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SYNTHESIS AND UV ABSORPTION SPECTRA OF 5-ISOXAZOLEPOLYENE ALDEHYDES

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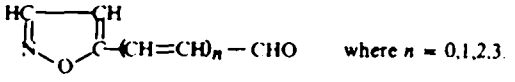
Abstract– The preparation and UV spectra of a series of 5-isoxazolepolyene aldehydes are reported and discussed. A linear relationship between the λ^2_{max} and the number of double bonds was found. A simple LCAO-MO calculation on this series of compounds and on the corresponding 2-furanepolyene aldehydes was carried out to interpret the experimental data.

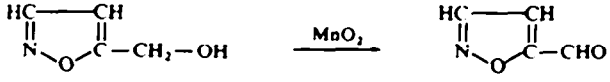
THE aim of this work is the preparation and the spectroscopic study of a new series of isoxazole derivatives, namely 5-isoxazolepolyene aldehydes with general formula



where $n = 0,1,2,3$.

A comparison of the UV spectra and Hückel MO charge distribution in these compounds with the corresponding 2-furanepolyene aldehydes, has provided useful information concerning the conjugation of the heterocyclic ring with the side chain.

The first member of the series, 5-isoxazolecarbaldehyde (II), was obtained,[1] originally as an intermediate in the preparation of the corresponding oxime, but the yield was low and compound II was not isolated. Compound II is better prepared by oxidation of I with MnO_2 in chloroform.



I II

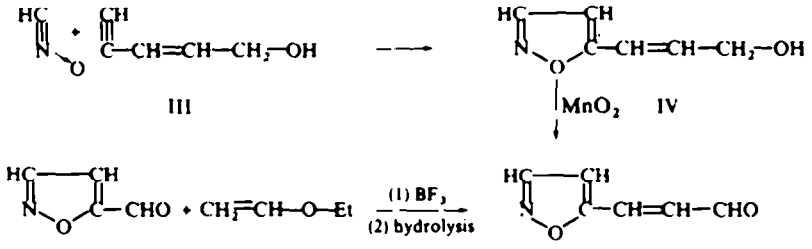
The yield depends mainly on the degree of activation of MnO_2 and under the best conditions was higher than 50% in aldehyde. Alcohol I and aldehyde II were easily separated because of the difference in their b.ps. Of the two different methods reported for the preparation of I, the first[2] gave a low yield, and the second[2] required a long series of reactions. Good results were obtained by a modification of the first method: the sodium fulminate solution was added more slowly and a dilute sulphuric solution containing a large excess of propargyl alcohol was used. The yield was over 90%

[1] A. Ricca and G. Gaudiano, *Atti Accad. naz. Lincei. Rend. Classe Sci. fis. mat. nat.* **26**, 240 (1959).

[2] A. Quilico and G. Stagno D'Alcontres, *Gazz. Chim. Ital.* **79**, 654 (1949).

with respect to the fulminate and again the products were easily separated because of the difference in the b.ps of the propargyl alcohol and I.

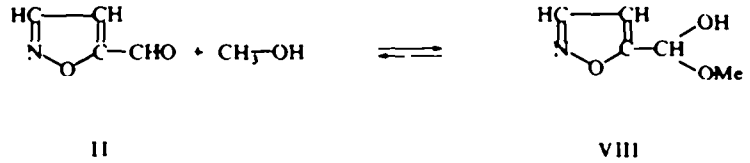
Because of instability of γ-unsubstituted isoxazoles in alkali, it was necessary to avoid the use of basic solutions during the preparation of 5-isoxazolepolyene aldehydes. The 3-(5-isoxazolyl)propenale (V) was prepared by two different methods. The first is similar to that described for the preparation of II, the alcohol IV being obtained by fulminic synthesis using 2-penten-4-yn-1-ol (III). Compound IV was then oxidized to the corresponding aldehyde V. In the other method ethyl vinyl ether was added to aldehyde II with BF_3 as catalist.[3] The hydrolysis of the intermediate product gave the aldehyde V.



