Reinvestigation of the Rearrangement of 2-Acetylbenzofuran Oxime Tosylate

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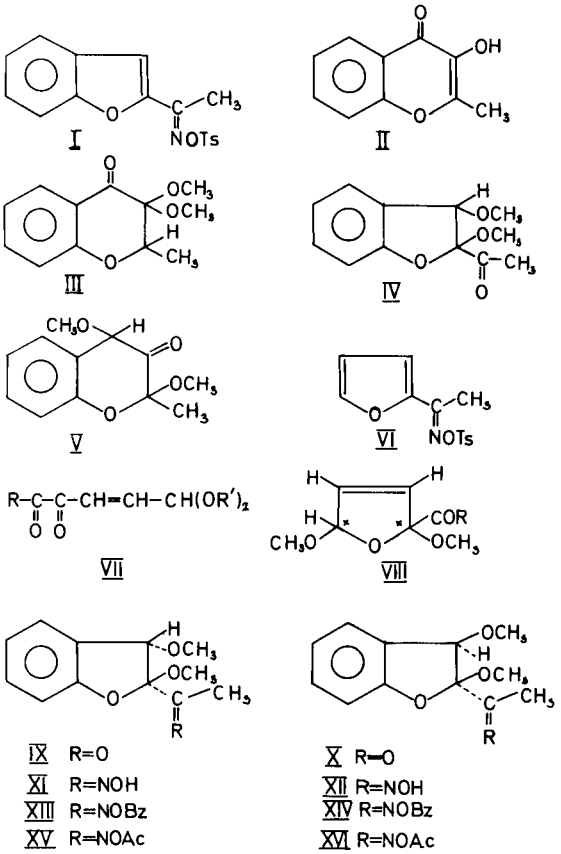
The acetal, resulting from the rearrangement of *anti*-2-acetylbenzofuran oxime tosylate (I) was proved to be a mixture of *trans*- (IX) and *cis*- (X) 2,3-dihydro-2-acetyl-2,3-dimethoxybenzofuran. The structure of these isomers as well as that of their oximes XI and XII was elucidated by ir, nmr, and mass spectral investigation and by the ir and nmr spectra of the benzoyl (XIII and XIV) and acetyl (XV and XVI) derivatives of the oximes. A new reaction mechanism concerning the rearrangement process is discussed.

Introduction.

The rearrangement of *anti*-2-acetylbenzofuran oxime tosylate (I) in aqueous methanol, leading to 2-methyl-3-hydroxychromone (II) and an acetal (III) was first described by Vargha, *et al.* (2). Some years later Geissman and Armen (3) reinvestigated this reaction, confirming the structure of compound II, but questioning both the structure of the acetal III and the proposed reaction mechanism. Due to spectroscopic data, structure IV was taken into consideration for the acetal, but was discarded due to some negative reactions. Finally structure V and a new reaction mechanism for the formation of this compound were suggested (3).



In 1958, Vargha, *et al.* published a series of papers (4-7) dealing with the structure and reactivity of different furyl-2-ketoxime derivatives, including 2-acetylbenzofuran, but no new structure was suggested for the acetal III. Later Greene and Lewis (8) investigating the acid-catalysed rearrangement of 2-acetylfuran oxime tosylate (VI), could show that the diacetal formed possesses, instead of structure VII proposed earlier (9), the cyclic structure VIII. They succeeded in separating the *cis*- and *trans*-isomers by fractional distillation and proved their structure by nmr investigation. These facts led to our reinvestigation of the rearrangement of the corresponding benzofuran derivative I.

Results.

