32,33] and we have taken the results of Kingsbury.[28] It is then possible to compare the experimental values obtained from the spectrum of 8 with the values calculated by use of the increments obtained from the flavone series.

Table IV shows that agreement is good and fully supports the assigned oxime structure.

C. Khellin Oxime (17). As no ^{13}C study of khellin is known to us, the first step is to assign all the carbon atoms of the parent compound, **9**.

The methyl (20.0 ppm) and the two methoxyls (61.4 and 62.3 ppm) are readily assigned, and the observation in sford mode of a ^{3}J coupling enables us to identify the furan carbon atoms C-2 (146 ppm) and C-3 (105 ppm), in agreement with values obtained for substituted benzofurans.[34] The only remaining nonquaternary carbon atom at 110 ppm is therefore C-6. The carbonyl group (178 ppm) has a δ similar to those borne by several natural γ-pyrone[35-37] and the absorption of the quaternary vinylic carbon (164 ppm) agrees with the value (162 ppm) observed for 3-methylcyclohex-2-enone.[38,39] The aromatic carbon atoms are assigned by means of the known qualitative effects of α, ortho, meta, and para carbon shifts.[40] Thus, carbon atoms 4, 8a, 9, and 9a (α to an oxygen atom) will be shifted downfield (relative to benzene). For carbon atom 9, one has to take into account (1) the effect of an ortho–meta furan ring (−15 ppm); (2) the ortho effect of an α,β-unsaturated ether (−10 ppm); (3) the methoxyl α effect (+30 ppm); (4) the para effect of a methoxyl (−10 ppm), which all leads us to assign the signal at 130 ppm to C-9.

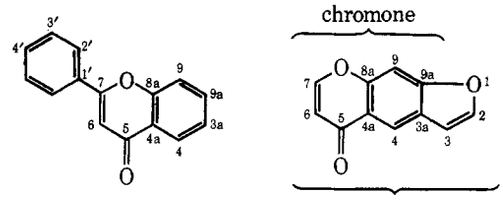
The same calculation is made for carbon atoms 4, 8a, and 9a but their absorption signals are observed within a range of 1 ppm and thus, the assignments cannot be considered to be unequivocal. However, the differentiation of these three signals is not important for subsequent calculations.

It is easily seen in comparing flavone[28] and benzofuran[34] that C-3a will be shifted downfield. Since the khellin skeleton can be formally considered as resulting of the coupling either of (1) flavone + carbon atoms 2 and 3 or (2) benzofuran + carbon atoms 5, 6, and 7, it is possible to determine the relative shift of carbon atoms 3a and 4a by two different approaches (Scheme VI).

The assignment of C-4a (119 ppm) is thus reasonable and is further supported in that, owing to the presence of a β hydrogen, its relaxation should be more efficient, which is indeed oserved.

Having assigned every carbon resonance of khellin (**9**), it is then possible to calculate the chemical shifts of the carbon atoms of khellin oxime (**17**) as has been done for chromone oxime (**8**). The agreement between calculated and observed

Table III. Calculation of Increments $\Delta\delta^{i} = \delta^{i}_{C=O} - \delta^{i}_{C=NOH}$[a]



Carbon no.	Flavone (1)	Flavone oxime (2)	Multiplicity	Increment $\Delta\delta^{i}$
3a	125.4[b]	124.8	d	0.6
4	124.9[b]	122.8	d	2.6
4a	123.7	118.4	s	5.3
5	178.0	145.2	s	32.8
6	107.3	93.5	d	13.8
7	163.0	155.3	s	7.7
8a	156.0	152.1	s	3.9
9	117.9	117.7	d	0.2
9a	133.5	132.8	d	0.7
1′	131.5	130.6	s	0.9
2′	126.0	125.8	d	0.2
3′	128.8	128.7	d	0.1
4′	131.3	130.4	d	0.9

[a] For the sake of clarity, we have taken the khellin numbering for all compounds. [b] These values might be interchanged.