The identity of the product obtained by the two methods[4] confirmed, once more, that the fulminic synthesis gives 5-substituted isoxazoles as reported.[5,6] Because of the difficulty of preparing large quantities of the alcohol III, we found it convenient to follow the second method even though the yield was only about 38%.

The homologous compounds VI and VII were prepared by reaction of ethyl vinyl ether on the aldehydes V and VI respectively.

UV spectra. The analysis and the IR spectrum of II were in agreement with the presence of a CO group on the isoxazole ring, but its UV spectrum in methanol (Fig. 1), shows one max at 214 mμ, which is at the same wavelength as isoxazole or any other 5-alkylisoxazole. This is due to II existing in methanol only as the hemiacetal VIII.



[3] H. Saikachi and H. Ogawa, *J. Am. Chem. Soc.* **80**, 3642 (1958).
[4] Both give the corresponding acid (m.p. 144–145°) by oxidation.
[5] A. Quilico and G. Speroni, *Gazz. Chim. Ital.* **69**, 508 (1939).
[6] A. Quilico and G. Speroni, *Gazz. Chim. Ital.* **70**, 779 (1940).

This behaviour is characteristic of many aldehydes like pyridinecarbaldehydes, nitro- and cyan-benzaldehydes.[7] If this is the case, the alcohol structure should have a marked influence on the aldehyde-hemiacetal equilibrium to the extent that conversion would decrease in the order primary > secondary > tertiary.

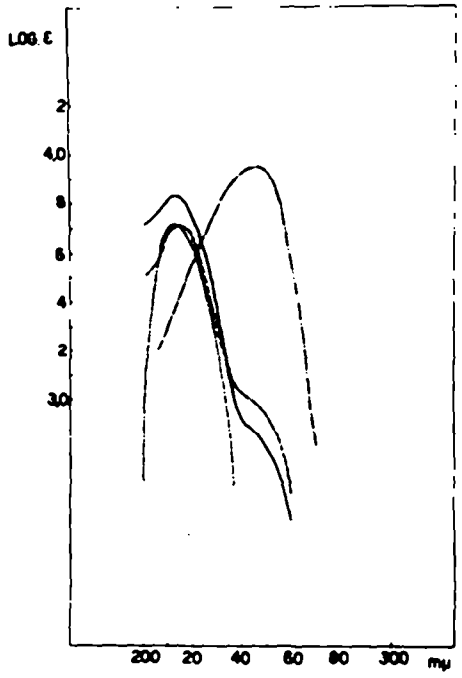


FIG. 1. Spectra of 5-isoxazolecarbaldehyde (II):
. . . in methanol. · · · in water. - - - in isopropyl alcohol. · · · · in cyclohexane.

This was confirmed by the UV spectrum of II in isopropyl alcohol, in which II shows a max (Fig. 1) at 214 mμ (log ε 3·8) and a shoulder at 245 mμ (log ε 2·8). In water, it is possible to identify two bands with different intensities (Fig. 1), but the spectrum of II in cyclohexane shows only one max (Fig. 1) at 244 mμ (log ε 3·9).

Further evidence of the formation of hemiacetal of II in methanol was obtained by recording the spectra of II in cyclohexane with 0·5–3 % of methanol. In this case two bands were recorded (Fig. 2), at 214 mμ and 244 mμ. The intensity of both max was related to the amount of methanol present in solution. The max at short wavelength increases with increasing methanol concentration, whereas that at 244 mμ decreases.

The diethyl acetal of II was also prepared and it was found that in methanol and cyclohexane it absorbs at the same wavelength as II in methanol.

The aldehyde V in cyclohexane shows a band at 276 mμ (log ε 4·3) (Fig. 3), red-shifted by 32 mμ with respect to II in the same solvent. Compound V in methanol has a broad band at 270 mμ (log ε 4·15), which could consist of two overlapping bands, one

[7] F. P. Crowell, W. A. Powell and C. J. Warsell, *Analyt. Chem.* 35, 184 (1963).

