Synthesis of Pyridine Oxides and Isoxazolines from 4-(2-Oxoalkylidene)-pyrans

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The reaction of 2,6-disubstituted and 2,5,6-trisubstituted 4-(2-oxoalkylidene)pyrans with hydroxylamine yields oximes of 4-(2-oxoalkyl)pyridine *N*-oxides or substituted Δ^2-isoxazolines, or a mixture thereof. The factors influencing the competition between the formation of these two types of product are discussed.

ALTHOUGH the reaction of 4-pyrones with hydroxylamine is well documented,[1] the behaviour of 4-methylenepyrans towards this reagent has not been investigated. Since methylenepyrans are now easily accessible [2,3] we became interested in this reaction.

Treatment of the phenacylidenepyran (1a) with hydroxylamine hydrochloride in refluxing ethanol-pyridine solution affords the substituted pyridine *N*-oxide (2a), in high yield.[4] Surprisingly, the same compound (2a) is isolated, in good yield, when 2-(2,6,-diphenylpyran-4-ylidene)cyclohexanone (3) [3] reacts with hydroxylamine under identical conditions. The structure (2a) is supported by an i.r. *N*-oxide band at *ca.* 1 220 cm^{-1}, absorption bands at $\lambda_{max.}$ 215 (log ε 4.30) and 246 nm (4.52), characteristic of pyridine *N*-oxides,[1] and the mass spectrum, which shows the molecular ion and a $M^+ - 16$ fragment, typical of *N*-oxides.[1,5] The isolation of the same pyridine *N*-oxide (2a) from either (1a) or (3) formally implies that the *N*-oxide is formed through a common intermediate. Mechanistically this may be rationalized as shown in Scheme 1, by hydroxylamine attack at the position α to the oxygen atom of the pyran ring [1,6] of (1a), leading to an open-chain intermediate of type (A), mesomeric with (B), also formed from (3). The δ-diketone (A) then cyclizes in a manner similar to that of γ-pyrones,[1,7] thus affording the pyridine *N*-oxide (2a).

Similarly, treatment of the methylated analogue (1b), obtained from (+)-pulegone,[3] with hydroxylamine gives the pyridine *N*-oxide (2b).

As in the case of the reaction of γ-pyrones with

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[1] A. R. Katritzky and J. M. Lagoski, 'Chemistry of the Heterocyclic *N*-Oxides,' Academic Press, New York, 1971; in particular pp. 17 and 74—79.

[2] H. Strzelecka, M. Simalty, and C. Prévost, *Compt. rend.*, 1963, **257**, 926.

[3] P. Crabbé, E. Diaz, J. Haro, G. Pérez, D. Salgado, and E. Santos, *Tetrahedron Letters*, 1970, 5069; *J.C.S. Perkin I*, 1972, 46.

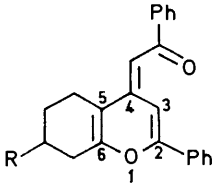
[4] Preliminary communication, P. Crabbé, J. Haro, C. Rius, and E. Santos, *J. Heterocyclic Chem.*, 1972, **9**, 1189.

[5] A. N. Porter and J. Baldas, 'Mass Spectrometry of Heterocyclic Compounds,' Wiley–Interscience, New York, 1971.

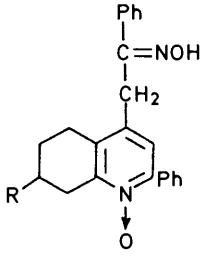
[6] P. Crabbé, L. A. Maldonado, and I. Sanchez, *Tetrahedron*, 1971, **27**, 711.

[7] F. Parisi, P. Bovina, and A. Quilico, *Gazzetta*, 1960, **90**, 903; 1962, **92**, 1138; see also E. Ochiai, 'Aromatic Amine Oxides,' Elsevier, Amsterdam, 1967.