Table IV. Comparison of Calculated and Observed ^{13}C Shifts for Chromone Oxime (8)

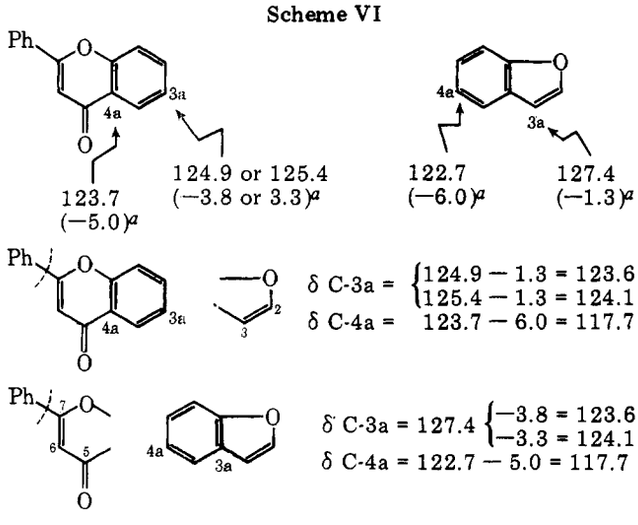
Carbon no.	Chromone (7), δ	Chromone oxime (8)		
		δ_{calcd}	δ_{obsd}	$\Delta\delta_{max}$
3a	125.4	125.4 or 124.3	124.8	0.6
4	124.9	122.4 or 123.4	123.0	0.6
4a	124.6	119.3	118.7	0.6
5	177.1	144.3	143.6	0.7
6	112.7	98.9	98.4	0.5
7	155.0	147.3	147.5	0.2
8a	156.2	152.3	151.7	0.6
9	117.9	117.7	117.6	0.1
9a	133.4	132.7	130.6	2.1

Table V. Comparison of Calculated and Observed ^{13}C Shifts for Khellin Oxime (17)

Carbon no.	Khellin (9), δ	Khellin oxime (17) δcalcd	Khellin oxime (17) δobsd	Khellin oxime (17) Δδmax
2	145.6		145.3 or 144.7	0.9
3	105.2		105.2	0
3a	119.3	119.2	118.2	1.0
4	148.7	145.9 or 145.5	144.7 or 145.3	1.2
4a	113.6	108.3	107.6	0.7
5	178.1	145.3	144.7 or 145.3	0.6
6	110.5	96.7	94.9	1.8
7	164.0	156.3	155.3	1.0
8a	147.2	143.3 or 143.1	143.2	0.1
9	129.8	129.7	129.7	0
9a	147.0	146.3 or 146.5	147.2	0.9
4-OCH_3	61.4[a]		61.2	1.1
9-OCH_3	62.3[a]		61.2	1.1
7-CH_3	20.0		19.8	0.2

[a] These values might be interchanged.

Scheme VI



[a] Differences relative to unsubstituted benzene are in parentheses.

values is very good, which confirms the structure **17** (Table V).

Chemical Proof of Structure 17. 17, treated by SO_3HNa, undergoes a smooth deoximation reaction[41] and gives back khellin, identical (melting point, IR) with an authentic sample.[42]

Conclusion

Having prepared by our oximation method authentic samples of chromone oxime (**8**) of khellin oxime (**17**), we were able to re-examine some results of the literature. Firstly, we have shown that the product obtained under standard oximation conditions from the chromone (**7**) was not the oxime **8**, and that instead the isoxazoles **10** and **11** were isolated. Secondly, we have shown that the main product obtained from khellin under standard oximation conditions was not the isoxazole **15**, as previously reported, but instead its isomer **14**.[45]

Experimental Section

General Procedure. Melting points were determined with a Kofler block and are corrected. The ^1H NMR spectra were obtained on a R12 Perkin-Elmer spectrometer with Me_4Si as internal standard. The ^{13}C spectra were obtained on a 22-MHz HX 90E Bruker apparatus. The IR spectra were recorded with an Infracord Perkin-Elmer instrument; the UV spectra were obtained with a Spectronic 505 Bausch and Lomb (ethanol solution). The mass spectra were obtained on a AEI MS9 spectrometer. Microanalysis were performed by the CNRS Service (Gif/Yvette) and satisfactory analytical data were obtained (±0.4% for C, H, N, O) for all new compounds.