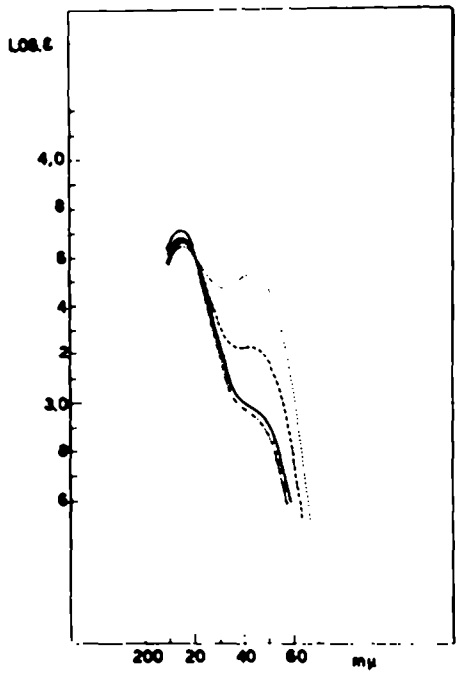


FIG. 2. Spectra of 5-isoxazolecarbaldehyde (II):
..... in cyclohexane + 0·5 MeOH. – – – in cyclohexane + 1% MeOH. – – – in cyclohexane + 2% MeOH. – · – · in cycloxhexane + 3% MeOH.

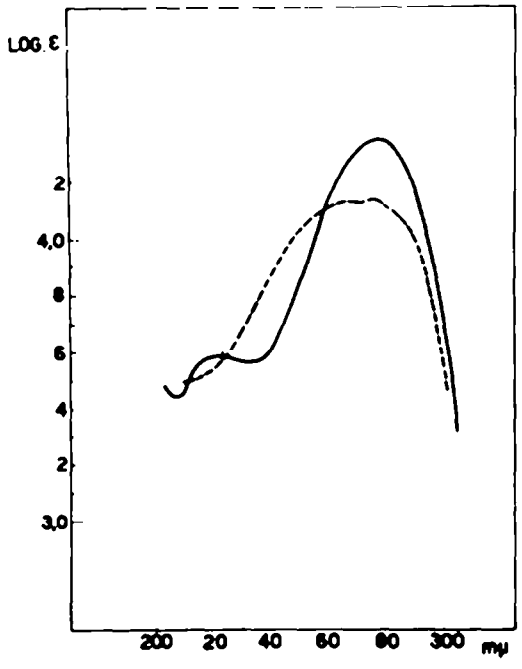


FIG. 3 Spectra of 3-(5-isoxazolyl)propenale (V):
— — in cyclohexane, · · · · in methanol.

due to the free aldehyde and the other to the hemiacetal. The latter can be expected to absorb at about 244 mμ.

Compound VI shows a band at 306 mμ (log ε 4·57) both in cyclohexane and methanol (Fig. 4); once more the band is red-shifted by 30 mμ with respect to V. In the first solvent a slight resolution can be noticed.

In cyclohexane VII has a band showing some vibrational structure (Fig. 4), the strongest absorption being at 334 mμ. In methanol the band is broader having two max at 334 and 345 mμ (log ε 4·66).

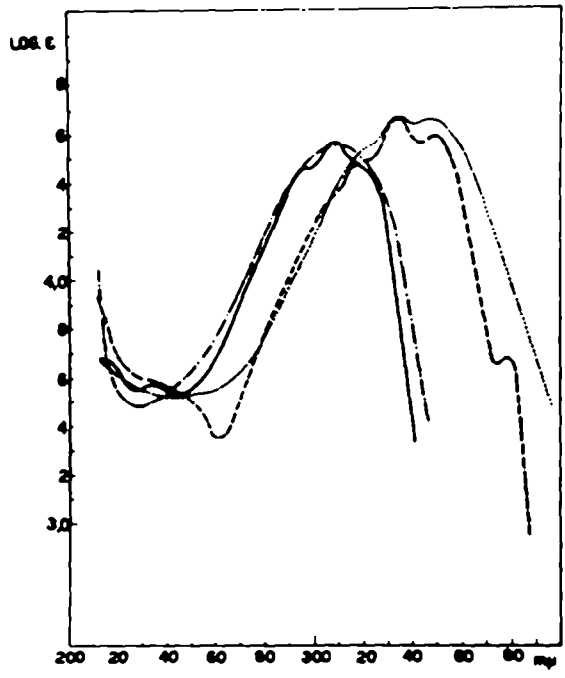


FIG. 4 Spectra of 5-(5-isoxazolyl)-2,4-pentadienale (VI):
– – – – in cyclohexane, – · – · in methanol.
Spectra of 7-(5-isoxazolyl)-2,4,6-eptatrienale (VII):
– · · – in cyclohexane, ... in methanol.