Glc investigation of the "acetal", obtained from 2-acetylbenzofuran oxime tosylate (I) according to the literature (2) revealed the presence of two main components *A* and *B* in the ratio 3:7. They were separated by preparative glc and proved to be isomers based upon their analytical data. They gave different oximes, the one from compound *B* being identical with the oxime obtained earlier from the acetal mixture (2). Both oximes gave the chromone derivative II on acidic hydrolysis. The structure of the two isomeric acetals *A* (IX) and *B* (X) as well as that of their oximes XI and XII was elucidated by ir, nmr, and mass spectral investigation and by the ir

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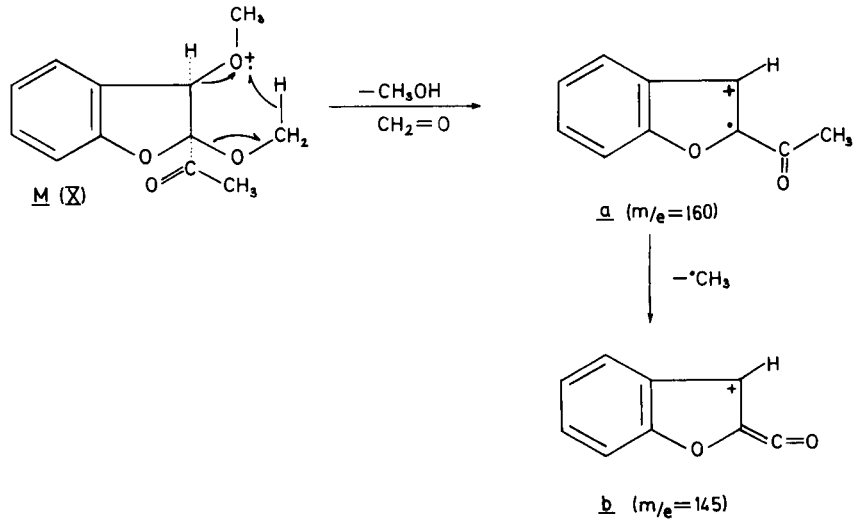

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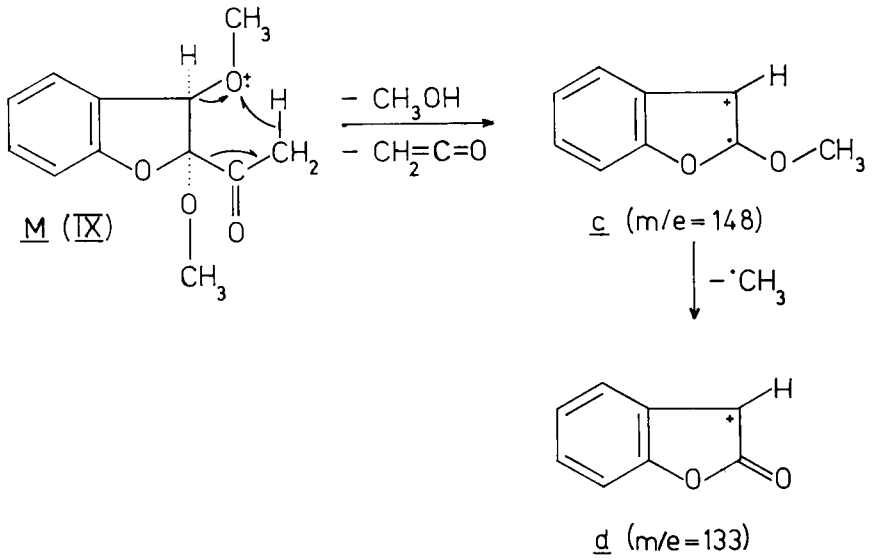


and nmr spectra of the benzoyl (XIII and XIV) and acetyl (XV and XVI) derivatives of the two oximes.

Ir and Nmr Investigation.