Our oximation method was as follows. A solution of γ-pyrone and hydroxylamine hydrochloride (w/w) in anhydrous methanol (obtained by treatment over magnesium and distillation) was refluxed, and the course of the reaction was monitored by TLC. Standard workup yielded the oxime which was purified by crystallization, after column chromatography (SiC_4 Mallinckrodt Silica) if necessary.

2-Phenyl-4*H*-benzopyran-4-one Oxime (Flavone Oxime, 2). The oxime **2** prepared by our method and crystallized from methanol in 37% yield was identical [mp 181–182 °C; IR ν_{max} 1645 (C=N), 1620 cm^{-1} (C=C); mass spectrum *m/e* 237 (M^+), 77] with an authentic sample prepared according to ref 37.

5-*o*-Hydroxyphenylisoxazole (10) and 3-*o*-Hydroxyphenylisoxazole (11). Under the conditions reported by the patent literature, i.e., reflux of a solution of chromone **7** (2 g) and hydroxylamine hydrochloride (2 g) in ethanol (80 mL), we obtained after 24 h a mixture which after column chromatography and benzene elution yielded **11** (1.44 g, 65%) as a colorless liquid. Subsequently ether eluted **10** (0.45 g, 20%) crystallized from benzene, mp 181 °C (lit.[9b] mp 184 °C).

4*H*-Benzopyran-4-one Oxime (Chromone Oxime, 8). Our oximation method yielded **8** in 31% yield, mp 127 °C (from benzene).

Anal. Calcd for $C_9H_7O_2$: C, 67.07; H, 4.38; N, 8.69. Found: C, 67.06; H, 4.37; N, 8.60.

1-(*o*-Hydroxyphenyl)-3-amino-2-propen-1-one (12). A solution of isoxazole **10** (0.161 g) in ethanol (15 mL) was hydrogenated at atmospheric pressure with PtO_2. After uptake of one hydrogen equivalent the catalyst was removed by fiber glass filtration and classical workup gave **12** (0.146 g, 89%): mp 99–100 °C; IR ν_{max} 3500 (OH), 1650–1620 cm^{-1} (C=N and C=O); NMR δ 5.9 (d) and 7.45 (d) (*J* = 8 Hz, AX system), 13.05 (OH), 9.5 (NH_2); mass spectrum *m/e* 163 (M^+), 146, 121, 70, 43.

Anal. Calcd for $C_9H_9NO_2$: C, 66.24; H, 5.56; N, 8.58. Found: C, 66.19; H, 5.54; N, 8.32.

5-(3-Methyl-5-isoxazoyl)-4,7-dimethoxy-6-hydroxybenzofuran (14), 5-(5-Methyl-3-isoxazoyl)-4,7-dimethoxy-6-hydroxybenzofuran (15), and 1-(4,7-Dimethoxy-6-hydroxy-5-benzofuranyl)-1,3-butanedione Dioxime (15'). A solution of khellin (**9**) and hydroxylamine hydrochloride (2 g) was refluxed in pyridine (50 mL) for 5 h according to Schonberg and Sidky.[23] Column chromatography of the crude extract and benzene elution yielded **15** (110 mg, 6%), mp 124–126 °C (from ether).

Anal. Calcd for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.73; N, 5.09. Found: C, 61.06; H, 4.73; N, 5.06.

Further elution (benzene–ether, 4:1) yielded **14** (1.41 g, 67%), mp 120 °C (from ethanol–water).

Final elution with pure ether yielded **15'** (0.21 g, 10%) purified by column chromatography, preparative thin layer chromatography, and crystallization: mp 155–159 °C (methanol–ether); IR ν_{max} 3400 (OH), 1620 cm^{-1} (C=N); NMR (CD_3OD) δ 1.6 (s) CH_3, 3.6 (m) $-CH_2-$. The mass spectrum shows peaks at *m/e* 308 (M^+), 275.