Ferguson[8] reported that for 2-furanepolyene aldehydes there is a linear relationship between λ^2_{max} and the number of double bonds, n. A linear relationship also exists for the 5-isoxazolepolyene aldehydes (Fig. 5). On the other hand, it is known[9] that by assigning the most intense absorption of the spectra of conjugated linear polyenes, α,ω-diphenylpolyenes and polyene aldehydes to the lowest energy allowed transition, it is possible to find linear relationships between the observed frequencies $\tilde{\nu}$, and the corresponding Hückel MO energy differences, Δm.

In order to find a similar correlation in the case of 5-isoxazolepolyene aldehydes

[8] L. N. Ferguson, *Electron Structure of Organic Molecules* p. 284, Prentice-Hall, Englewood Cliffs, N.J. (1952).

[9] A. Streitwieser, Jr., *Molecular Orbital Theory for Organic Chemists* p. 207. Wiley, New York-London (1961).

and to compare their properties with those of 2-furanepolyene aldehydes, we treated the π electrons of both series of compounds by the Hückel method.

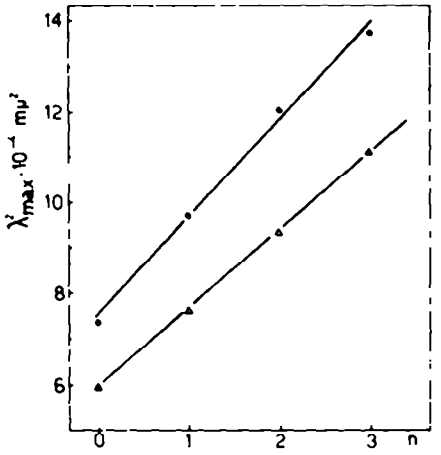


FIG. 5. Plot of λ^2_{max} versus the number of ethylenic bonds, n, in isoxazolepolyene aldehydes (Δ) and in furanepolyene aldehydes (O)

We used the parameters determined[10] for a large series of heterocyclic compounds, containing N and O, that is, according to Streitwieser's notations:

$h_O = 0{\cdot}65$ $h_\delta = 2{\cdot}6$ $K_{C\text{-}O} = 0{\cdot}7$ $K_{C\text{-}O} = 1$ $\delta_{\bar{1}} = \frac{1}{2\delta}$

$h_N = 0{\cdot}55$ $K_{N\text{-}O} = 0{\cdot}5$ $K_{C\text{-}N} = 1$ $\delta_{\bar{1}} = \frac{1}{1\delta}$

The energies of the occupied and the first unoccupied molecular orbitals are given

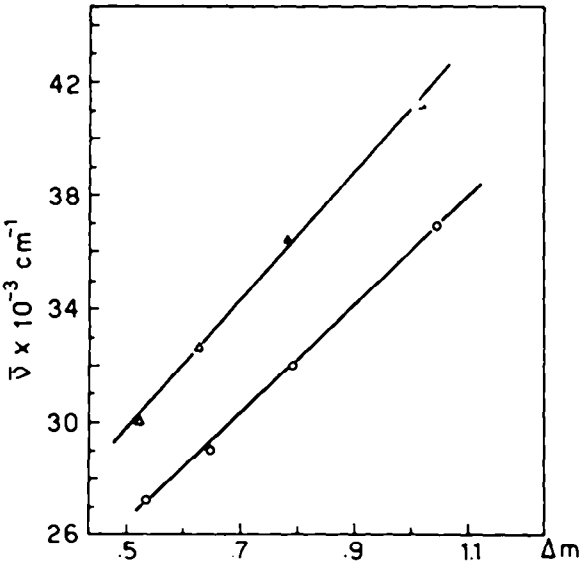


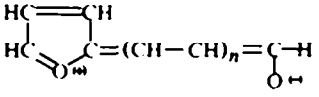
FIG. 6 Absorption spectra and HMO energy differences of isoxazolepolyene aldehydes (Δ) and furanepolyene aldehydes (o).