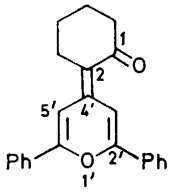
hydroxylamine,[1] different structural features may affect the course of the formation of pyridine *N*-oxides from



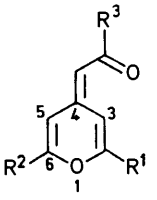
(1) a; R = H
b; R = Me



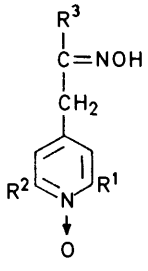
(2) a; R = H
b; R = Me



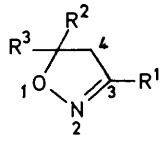
(3)



(4) a; $R^1 = R^2 = R^3 = Me$
b; $R^1 = R^2 = Ph$, $R^3 = Me$
c; $R^1 = R^3 = Ph$, $R^2 = Me$
d; $R^1 = Me$, $R^2 = R^3 = Ph$
e; $R^1 = R^2 = Ph$, $R^3 = OMe$
f; $R^1 = R^2 = Me$, $R^3 = OMe$



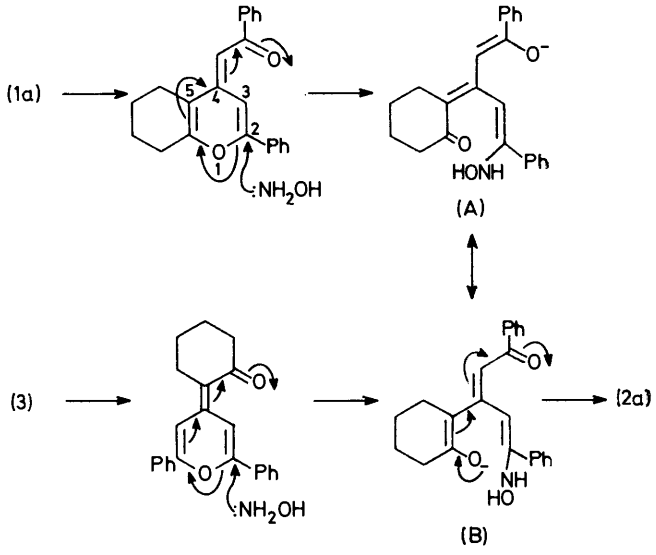
(5) a; $R^1 = R^2 = R^3 = Me$
b; $R^1 = Me$, $R^2 = R^3 = Ph$



(6) a; $R^1 = Me$, $R^2 = R^3 = CH_2 \cdot C(:NOH)Me$
b; $R^1 = Ph$, $R^2 = CH_2 \cdot C(:NOH)Ph$, $R^3 = CH_2 \cdot C(:NOH)Me$
c; $R^1 = Ph$, $R^2 = CH_2Ph$, $R^3 = CH_2 \cdot C(:NOH)Ph$
d; $R^1 = Ph$, $R^2 = CH_2 \cdot CO_2Me$, $R^3 = CH_2 \cdot C(:NOH)Ph$
e; $R^1 = Me$, $R^2 = CH_2 \cdot CO_2Me$, $R^3 = CH_2 \cdot C(:NOH)Me$

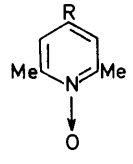
methylenepyrans. Moreover, since chromones are known to afford isoxazoles by reaction with hydroxylamine,[1,6] one might expect that sometimes the formation of pyridine *N*-oxide would compete with that of isoxazoline.

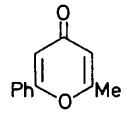
First, the compound (4a) with methyl groups replacing the phenyl groups and six-carbon ring in compounds (1a and b) and (3) was studied, in order to investigate the possible influence of the nature of these substituents on the course of the reaction. When 4-acetonylidene-2,6-dimethylpyran (4a) [8] was treated with hydroxylamine in



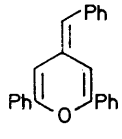
SCHEME 1

pyridine solution, a 6 : 1 mixture of the substituted *N*-oxide (5a) and the isoxazoline (6a) was formed. Compound (5a) was reduced catalytically with Raney nickel to the primary amine (7a), thus confirming the presence of an oxime. The pyridine *N*-oxide structure (5a) was established unambiguously by cleavage of the oxime group with thallium nitrate,[9] followed by treatment with hydrogen peroxide,[10] thus affording the known 2,6-dimethylpyridine-4-carboxylic acid *N*-oxide (7b).[11]