Anal. Calcd for $C_{14}H_{16}O_6N_2$: C, 54.54; H, 5.19; N, 9.09. Found: C, 54.69; H, 5.28; N, 9.06.

1-(4,7-Dimethoxy-6-hydroxy-5-benzofuranyl)-3-amino-2-buten-1-one (16). Under the same hydrogenation conditions as used for **10**, the isoxazole **14** yielded **16**: mp 87 °C (from ether); IR ν_{max} 3480 (OH), 1640–1600 cm^{-1} (C=C, C=O); NMR δ 2.02 (s, $W_{1/2}$ = 0.8 Hz, CH_3C=C), 6.2 (s, $W_{1/2}$ = 0.8 Hz, CH_3C=CH). The mass spectrum shows peaks at *m/e* 277 (M^+), 220, 205.

Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.41; N, 5.05. Found: C, 60.92; H, 5.64; N, 5.22.

Deuteration of 16. 16 (100 mg) was refluxed with MeOD (1 mL), D_2O (1 drop), and a small piece of sodium for 2 h. After workup **16-d_4** was obtained. NMR: the peaks at δ 2.02 and 6.2 have disappeared. The mass spectrum shows peaks at *m/e* 281 (277 + 4) (M^+), 220, 203, 177.

4,9-Dimethoxy-7-methyl-5*H*-furo[3,2-*g*]-1-benzopyran-5-one Oxime (Khellin Oxime, 17). Our oximation method on khellin (see **8**) yielded **17** (84% yield), mp 224–225 °C dec (from acetone–ether).

Anal. Calcd for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09. Found: C, 60.94; H, 4.86; N, 4.94.

Deoximation of 17. 17 (100 mg) was refluxed with sodium bisulfite (0.5 mL) for 1 h, acidified with diluted HCl, and then worked up. After

crystallization from methanol and filtration on a column of silica, khellin, identical with **9**, was obtained.

Registry No.—**1**, 525-82-6; **2**, 22115-89-5; **7**, 491-38-3; **8**, 61348-46-7; **9**, 82-02-0; **10**, 61348-47-8; **11**, 61348-48-9; **12**, 30992-84-8; **14**, 61348-49-0; **15**, 61348-50-3; **15'**, 61348-51-4; **16**, 61348-52-5; **17**, 61348-53-6; hydroxylamine hydrochloride, 5470-11-1.