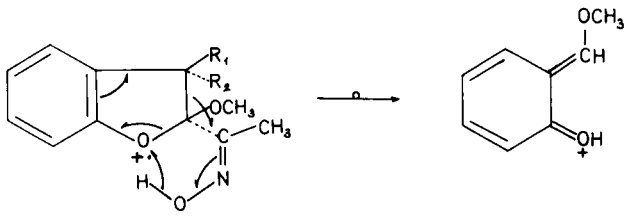
From the ir and nmr data of compounds IX-XVI (Table I) the following conclusions can be drawn:

The high carbonyl frequency (1735 cm^{-1}) in the ir and the singlets of the *C*-methyl and methyne protons in the nmr spectra of the isomeric acetals excludes both structure III, which should give a carbonyl frequency (11) of about 1650 cm^{-1}, a methyl doublet and a methyne quartet, and structure V with a predictable carbonyl frequency (12) of 1715^{-1} and a methyl singlet at about 1.3 ppm (13) (instead of the observed 2.33 and 2.39 ppm, respectively).

Structures IX and X were assigned to the isomers *A* and *B* based on the chemical shift of the methine proton which is shifted paramagnetically by 0.54 ppm in the spectrum of compound *A*. It is known that in saturated ring compounds acetyl and methoxy substituents have a stronger affect on the vicinal *trans* than on the vicinal *cis* protons, and that the former group causes a stronger paramagnetic shift (13) than the latter. Consequently, structure IX corresponds to compound *A* and structure X to *B*.

In accord with this assignment, a similar difference can also be observed in the chemical shift of the methyne protons in the nmr spectra of compounds XI-XVI. The oximes XI and XII give a $\Delta\ \delta$ CH value of 0.47 ppm and

SCHEME 3



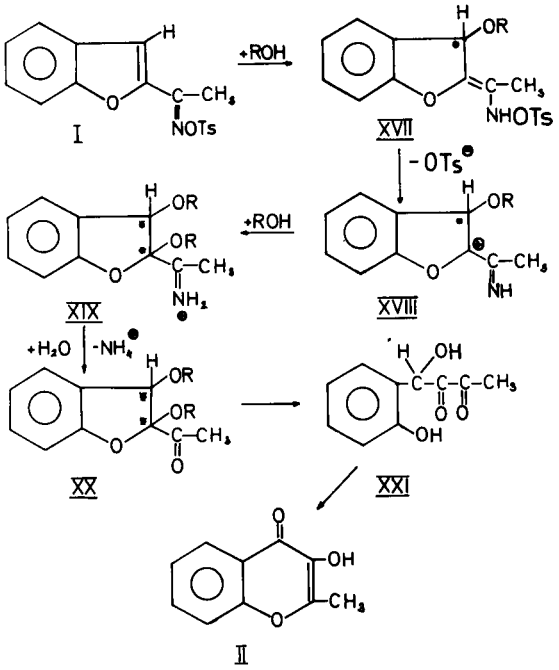
M

XI $R_1 = H$; $R_2 = OCH_3$

XII $R_1 = OCH_3$; $R_2 = H$

$\mathfrak{L}$ (m/e=137)

SCHEME 4



II

this difference is even greater in the benzoates XIII and XIV and the acetates XV and XVI (0.99 and 0.89 ppm, respectively), due to the stronger -I affect of the acyloxy groups. An anisotropic effect of the benzoyl group can be ruled out, since the benzoyl and acetyl groups cause similar shifts.

The different chemical shifts of the methoxy groups in IX and X as well as in their corresponding derivatives can be explained by the suggested structures also. In the *cis*-dimethoxy isomer X, the -I effect of the acetyl group will have a relatively stronger influence on the vicinal *trans* methoxy group than on the vicinal *cis* methoxy group in isomer IX. Consequently, the difference between the chemical shift of the two adjacent methoxy groups will become diminished in compounds X, XII, XIV, and XVI.

The same effect will also influence the hydrogen bridges of the oximes causing a stronger association in compound XII which can be detected in the nmr, δ OH (XII) > δ OH (XI) as well as in the ir spectrum ν OH (XII) < ν OH (XI). The shape of the ν OH band proves the *anti* structure of the oximes (14).

Mass Spectral Investigation.