(8)



(9)

(7) a; $R = CH_2 \cdot CH(NH_2)Me$
b; $R = CO_2H$
c; $R = CH_2 \cdot CO_2Me$

An authentic sample of the carboxylic acid (7b) was prepared by treatment of 4-acetonylidene-2,6-dimethylpyran (4a) with ammonia,[12] followed by oxidation of the substituted pyridine with hydrogen peroxide.[10]

The Δ^2-isoxazoline (6a) shows a molecular ion (*m/e* 227) in its mass spectrum and does not display any u.v. absorption above 220 nm. Moreover, it exhibits a characteristic n.m.r. spectrum, with a three-proton signal at δ 1.75 (3-Me), a six-proton signal at 2.18

[8] A. T. Balaban, P. T. Frangopol, A. R. Katritzky, and C. D. Nenitzescu, *J. Chem. Soc.*, 1962, 3889.
[9] A. McKillop, J. D. Hunt, R. D. Naylor, and E. C. Taylor, *J. Amer. Chem. Soc.*, 1971, **93**, 4918.
[10] H. S. Mosher, L. Turner, and A. Carlsmith, *Org. Synth.*, 1963, **4**, 828; see also ref. 1.
[11] W. Mathes and W. Sauermilch, *Chem. Ber.*, 1955, **88**, 1276.
[12] J. A. Van Allan, G. A. Reynolds, G. D. Petropoulos, and D. P. Maier, *J. Heterocyclic Chem.*, 1970, **7**, 495; see also ref. 1.

[two MeC(:N·OH)], and a two-proton signal at 12.4, removed by D_2O (two N·OH).

Since the acetonylidene-dimethylpyran (4a) affords simultaneously the pyridine oxide (5a) and the isoxazoline (6a) by reaction with hydroxylamine, it seems that in the case of compounds (1a and b) and (3), the phenyl groups as well as the six-carbon ring are responsible for the exclusive formation of the pyridine *N*-oxides (2a and b).

The potential influence on the reaction of a phenyl group at the 2(6)-position of the methylenepyran was then investigated. 4-Acetonylidene-2,6-diphenylpyran (4b) was prepared by the reaction between phenacylidenetriphenylphosphorane and ethyl acetoacetate.[13] In addition to the γ-pyrone (8) and the 2,6-diphenyl derivative (4b) reported earlier,[13] the isomeric oxoalkylidenepyrans (4c and d) were also isolated in minute amounts by careful t.l.c. of the mother liquors.

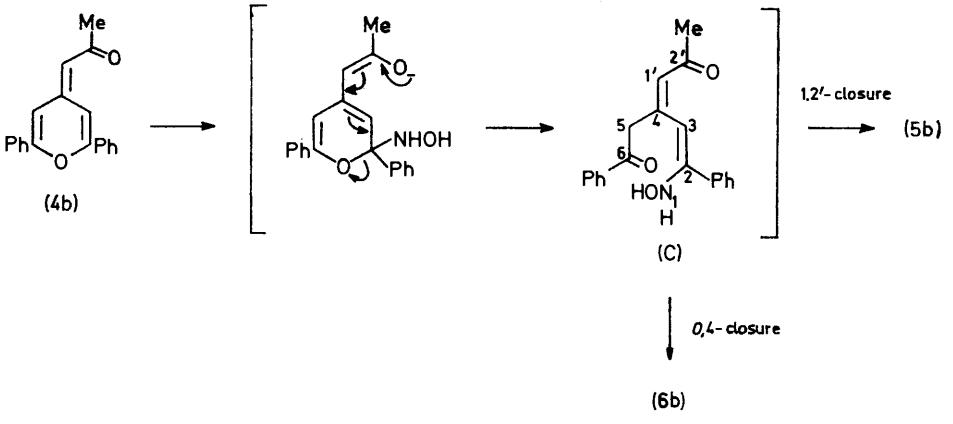
4-Acetonylidene-2,6-diphenylpyran (4b) reacted with hydroxylamine to give, in addition to the 4-alkylpyridine *N*-oxide (5b) (38%), a 52% yield of the substituted isoxazoline (6b). The production of the pyridine *N*-oxide (5b) in this reaction seems to support its formation by ring-opening of (4b) (Scheme 2). The intermediate (C) cyclizes by nucleophilic attack of the nitrogen on the carbonyl at C-2′.