[10] R. Cencioni, P. F. Franchini and M. Orienti, *Tetrahedron*, to be published (1968).

in Table 1 in terms of $x = (\alpha - E)/\beta_0$. Fig. 6 shows that the relationships between Δm and $\bar{\nu}$ are linear for both series; the slopes correspond to $\beta_0 = -63{\cdot}2$ Kcal/mole for 5-isoxazolepolyene aldehydes and $\beta_0 = -55{\cdot}0$ Kcal/mole for 2-furanepolyene aldehydes. Both values are in the range of the values of β_0 found previously.[9]

Interpretation of the charge distribution of polyene aldehydes (Table 2) and a comparison with the values calculated for furane and isoxazole,[10] enable certain conclusions to be drawn.

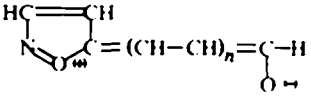
The introduction of the aldehyde group on the furane ring brings about, on the positions 2 and 4, a strong variation of net charge, which becomes positive. Such charges remain positive in all the 2-furanepolyene aldehydes investigated even if their values decrease because of charge redistribution on all the carbon atoms of polyene chain. The negative charge on the carbonyl oxygen increases with the increasing length of the chain, while the positive charge on the ring oxygen is essentially constant with a value approximately equal to that in furane. These results are in agreement with the hypothesis[11] that furane oxygen plays an effective part in conjugation. Therefore, beside the ionic structures with the positive charge on the even carbon atoms (Table 2), a structure like



is expected to contribute significantly.

The introduction of the aldehyde group has similar consequences in isoxazole. The net charge on position 4 becomes positive, while that on nitrogen has a less negative value than in isoxazole; the charge on the ring oxygen decreases, but is still about the calculated value for isoxazole. Yet, in contrast to the charge distribution in the series of 2-furanepolyene aldehydes, in the higher members of isoxazole series the charge on nitrogen tends rapidly to assume again the value taken in isoxazole; this trend, though less pronounced, is noticeable also for the charge on position 4, which again has a slightly negative value in the last member of the series.

This means that the contribution of a form like



decreases quickly with increasing length of polyene chain.

As can be seen from Table 2, in the furanepolyene aldehydes the alternating charge signs on the carbon atoms show that all double bonds are uniformly polarized by the highly polar C=O group while in isoxazolepolyene aldehydes there is no such alternation of sign due to the presence of the electronegative nitrogen atom. The electron-withdrawing effect of nitrogen atom also explains why 5-isoxazole-carbaldehyde, in contrast with 2-furaldehyde, gives the hemiacetal in methanol. However, the net charge difference on the carbonyl carbon, even if in the right sense, is too small to confirm the hypothesis[7] that the electron-withdrawing groups increase the positive character of the carbonyl carbon.

[11] E. R. Blout and M. Fields, *J. Am Chem Soc* **70**, 189 (1948)

TABLE 1. ENERGIES OF MOLECULAR ORBITALS

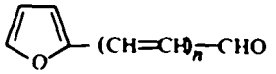
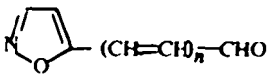
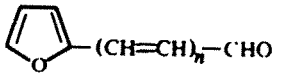
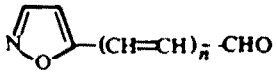
	n	Occupied MO							First unocc. MO
	0	-3·042910	-1·740501	-1·365865	-0·696034	–	–		+0·347790
	1	-3·041499	-1·855861	-1·512186	-1·168293	-0·532848			+0·260288
	2	-3·041473	-1·909805	-1·635474	-1·377792	-0·985943	-0·428973		+0·207579
	3	-3·041478	-1·938007	-1·736379	-1·492348	-1·239463	-0·843999	-0·358139	+0·172511
	0	-2·981707	-1·745214	-1·505115	-0·811900	–	–		+0·209376
	1	-2·980087	-1·854210	-1·593477	-1·267525	-0·621858			+0·158142
	2	-2·980056	-1·908694	-1·659381	-1·482290	-1·059343	-0·500838		+0·126880
	3	-2·980056	-1·937330	-1·739296	-1·570526	1·314255	-0·904242	-0·418330	+0·105880