References and Notes

(1) (a) S. Fried in "Heterocyclic Compounds", Vol. 2, R. C. Elderfield, Ed., Wiley, New York, N.Y., 1950, p 254; (b) L. F. Cavalieri, *Chem. Rev.*, **41**, 525 (1947).
(2) The oximes may be obtained by indirect methods, the most common of which involves first the formation of the pyrthione which is then treated with the nucleophile. This method has not found wide application because of (1) low yields, (2) by-products formation, and (3) lack of generality.[3]
(3) For a comprehensive review, see R. Beugelmans and C. Morin, to be published.
(4) K. Gulati and J/ Ray, *Curr. Sci.*, **5**, 75 (1936); *Chem. Abstr.*, **30**, 8214 (1936).
(5) W. Baker, J. B. Harborne, and W. D. Ollis, *J. Chem. Soc.*, 1303 (1952).
(6) G. Wittig and F. Bangert, *Chem. Ber.*, **58B**, 2636 (1925).
(7) W. Basinski and Z. Jerzmanowska, *Rocz. Chem.*, **48**, 2217 (1974).
(8) (a) R. Beugelmans and C. Morin, *Tetrahedron Lett.*, 2145 (1976); (b) C. Morin, Thèse de Docteur-Ingénieur, Orsay, 1976
(9) (a) M. W. Moon and J. C. Sharp, German Offen. 2 513 652; *Chem. Abstr.*, **84**, P30890 (1976). (b) J. Colonge and A. Guyot, *Bull. Soc. Chim. Fr.*, 329 (1958).
(10) A. Krishna Murthy, K. Krishna Mohan Rao, and N. Subba Rao, *Aust. J. Chem.*, **21**, 2315 (1968).
(11) P. Crabbé, L. A. Maldonado, and I. Sanchez, *Tetrahedron*, **27**, 711 (1971).
(12) (a) J. Bowie, R. Kallury, and R. Cooks, *Aust. J. Chem.*, **22**, 563 (1969); (b) G. Aldous and J. Bowie, *Org. Mass Spectrom.*, **10**, 64 (1975).
(13) M. Ohashi, H. Kamachi, H. Kakisawa, A. Tatematsu, H. Yoshizumi, H. Kano, and H. Nakata, *Org. Mass Spectrom.*, **2**, 195 (1969).
(14) D. Nonhebel, *Org. Mass Spectrom.*, **3**, 1519 (1971).
(15) C. Beam, M. Dyer, R. Schwarz, and C. Hauser, *J. Org. Chem.*, **35**, 1806 (1970).
(16) G. D'Alcontres, *Gazz. Chim. Ital.*, **80**, 441 (1950).
(17) N. Kochetkov and S. Sokolov, *Adv. Heterocycl. Chem.*, **2**, 416 (1969).
(18) G. Stork, M. Ohashi, H. Kamashi, and H. Kakisawa, *J. Org. Chem.*, **36**, 2784 (1971).
(19) C. Kashima, S. Tobe, N. Sugiyamo, and M. Yamamoto, *Bull. Chem. Soc. Jpn.*, **46**, 310 (1973).
(20) G. Buchan and A. Turner, *J. Chem. Soc., Perkin Trans. 1*, 2115 (1975).
(21) The formation of similar dioximes has previously been reported; see ref 6, 22.
(22) M. A. F. Elkaschef, F. M. E. Abdel-Megeid, K. E. M. Mokhtar, and M. F. Elbarnashawi, *Indian J. Chem.*, **11**, 860 (1973).
(23) A. Schonberg and M. M. Sidky, *J. Am. Chem. Soc.*, **75**, 5128 (1953).
(24) C. Kashima and Y. Tsuda, *Bull. Chem. Soc. Jpn.*, **46**, 3533 (1973).
(25) R. Wasylishen, J. Rowbotham, and T. Schaefer, *Can. J. Chem.*, **52**, 833 (1974).
(26) Vinylic proton does indeed exchange in vinylogous amides; see Y. Tamura, H. Ishibashi, M. Hirai, Y. Kita, and M. Ikeda, *J. Org. Chem.*, **40**, 2703 (1975).
(27) D. Ostercamp, *J. Org. Chem.*, **30**, 1169 (1965).
(28) C. Kingsbury and J. Cooker, *J. Org. Chem.*, **40**, 1120 (1975).
(29) Other studies whose results are similar have been recently published; see ref 30–32.
(30) P. Joseph-Nathan, J. Mares, C. Hernandez, and J. Schoolery, *J. Magn. Reson.*, **16**, 447 (1974).
(31) B. Ternai and K. Markham, *Tetrahedron*, **32**, 565 (1976).
(32) I. Still, N. Plavac, D. Mc Kinnon, and M. Chauhan, *Can. J. Chem.*, **54**, 280 (1976).
(33) M. Chauhan and I. Still, *Can. J. Chem.*, **53**, 2880 (1975).
(34) N. Platzer, J.-J. Basselier, and P. Demerseman, *Bull. Soc. Chim. Fr.*, 905 (1974).
(35) M. Yamazaki, Y. Maebayashi, H. Katoh, J. Ohishi, and K. Koyama, *Chem. Pharm. Bull.*, **23**, 573 (1975).
(36) M. Tanabe, T. Hamasaki, H. Seto, and L. Johnson, *Chem. Commun.*, 1539 (1970).
(37) K. Kakinuma, C. Hanson, and K. Rinehart, Jr., *Tetrahedron*, **32**, 219 (1976).
(38) J. Torri and M. Azzaro, *Bull. Soc. Chim. Fr.*, 1633 (1974).
(39) D. Marr and J. Stothers, *Can. J. Chem.*, **43**, 596 (1965).
(40) J. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972, p 197.
(41) S. Pines, J. Chemerda, and M. Kozlowski, *J. Org. Chem.*, **31**, 4446 (1966).
(42) A radiocrystallographic study of a suitable crystalline derivative of the khellin oxime (methyl ether) carried out by Dr. Guilhem (I.C.S.N., C.N.R.S., Gif-sur-Yvette) which will be published elsewhere confirms the oxime structure of **17** and therefore also the structures **8** and **2**. The khellin oxime methyl ether has the geometry anti, which is the more stable one. This result does not allow us to ascribe the stereochemistry of the parent oxime.
(43) We believe that under our conditions the chromone behaves like a 4-hydroxypyrilium derivative and the nucleophilic attack occurs at position 4 as has been observed on other pyrylium compounds bearing a leaving group in position 4 [see J. Farkas, B. Costisella, M. Rabosi, H. Gross, and R. Bognar, *Chem. Ber.*, **102**, 1333 (1969); S. Yoneda, T. Sugimoto, O. Tanaka, Y. Moriya, and Z. Yoshida, *Tetrahedron*, **31**, 2669 (1975)].
(44) The ^{13}C NMR spectra of the isoxazoles have been recorded; they are different from those of the isomeric oximes but do not allow differentiation between isomeric isoxazoles [see G. M. Buchan and A. B. Turner, *J. Chem. Soc., Perkin, Trans. 1*, 2115 (1975)].
(45) **Notes Added in Proof.** (i) W. Basinski and Z. Jerzmanovska, *Rocz. Chem.*, **50**, 1067 (1976), report that flavone **1** heated with hydroxylamine hydrochloride in pyridine yields oxime **2** and a coproduct previously assigned structure **3** (**5**) but now reassigned as the isomeric 3-phenyl-5-*o*-hydroxyphenylisoxazole. (ii) Recently a number of pryones and flavones ^{13}C studies relevant to our work have appeared: M. J. Looks, L. R. Weingarten, and R. Levin, *J. Am. Chem. Soc.*, **98**, 4571 (1976); C. A. Kingsbury, M. Clifton, and J. H. Looker, *J. Org. Chem.*, **41**, 2777 (1976); A. Pelter, R. S. Ward, and T. I. Gray, *J. Chem. Soc., Perkin Trans. 1*, 2475 (1976). (iii) We have been able to improve the yield of oxime formation by passing dry gaseous hydrogen chloride in anhydrous methanol until pH 1 is reached; thus khellin oxime (**17**) is obtained in >95% yield.