the course of the reaction is affected when it is an ester function which is conjugated with the methylenepyran. The 4-methoxycarbonylmethylene-2,6-diphenylpyran (4e), prepared by a Wittig-type reaction between phenacylidenetriphenylphosphorane and dimethyl malonate, reacted with hydroxylamine to afford exclusively the isoxazoline (6d). However the ester (4f), obtained by an analogous method, yielded a 4 : 3 mixture of the pyridine *N*-oxide (7c), and the isoxazoline (6e). Thus, it seems that carbonyl-containing groups less polar than ketones, such as esters, tend to favour the formation of isoxazoline.

From the aforementioned observations it appears that 4-methylenepyrans, on treatment with hydroxylamine, undergo ring opening with cleavage of the carbon–oxygen bond, as in the reaction with primary and secondary amines.[12,14] Heteroaromatic cyclization then occurs either at position 6 or 2′ (C), providing the substituted *N*-oxides (2) and (5), or position 4, affording the Δ^2-isoxazolines (6) (Scheme 2).

In agreement with previous observations with 4-pyrones,[8,15] a few experiments with oxoalkylidenepyrans and hydroxylamine indicate the course of the reaction to be pH-dependent.

This reaction constitutes a new route to the Δ^2-isoxazoline system.[16]



SCHEME 2

The presence of a carbonyl group conjugated with the methylenepyran system is another factor which seems to be required for the formation of a pyridine *N*-oxide. Indeed, in the reaction of 4-benzylidene-2,6-diphenylpyran (9) [2] with hydroxylamine, no *N*-oxide was isolated, but only the isoxazoline (6c), identified by its typical spectroscopic properties (see Experimental section).

In addition, the polarizability of the carbonyl group has some effect on the *N*-oxide : isoxazoline ratio, since

EXPERIMENTAL

Microanalyses were performed by Dr. A. Bernhardt, Mühlheim, Germany. M.p.s. were determined with a Meltemp apparatus; they are corrected. Optical rotations were taken for solutions in chloroform between 16 and 22 °C with a 1 dm tube at the sodium D-line. The c.d. curve was obtained with a Jouan Dichrograph. I.r. spectra were taken with a Perkin-Elmer 21 instrument (NaCl prism). U.v. spectra were obtained with a Beckman DU spectrophotometer. Unless otherwise stated, n.m.r. spectra were

[13] H. Strzelecka and M. Simalty-Siemiatycki, *Compt. rend.*, 1965, **260**, 3989.
[14] J. Turk, W. M. Haney, G. Heid, R. E. Barlow, and L. B. Clapp, *J. Heterocyclic Chem.*, 1971, **8**, 149.
[15] G. Soliman and E. El-Sayed El-Kholy, *J. Chem. Soc.*, 1955, 1755; P. Yates, M. J. Jorgenson, and S. K. Roy, *Canad. J. Chem.*, 1962, **40**, 2146.
[16] A. Quilico, 'Five- and Six-membered Compounds with Nitrogen and Oxygen,' ed. R. H. Wiley, Wiley, New York, 1962; C. Grundmann and P. Grünanger, 'Nitrile Oxides,' Springer Verlag, New York, 1971; I. Adachi, K. Harada, R. Miyazaki, and H. Kang, *Chem. and Pharm. Bull.* (*Japan*), 1974, **22**, 61, and references therein.

recorded with a Varian T-60 instrument for 5—8% w/v solutions in deuteriochloroform containing tetramethylsilane as internal reference. Coupling constants (J/Hz) are accurate to ±1 Hz. Mass spectra were obtained with an Atlas CH-4 spectrometer. We thank E. Diaz and E. Cortès (U.N.A.M.) and Dr. L. Tökès, Syntex Research, Palo Alto, California, for several n.m.r. and mass spectra.