The mass spectra of compounds *A* and *B*, excluded structures III and V because of the extremely high abundance of ion, m/e = 179, formed by the loss of $CO\text{-}CH_3$ from the molecular ion which, according to the literature (15), is only a favoured process in acetyl-group containing compounds like IV.

Interpreting the spectra, it was found that there are specific rearrangements on the basis of which the structure of compound *A* (IX) and *B* (X) could be proved.

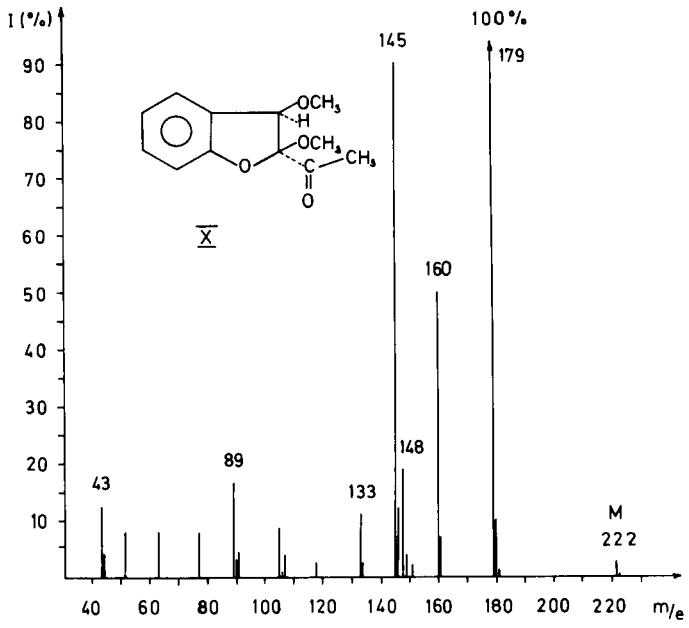


Figure 1a. 70 eV Mass Spectrum of *cis*-2,3-Dihydro-2-acetyl-2,3-dimethoxybenzofuran (X; compound *B*).

The influence of configuration on the fragmentation of di- and polymethoxy alicycles was discussed by Winkler and Grützmacher (16). A fragment ion, $(M\text{-}CH_2{=}O)$ was observed only if two methoxy groups were on the same side of an alicyclic ring in 1,3 or 1,4 position. The formation of this ion was explained by the interaction of the methoxy groups, *i.e.*, by hydrogen rearrangement from one methoxy group to the oxygen of the other and a consecutive homolytic fission. However, this ion could not be observed in 1,2 dimethoxy alicycles because of the more pronounced tendency for rupture of the ring by

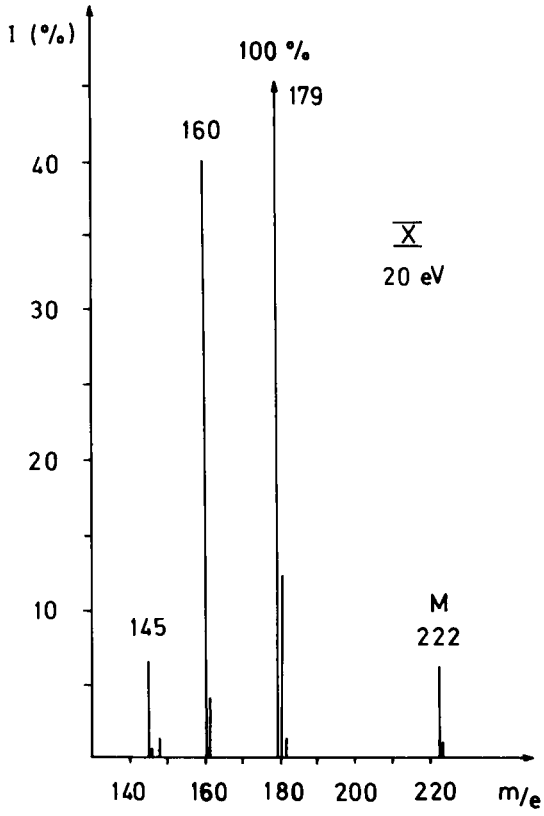


Figure 1b. 20 eV Mass Spectrum of *cis*-2,3-Dihydro-2-acetyl-2,3-dimethoxybenzofuran (X; compound *B*).