TABLE 2. CHARGE DISTRIBUTION IN FURANE, ISOXAZOLE AND RELATED POLYENE ALDEHYDES

Atom number*	 †					 †				
		$n = 0$	$n = 1$	$n = 2$	$n = 3$		$n = 0$	$n = 1$	$n = 2$	$n = 3$
1	0·124	0·119	0·116	0·115	0·114	0·101	0·093	0·090	0·088	0·087
2	0·041	0·056	0·036	0·023	0·014	−0·277	−0·205	−0·239	−0·259	−0·273
3	−0·021	−0·022	−0·019	−0·018	−0·018	0·127	0·118	0·116	0·114	0·113
4	−0·021	0·086	0·057	0·042	0·032	−0·030	0·072	0·032	0·010	−0·004
5	−0·041	−0·065	−0·045	−0·039	−0·036	0·078	0·026	0·042	0·045	0·046
6		0·205	0·125	0·092	0·075		0·209	0·114	0·073	0·050
7		−0·379	−0·054	−0·025	−0·016		−0·314	0·004	0·030	0·038
8			0·186	0·111	0·081			0·194	0·110	0·074
9			−0·402	−0·062	−0·030			−0·355	−0·019	0·012
10				0·177	0·104				0·185	0·106
11				−0·415	−0·068				−0·378	−0·034
12					0·171					0·179
13					−0·424					−0·393

* The numbering system is that used in LCAO-MO calculation: it starts from the ring oxygen and goes clockwise towards the side chain.
† Ref. 10.

These considerations agree with the fact that the net charge on the carbonyl oxygen of furanepolyene aldehydes is greater than that of the corresponding isoxazolepolyene aldehydes and the latter absorb at shorter wavelengths.

EXPERIMENTAL

5-Isoxazolemethanol (I). A soln of sodium fulminate prepared from mercuric fulminate (40 g) and 8% Na Hg (93 g) in 400 ml water was added dropwise into 140 ml H_2SO_4 (20% w w) and 80 ml propargyl alcohol. The rate of addition was one drop per sec with vigorous stirring. The soln was then filtered and the filtrate was saturated with $(NH_4)_2SO_4$ and extracted with ether. The ethereal soln was dried with Na_2SO_4, filtered and the solvent distilled off leaving a yellow oil. The excess of propargyl alcohol was removed from the oil at 35° (14 mm).

The 5-isoxazolemethanol (I) distilled at 118° (16 mm) (yield 90% with respect to the mercuric fulminate).

5-Isoxazolecarbaldehyde (II). Compound I (10 g) and $CHCl_3$ (300 ml) were heated under reflux and stirred with MnO_2 (100 g dried at 125° for 24 hr). Among the different samples of MnO_2 used, we found that the product supplied by C. Erba S.A. (Milan, Italy) had the required activity. The MnO_2 prepared by the method in Ref. 12 was too active; in this case the alcohol gave the corresponding acid by oxidation. In our case the reaction was completed by heating under reflux with MnO_2 for 5 hr. The mixture was then filtered and extracted in a Soxhlet using ether as solvent. The ethereal soln was added to the chloroformic one. Evaporation of solvents gave a liquid which on distillation gave the aldehyde II, b.p. 64° (13 mm), and the unreacted alcohol I. The yield was 52% with respect to the unrecovered 5-isoxazolemethanol. II was purified by vacuum sublimation at 25° (20 mm), m.p. 31–32°. (Found: C, 49·4; H, 3·1; N, 14·6. $C_4H_3NO_2$ requires: C, 49·4; H, 3·1; N, 14·4%.)