Reaction of the Phenacylidenepyran (1a) *with Hydroxylamine.*—A solution containing the methylenepyran (1a) [3] (75 mg) and hydroxylamine hydrochloride (150 mg) in ethanol (1.9 ml) and pyridine (0.9 ml) was gently heated under reflux for 2 h, until the yellow colour had disappeared. The solvents were evaporated off and dilute aqueous acetic acid was then added to the residue. The white crystalline precipitate was filtered and washed with water until neutral to give 5,6,7,8-*tetrahydro*-4-(β-*hydroxyiminophenethyl*)-2-*phenylquinoline* N-*oxide* (2a) (70 mg, 85%), m.p. 234—235° (from chloroform–ether); $\lambda_{max.}$ 215 (log ε 4.30) and 246 nm (4.52); $\nu_{max.}$ 3 400, 1 600, 1 290, and 1 220 cm^{-1}; δ [$(CD_3)_2SO$] 1.75 (4H), 2.75 (4H), 4.06 (CH_2·C:NOH), 6.92 (1H), *ca.* 7.5 (10 aromatic H), and 11.50 (NOH, exchanged with D_2O); *m/e* 358 (92%, M^+), 342 ($M^+ - 16$), and 220 {$M^+ - [PhC(:NOH) + H_2O]$, base peak} (Found: C, 77.25; H, 6.3; N, 7.75. $C_{23}H_{22}N_2O_2$ requires C, 77.05; H, 6.2; N, 7.8%).

Treatment of 2-(2,6-*Diphenylpyran*-4-*ylidene*)*cyclohexanone* (3) *with Hydroxylamine.*—A solution of compound (3) [3] (65 mg) and hydroxylamine hydrochloride (150 mg) in ethanol (1.8 ml) and pyridine (0.8 ml) was heated under reflux for 2 h, until the yellow colour had disappeared. The solvents were removed *in vacuo* and dilute acetic acid was added. The precipitate was washed with water until neutral and dried. Crystallization from chloroform–ether afforded the *N*-oxide (2a) (58 mg, 82%), m.p. 233—234°, identical (mixed m.p., i.r., u.v., n.m.r., and t.l.c.), with the foregoing sample.

Reaction of the Phenacylidenepyran (1b) *with Hydroxylamine.*—A mixture of the phenacylidenepyran (1b) [3] (250 mg) and hydroxylamine hydrochloride (633 mg) in ethanol (7 ml) and pyridine (3.5 ml) was heated under reflux for 50 min. The usual work-up gave 5,6,7,8-*tetrahydro*-4-(β-*hydroxyiminophenethyl*)-7-*methyl*-2-*phenylquinoline* N-*oxide* (2b) (221 mg, 81%) as white crystals, m.p. 220—222° (from chloroform–ether); $[\alpha]_D$ +51°; c.d. (MeOH) $[\theta]_{280}$ +4 090, $[\theta]_{240}$ −6 140; $\lambda_{max.}$ 215 (log ε 4.30) and 246 nm (4.53); $\nu_{max.}$ 3 400, 1 610, 1 270, and 1 225 cm^{-1}; δ [$(CD_3)_2SO$] 1.08 (d, *J* 6 Hz, Me), 4.08 (2H, s), 6.84 (1H, s), *ca.* 7.5 (10 aromatic H), and 11.6 (1H, exchanged with D_2O); *m/e* 372 (M^+, base peak) and 358 ($M^+ - 16$) (Found: C, 77.25; H, 6.45; N, 7.6; O, 8.9. $C_{24}H_{24}N_2O_2$ requires C, 77.4; H, 6.5; N, 7.5; O, 8.6%).