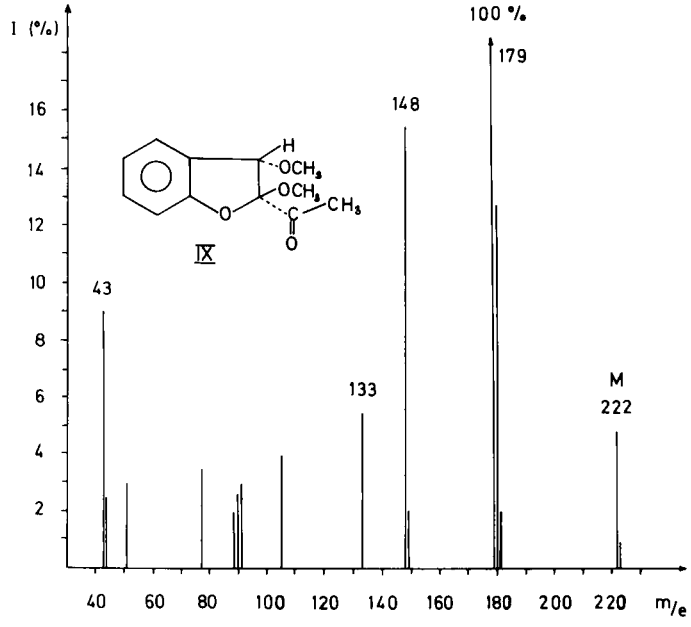


Figure 2b. 20 eV Mass Spectrum of *trans*-2,3-Dihydro-2-acetyl-2,3-dimethoxybenzofuran (IX; compound *A*).

Figure 2a. 70 eV Mass Spectrum of *trans*-2,3-Dihydro-2-acetyl-2,3-dimethoxybenzofuran (IX; compound *A*).

cleavage of the bond between the two substituated carbon atoms.

The appearance of ions (M - CH_2=O) and/or (M - CH_2=O - CH_3OH), formed by this kind of rearrangement was not reported on permethylated furanosides and pyranosides of appropriate configuration (17).

In our case this kind of rearrangement can take place only if the two methoxy groups are on the same side of the dihydrobenzofuran ring, *i.e.*, in structure X (Scheme 1). The resulting ion *a* will then be stabilized by the loss of ·CH_3 from the acetyl group yielding ion *b*. The appearance of these ions in contrast with compounds cited above is probably due to the presence of the condensed aromatic ring. Ions *a* and *b* can be observed only in the spectra of compound B (Figure 1a,b) and accordingly its structure has to be X.

The 20 eV spectrum of X (Compound *B*) confirms the fragmentation mechanism, depicted in Scheme 1 by the enhanced relative abundance of ion *a* and by the diminished one of ion *b* (18). Furthermore, the part below ion *a* of the 70 eV spectrum (Figure 1a) of X is qualitatively identical with the known mass spectrum (19) of 2-acetylbenzofuran.

The loss of alcohol from aliphatic ethers is ascribed to go, at least in part, *via* a six-membered ring transition

TABLE I

Ir and Nmr Data of Compounds IX-XVI

Compound	Ir (KBr) cm^{-1}		Nmr, δ TMS = 0 ppm ($CDCl_3$)				
	ν OH	ν C=O	δ CH	δ OCH_3	δ OCH_3	δ CH_3CO	δ OH
IX		1735	5.31	3.51	3.60	2.39	
XI	3400 (a)		5.20	3.46	3.56	2.03	9.4
XIII		1745	5.80	3.52	3.72	2.31	
XV		1775	5.67	3.51	3.68	2.18	
X		1735	4.77	3.38		2.33	
XII	3210 (b)		4.73	3.29	3.33	2.06	10.1
XIV		1745	4.81	3.37	3.46	2.23	
XVI		1745	4.78	3.37	3.42	2.12 2.24	

(a) Sharp. (b) Broad.