Selective Monodeoxygenation of Certain Quinoxaline 1,4-Dioxides with Trimethyl Phosphite

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Received November 8, 1976

The reduction of some 2,3-disubstituted quinoxaline 1,4-dioxides with trimethyl phosphite in refluxing alcohol solvent furnished the corresponding monooxides selectively in good yield. Deoxygenation occurred exclusively at the nitrogen adjacent to carbon bearing an electron-withdrawing group. These results are quite remarkable when compared with the reduction of the same quinoxaline 1,4-dioxides with other commonly used reducing agents such as phosphorus trichloride and sodium dithionite which afforded a mixture of isomeric monooxides and dideoxygenated product. The scope and limitations of this reaction are discussed.

Recent interest in the preparation and reactions of quinoxaline 1,4-dioxides (QNO's) has remained at a high level[1] owing in part to the commercial importance of this class of compounds. For example, the QNO carbadox[2] is highly effective as a growth promotant for swine.[3] Quinoxaline monooxides have been isolated as QNO metabolites in several different experimental animals.[4] We desired to prepare a number of quinoxaline 1-oxides for biological study, and have discovered that trimethyl phosphite is a superior reducing agent for the selective monodeoxygenation of certain QNO's.

Although trialkyl phosphites have been used in several instances for the deoxygenation of heterocyclic *N*-oxides, to our knowledge their application in the QNO series has not been reported. Emerson and Rees[5] were able to reduce pyridine 1-oxides with triethyl phosphite in diethylene glycol diethyl