Reaction of 4-*Acetonylidene*-2,6-*dimethylpyran* (4a) *with Hydroxylamine.*—(*a*) A solution of the substituted pyran (4a) [8] (1 g) and hydroxylamine hydrochloride (4.24 g) in ethanol (100 ml) and pyridine (20 ml) was heated under reflux for 3 h. The solvents were removed *in vacuo*. Methylene chloride was added to the residue and the organic fraction was washed, dried, and evaporated. The amorphous material (1.38 g) was purified by preparative t.l.c. on silica gel to give two substances.

The less polar substance (148 mg, 13%) was recrystallized from ethyl acetate affording 5,5-*bis*-(2-*hydroxyiminopropyl*)-3-*methyl*-Δ²-*isoxazoline* (6a), m.p. 154—155°; $\nu_{max.}$ 3 500 and 1 646 cm^{-1}; δ (C_5D_5N) 1.75 (3-Me), 2.18 (2 × *Me*C:NOH), 2.75 (2 × CH_2C:NOH), 3.10 (4-H_2), and 12.4 (2 × NOH, exchanged with D_2O); *m/e* 227 (M^+) and 155 [$M^+ - CH_2C(:NOH)Me$, base peak] (Found: C, 52.8; H, 7.5; N, 18.6; O, 21.1. $C_{10}H_{17}N_3O_3$ requires C, 52.85; H, 7.55; N, 18.5; O, 21.1%).

The second compound (757 mg, 78%) was purified by t.l.c. and recrystallized from ethyl acetate–acetone, affording 4-(2-*hydroxyiminopropyl*)-2,6-*dimethylpyridine* N-*oxide* (5a), m.p. 159—161°; $\lambda_{max.}$ 216 (log ε 4.47) and 262 nm (4.17); $\nu_{max.}$ 3 450, 1 675, 1 625, and 1 220 cm^{-1}; δ (C_5D_5N) 1.9 (Me), 2.46 (2- and 6-Me), 3.45 (CH_2·C:NOH), *ca.* 4.5—5.5 (NOH, exchanged with D_2O), and 7.0 (3- and 5-H); *m/e* 194 (M^+, base peak) and 177 (M^+ — OH) (Found: C, 61.55; H, 7.35; N, 14.3. $C_{10}H_{14}N_2O_2$ requires C, 61.85; H, 7.25; N, 14.4%).

(*b*) Compound (4a) (1.50 g) was dissolved in ethanol (300 ml) containing hydroxylamine hydrochloride (8.48 g) and sodium acetate (10 g) (after removal of sodium chloride). The mixture was gently refluxed for 1 h. The solvent was removed under reduced pressure, and the filtrate was concentrated *in vacuo*. The residue was separated by t.l.c. to give the isoxazoline (6a) (1.30 g) and the pyridine *N*-oxide (5a) (265 mg), identified by direct comparison with the foregoing samples.

Catalytic Hydrogenation of the Oxime (5a).—The oxime (5a) (800 mg) dissolved in methanol (10 ml) was hydrogenated over Raney nickel [1 g suspended in methanol (5 ml)] for 20 h. After removal of the catalyst and solvent the crude product was purified by preparative t.l.c. to give the crystalline amine (7a) (77%), m.p. 230° (decomp.) (from methanol–ethyl acetate); $\lambda_{max.}$ 217 (log ε 4.33) and 262 nm (4.05); $\nu_{max.}$ 3 400, 1 630, 1 580, 1 230 and 1 170 cm^{-1}, δ [$(CD_3)_2SO$] 1.14 (d, *J* 6 Hz, *Me*CH·NH_2), 2.31 (2- and 6-Me), *ca.* 3.5 (MeC*H*·NH_2), 7.22 (3- and 5-H), and *ca.* 8.20 (NH_2); *m/e* 180 (M^+), 164 ($M^+ - 16$), 137 (M^+ — MeCH-NH_2), and 120 (137 — OH, base peak).