TABLE II

Relative Abundances of Ion *e* and (*e* + 1) in the Mass Spectra Investigated in Percent.

	IX	X	XI	XIa	XII
e (m/e = 137)	1.0	1.0	20.0	16.2	22.0
e + 1 (m/e = 138)	-	-	5.0	6.5	2.5

state (20). If the 2-acetyl and 3-methoxy groups are situated on the same side of the dihydrobenzofuran ring (structure IX), the above process yields ion *c* by the rearrangement of one hydrogen from the acetyl to the methoxy group, followed by the elimination of ketene and methanol (Scheme 2). Ion *c* will then be stabilized by the loss of $\cdot CH_3$ from the remaining methoxy group yielding ion *d*.

Ions *c* and *d* are almost equally abundant in the 70 eV spectra of X (Figure 1a) and IX (Figure 2a), respectively, due to the alternative possibility for the formation of ion *c* by the loss of $\cdot OCH_3$ from ion M-·CO-CH_3 (m/e = 179). However, in the 20 eV spectrum of IX (Figure 2b) the relative abundance of ion *c* remains almost the same as in the 70 eV one, while in that of X it decreases to 5% of the value of the 70 eV spectrum, confirming (18) the formation of ion *c* by rearrangement in the former and by simple cleavage in the latter compound.

For compound *A* the possible isomeric structure, containing the two methoxy groups in position 3 could be ruled out because of the lack of the characteristic fragmentation of geminal diethers (21) and because of a rearrangement ion (*e*), found in the spectrum of oxime XI, containing C_3 but only one methoxy group (Scheme 3). This ion was shifted towards *e*+1 in the spectrum of the partially *O*-deuterated oxime XIa (Table I).

Mass measurements on ions shown in Schemes 2 and 3 were made on the corresponding peaks of the oxime XI and are listed in Table II.

Discussion.

The structure elucidation of the acetyl isomers IX and X enabled us to reevaluate the reaction mechanism (2,3) proposed for the rearrangement of the oxime tosylate I. The mechanism, suggested by Dunlop and Peters (10) for the rearrangement of 2-acetofuran oxime tosylates can be applied with some alterations to the benzofuran derivative I (Scheme 4).

The conjugated double bonds of the furan ring and the oxime may undergo a 1,4-type addition yielding intermediate XVII. As the RO group may attack the furan ring from both sides, XVII will be a racemate. Rearrangement of the double bond accompanied by the subsequent loss of the tosylate anion leads to the carbonium cation XVIII, which may be attacked from either side by a second RO group, forming a mixture of four isomers (XX), containing a racemate with the methoxy groups at C-2 and C-3 in *trans* position (IX) and one with the same groups in *cis*-position (X). The shift of the ratio of these racemates towards the *cis*-derivative X can be explained by steric effect as those molecules having the bulky acetyl group in a position *trans* to the methoxy group at C-3 will be energetically favoured compared to those with the same groups in the *cis* position.

If ROH taking part in this reaction is an alcohol, the two resulting racemates IX and X are stable compounds and can be separated. However, when ROH is water, the mixture of the resulting hydroxy compounds XX (R = H) will rearrange to the diketone XXI, which immediately forms the cyclic hydroxychromone II.

The heretofore unexplained stability of IV towards acids may be due to the presence of the carbonyl oxygen which will be protonated first, preventing a further protonation at the adjacent furan or methoxy oxygen. The oxime of compound IV, however, can be hydrolized to the hydroxychromone II, as the oxime group will not prevent protonation of the oxygens as mentioned above.