The 2,4-dinitrophenylhydrazone of II is a yellow flaky solid which was recrystallized from alcohol, m.p. 222° dec. (Found: N, 25·4. $C_{10}H_7N_5O_5$ requires: N, 25·2%.)

5-Isoxazolecarbaldehyde diethyl acetal. Compound II (4 g) was refluxed for 24 hr with anhyd EtOH (10 ml) and *p*-toluensulfonic acid (0·5 g) as catalyst. 5% $NaHCO_3$ aq was then added till an oil separated. This was extracted with ether and dried with Na_2SO_4. The ether was then distilled off and a colourless liquid collected; b.p. 52° (0·15 mm). (Found: N, 8·3. $C_8H_{13}NO_3$ requires: N, 8·1%.)

3-(5-Isoxazolyl)-2-propen-1-ol (IV). A soln of sodium fulminate (150 ml) prepared from mercuric fulminate (15 g) was added dropwise into a flask containing III (12 g), EtOH (30 ml) and a few drops of dil H_2SO_4; at the same time 20% H_2SO_4 (w w; 40 ml) was added dropwise.

Each addition was at the rate of one drop every 15 sec with vigorous stirring. When the reaction ceased the soln was neutralized with NH_4OH under stirring and was then saturated with $(NH_4)_2SO_4$ and extracted with ether. The extract was dried with Na_2SO_4 and distilled. A pale yellow viscous liquid (24% yield) was collected; b.p. 92° (0·15 mm). (Found: C, 57·4; H, 5·7; N, 11·0. $C_6H_7NO_2$ requires: C, 57·5; H, 5·6; N, 11·1%.)

3-(5-Isoxazolyl) propenale (V). Method A. Compound IV (2 g) and MnO_2 (40 g) were refluxed for 4 hr in anhyd ether (150 ml) under stirring. The MnO_2 was then filtered off and washed with ether. After distilling off the ether, a solid was collected and purified by vacuum sublimation at 45° (0·01 mm); m.p. 47°. The sample prepared by this method had the same m.p. and IR spectrum as that prepared by method B.

Method B. To a soln of II (4·1 g) in anhyd benzene (20 ml) were added a few drops of BF_3 in ethereal soln and then a soln of anhyd ethyl vinyl ether (3 ml) in anhyd benzene (20 ml). The mixture was heated at 40° for 1 hr; the benzene was removed under vacuum and the red coloured residue heated at 70–80° for 1 hr with dil HCl (10 ml). Water was then added (10 ml) and the aqueous layer saturated with $(NH_4)_2SO_4$. After extraction with ether, the extract was decolourized with animal charcoal and dried with Na_2SO_4. The ether was removed and a solid (38% yield) was collected and purified by vacuum sublimation at 45° (0·01 mm); m.p. 47°. (Found: C, 58·4; H, 4·0; N, 11·7. $C_6H_5NO_2$ requires: C, 58·5; H, 4·0; N, 11·3%.)

5-(5-Isoxazolyl)-2,4-pentadienale (VI). Compound VI was prepared using the conditions described for V (method B). The quantities used were: V (2·6 g) in anhyd benzene (12 ml) and ethyl vinyl ether (2 ml) in anhyd benzene (10 ml). VI was purified by vacuum sublimation at 45° (0·01 mm); m.p. 70–71° (yield 26%). VI could be maintained unaltered for a long period only by keeping it at 0–5°. (Found: C, 64·4; H, 5·1; N, 9·6. $C_8H_7NO_2$ requires: C, 64·4; H, 4·7; N, 9·3%.)

[12] F. F. Pratt, *J. Org. Chem.* **28**, 638 (1963).

7-(5-*Isoxazolyl*)-2,4,6-*eptatrienale* (VII) Compound VII was prepared using the conditions described for V (method B). The quantities used were: VI (0·9 g) in anhyd benzene (20 ml) and ethyl vinyl ether (1 ml) in anhyd benzene (5 ml). VII (9·7% yield) was purified by vacuum sublimation at 80° (0·01 mm); m.p. 123–124°. (Found: C, 68·7; H, 5·5; N, 7·7. $C_{10}H_9NO_2$ requires: C, 68·5; H, 5·1; N, 8·0%.)