Conversion of the Oxime (5a) *into* 2,6-*Dimethylpyridine*-4-*carboxylic Acid* N-*Oxide.*—The oxime (5a) (150 mg) was dissolved in methanol (10 ml). Thallium nitrate (300 mg) was added and the mixture was kept at room temperature for 1 h. The thallium(I) which precipitated was filtered off. Dilute sulphuric acid was added to the filtrate, which was then extracted with ethyl acetate. The organic layer was washed until neutral, dried, and concentrated *in vacuo*. The crude product (41 mg), which showed typical *N*-oxide u.v. absorption ($\lambda_{max.}$ 216 and 262 nm), was treated, without isolation, with 30% hydrogen peroxide (2 ml) in glacial acetic acid (2 ml) for 3 h at 80 °C. The solvents were removed under vacuum and water (5 ml) was added. After removal of all the acetic acid the crystalline product exhibited m.p. 245—247°, $\lambda_{max.}$ 216 (log ε 3.68) and 288 nm (3.66), and was identical with an authentic sample of the acid (7b) [11] (see below).

2,6-*Dimethylpyridin*-4-*carboxylic Acid* N-*Oxide* (7b).[11]—(a) *Treatment of* 4-*acetonylidene*-2,6-*dimethylpyran* (4a) *with ammonia.* A mixture of the methylenepyran (4a) (6 g) and aqueous 28% ammonia (70 ml) was heated for 8 h at 92 °C in a sealed Pyrex tube. After cooling, the organic material was extracted with methylene chloride; the extract was dried and evaporated *in vacuo*. The residual liquid was distilled under high vacuum affording, as a slightly yellow oil, the substituted pyridine derivative (4.5 g), b.p. 79—80° at 0.1 mmHg which solidified below 10 °C; $\lambda_{max.}$ 218 (log ε 3.82), 268 (3.62), and 382 nm (3.54); $\nu_{max.}$ 3 350, 1 710, 1 680, 1 605, and 1 570 cm^{-1}; δ (CCl_4) 2.07 (Ac), 2.44 (2- and 6-Me), 3.5 (CH_2), and 6.73br (s, 3- and 5-H). Since this material

is a mixture of tautomers it was used as such for the next reaction.

(b) *Oxidation of the substituted pyridine.* A solution of the substituted pyridine (516 mg) in glacial acetic acid (2.5 ml) was heated with 30% hydrogen peroxide (1.25 ml) for 3 h at 65 °C. More hydrogen peroxide (1.25 ml) was added and the mixture was kept for another 5 h at 65 °C. The solution was then evaporated to dryness, water (10 ml) was added, and the mixture was evaporated *in vacuo* to remove the acetic acid. The residue was recrystallized from methanol affording the carboxylic acid *N*-oxide (7b) (212 mg), m.p. 245—247° (lit.,[11] 247°); $\lambda_{max.}$ 216 (log ε 3.68) and 288 nm (3.66); $\nu_{max.}$ 1 715, 1 630, and 1 230 cm^{-1}; δ (C_5D_5N) 2.59 (2- and 6-Me), 7.83br (s, 3- and 5-H), and 8.47 (CO_2H, exchanged with D_2O); *m/e* 167 (M^+) and 151 ($M^+ - 16$, base peak).

Reaction of 4-*Benzylidene*-2,6-*diphenylpyran* (9) *with Hydroxylamine.*—A solution of compound (9) [2] and hydroxylamine hydrochloride (2.58 g) in ethanol (66 ml) and pyridine (25 ml) was gently refluxed for 1 h. Isolation by the usual procedure (see above) and recrystallization from methanol gave 5-*benzyl*-5-(β-*hydroxyiminophenethyl*)-2-*phenyl*-Δ^2-*isoxazoline* (6c) (836 mg), m.p. 159—161°; $\lambda_{max.}$ 209 (log ε 4.49) and 258 nm (4.24); $\nu_{max.}$ 3 500, 1 610, 1 580, 1 190, and 1 030 cm^{-1}; δ 2.9—3.6 (6H, m), *ca.* 7.4 (15 aromatic H), and 8.4 (NOH, exchanged with D_2O); *m/e* 370 (M^+) and 91 ($PhCH_2$, base peak) (Found: C, 77.7; H, 5.9; N, 7.7; O, 8.65. $C_{24}H_{22}N_2O_2$ requires C, 77.8; H, 6.0; N, 7.5; O, 8.65%).