EXPERIMENTAL

Melting points are uncorrected. Nmr spectra were recorded at 60 MHz with a Varian A-60D spectrometer, using TMS as the internal standard. Mass spectra were recorded on a Varian MAT-SM-1 instrument under the following operating conditions: resolution 1250; electron energy 70 *vs.* 20 eV; source temperatures 150° (for IX and X) and 250° (for XI, XIa and XII); evaporation temperatures 0° (for IX and X), 20° (for XI and XIa) and 37° (for XII). Mass measurements were made at resolution 10,000, using PFK as reference standard.

Preparative glc was carried out on a F-21 Perkin Elmer gas

TABLE III

Mass Measurements of Some Ions of Compound XI

m/e	Symbol	Mass Decimals measured	Mass Decimals required for	Elemental composition	Difference (ppm)
237	*M*	.100297	.10011	$C_{12}H_{15}NO_4$	0.6
148	*c*	.052327	.05243	$C_9H_8O_2$	0.7
137	*e*	.060008	.06026	$C_8H_9O_2$	1.8
133	*d*	.029213	.02896	$C_8H_5O_2$	1.9

chromatograph. Tlc was carried out on Kieselgel G coated microscope slides using carbon tetrachloride-ethyl acetate 5:1 (1) and 10:1 (2) as solvent. Detection was by 0.1 *M* potassium permanganate in 2 *N* sulfuric acid (1:1) at 100°.

All evaporations were carried out in a rotary evaporator under diminished pressure after drying the organic solutions over sodium sulphate.

Trans-2,3-Dihydro-2-acetyl-2,3-dimethoxybenzofuran (IX) and *cis*-2,3-Dihydro-2-acetyl-2,3-dimethoxybenzofuran (X).

The mixture of the acetals (2) was separated by preparative glc using a 8 mm x 2m QF-1 column. Temperature: 200°; carrier: nitrogen; pressure: 0.8 atm. Retention time of the *trans* isomer IX was 16 minutes and that of the *cis* isomer X, 22.5 minutes.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: for IX: C, 64.92; H, 6.45; for X: C, 64.73; H, 6.51.

Trans-2,3-Dihydro-2-acetyl-2,3-dimethoxybenzofuran Oxime (XI).

A solution of the *trans* isomer IX (1.4 g.) in ethanol (16 ml.) was boiled for 4 hours in the presence of hydroxylamine hydrochloride (0.63 g.) and sodium acetate (0.63 g.). The evaporated residue was treated with water to give after recrystallization from 70% ethanol (2.5 ml.), oxime XI (0.7 g., 47%), m.p. 107-109°; R_f 0.6 (solvent 1).

Anal. Calcd. for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.33; N, 5.91. Found: C, 60.78; H, 6.42; N, 6.05.

Cis-2,3-Dihydro-2-acetyl-2,3-dimethoxybenzofuran Oxime (XII).

The *cis* isomer X (1.4 g.) gave in a similar treatment oxime XII (0.95 g., 63%), m.p. 156-157°, R_f 0.6 (solvent 1) (lit. (2) m.p. 156-157°).

Benzoylation of the Oximes.

A solution of oxime XI (0.25 g. in pyridine (2 ml.) was treated with benzoyl chloride (0.2 ml.). The mixture was kept at room temperature overnight, then diluted with water and extracted with chloroform. The organic solution was washed, dried and evaporated to yield after recrystallization from ethanol (3 ml.) the oxime benzoate XIII (0.1 g., 28%, m.p. 82-83°), R_f 0.55 (solvent 2).

Anal. Calcd. for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.11. Found: C, 67.02; H, 5.72; N, 4.28.

The same treatment of oxime XII (0.25 g.) afforded the benzoate XIV (0.14 g.) 39%, m.p. 142-143°, R_f 0.75 (solvent 2) (lit. (2) m.p. 140°).

Hydrolysis of the Oximes.

The oximes (0.5 g.) were hydrolysed in ethanol (10 ml.) and 2 *N* sulfuric acid (10 ml.) at 100° for 2 hours. The hydroxy chromone II was filtered after cooling and was washed with water. The *trans* isomer XI gave 0.20 g. of the *cis* isomer XII, 0.15 g. of II, m.p. 183-184°, alone and in admixture with authentic II.

REFERENCES

(1) To whom correspondence should be addressed.

(2) L. Vargha, J. Ramonczai, and J. Báthory, *J. Am. Chem. Soc.*, 71, 2652 (1949).

(3) T. A. Geissman and A. Armen, *ibid.*, 77, 1623 (1955).

(4) G. Ocskay and L. Vargha, *Tetrahedron*, 2, 140 (1958).

(5) L. Vargha and G. Ocskay, *ibid.*, 2, 151 (1958).

(6) L. Vargha and G. Ocskay, *ibid.*, 2, 159 (1958).

(7) L. Vargha and G. Ocskay, *Acta Chim. Acad. Sci. Hung.*, 19, 143 (1959).

(8) B. B. Greene and K. G. Lewis, *Tetrahedron Letters*, 39, 4759 (1966); *Aust. J. Chem.*, 21, 1845 (1968).

(9) L. Vargha, J. Ramonczai, and P. Bite, *J. Am. Chem. Soc.*, 70, 371 (1948).

(10) A. P. Dunlop and F. Peters, "The Furans," Reinhold, New York, N. Y., 1953, p. 659.

(11) P. Sohár, L. Vargha, and J. Kuszmann, *Acta Chim. Acad. Sci. Hung.*, 70, 79 (1971).

(12) S. Holly and P. Hohár, "Infrared Spectroscopy," Müszaki Kiadó, Budapest, 1968.

(13a) H. Suhr, "Anwendungen der Kernmagnetischen Resonanz in der organischen Chemie," Springer-Verlag, Berlin, (1965). (b) C. A. Reilly and J. D. Swalen, *J. Chem. Phys.*, 34, 980 (1961). (c) F. S. Mortimer, *J. Mol. Spectrosc.*, 5, 199 (1960). (d) J. D. Graham and M. T. Rogers, *J. Am. Chem. Soc.*, 84, 2249 (1962). (e) D. J. Patel, M. E. H. Howden, and J. D. Roberts, *ibid.*, 85, 3218 (1963).

(14) P. Sohár, Gy. Varsányi, L. Vargha, and G. Ocskay, *Acta Chim. Acad. Sci. Hung.*, 40, 431 (1964).

(15) P. E. Butler, *J. Org. Chem.*, 29, 3024 (1964).

(16) J. Winkler and H. F. Grützmacher, *Org. Mass Spectrom.*, 3, 1139 (1970).

(17a) N. K. Kochetkov and O. S. Chizhov, "Advances in Carbohydrate Chemistry," Vol. 21, M. L. Wolfrom, Ed., Academic Press, New York, N. Y., 1966. (b) K. Heyns, H. F. Grützmacher, H. Scharmann, and D. Muller, *Fortschr. Chem. Forsch.*, 5, 448 (1966).

(18) *Cif. e.g.:* (a) D. H. Williams and R. G. Cooks, *Chem. Commun.*, 663 (1968). (b) R. G. Cooks, I. Howe, and D. H. Williams, *Org. Mass Spectrom.*, 3, 137 (1969).

(19) B. Willhalm, A. F. Thomas, and F. Gautschi, *Tetrahedron*, 20, 1185 (1964).

(20a) G. Spiteller and M. Spiteller-Friedmann, *Monatsh. Chem.*, 95, 257 (1964). (b) C. Djerassi and C. Fenselau, *J. Am. Chem. Soc.*, 87, 5747 (1965).

(21a) R. B. LeBlanc, *Anal. Chem.*, 30, 1797 (1958). (b) W. H. McFadden, J. Wasserman, J. Corse, R. E. Lundin, and R. Teranishi, *ibid.*, 36, 1031 (1964).