4-*Acetonylidene*-2,6-*diphenylpyran* (4b).[13]—A solution of phenacylidenetriphenylphosphorane (17 g) and ethyl acetoacetate (3 g) in *p*-xylene (300 ml) was heated under nitrogen, at reflux temperature, for 9 h in the dark. The mixture was cooled to room temperature and filtered, and the solution was concentrated *in vacuo*. The crude product was chromatographed over Florisil. The expected 2-methyl-6-phenylpyrone (8) [13] and triphenylphosphine oxide were the first compounds isolated. The mother liquors were then separated by preparative t.l.c.

The less polar material (1 g) was the diphenylpyran (4b), m.p. 111—112° (from benzene–hexane) (lit.,[13] 110°); $\lambda_{max.}$ 218 (log ε 4.20), 241 (4.08), 270 (4.05), 307 (4.24), 387 (4.41), and 390 nm (4.37); $\nu_{max.}$ 1 680, 1 630, and 1 550 cm^{-1}; δ 2.18 (Ac), 5.68 (vinylic H), 6.45 (d, *J* 2 Hz, 5-H), 7.45—7.8 (10 aromatic H), and 8.55 (d, *J* 2 Hz, 3-H). The next product (933 mg) was an amorphous mixture of the *cis*- and *trans*-isomers (4c and 4d) which could not be separated; $\nu_{max.}$ 1 670, 1 630, 1 580, 1 550, and 1 260 cm^{-1}; δ 2.27 (d, *J* 4 Hz, 2 × Me), 6.22 and 6.28 (s, vinylic H), and 6.61, *ca.* 7.5, 8.04, and 8.75 (aromatic H).

Reaction of the Diphenyl-methylenepyran (4b) *with Hydroxylamine.*—To the methylenepyran (4b) (200 mg) and hydroxylamine hydrochloride (1.93 g) dissolved in ethanol (50 ml) was added pyridine (6 ml). The mixture was gently refluxed for 1 h until the solution was colourless (disappearance of the yellow starting material). The mixture was cooled and evaporated to dryness *in vacuo*. Water (30 ml) was added to the residue. The insoluble organic product was filtered off, dissolved in acetone, and purified by preparative t.l.c.

4-(β-*Hydroxyiminophenethyl*)-2-*methyl*-6-*phenylpyridine N-oxide* (5b) (80 mg) had m.p. 119—121° (from acetone–benzene); $\lambda_{max.}$ 206 (log ε 4.56) and 246 nm (4.56); $\nu_{max.}$ 3 600, 1 625, 1 475, 1 429, 1 220, 1 167, and 964 cm^{-1}; δ [$(CD_3)_2SO$] 2.36 (Me), 4.20 (CH_2), *ca.* 7.1—7.9 (12H, m), and 9.98 (s, NOH, exchanged with D_2O); *m/e* 318 (M^+, base peak), 302 ($M^+ - O$), and 78 (C_6H_6) (Found: C, 76.25; H, 5.9; N, 8.6. $C_{20}H_{18}NO_2,0.25C_6H_6$ requires C, 76.3; H, 5·8; N, 8·4%).

5-(β-*Hydroxyiminophenethyl*)-5-(β-*hydroxyiminopropyl*)-3-*phenyl*-Δ^2-*isoxazoline* (6b) (132 mg) (52%) had m.p. 81—84° (from acetone–benzene); $\lambda_{max.}$ 205 (log ε 4.50) and 254 nm (4.19); $\nu_{max.}$ 3 675—2 530, 1 604, 1 450, and 1 363 cm^{-1}; δ [$(CD_3)_2SO$] 1.90 (3H), 2.40—2.70 (6H, m), *ca.* 7.20—7.90 (10H, m), and 9.43 and 9.91 (s, 2 × NOH, exchanged with D_2O); *m/e* 351 (M^+), 279 [$M^+ - CH_2C(NOH)CH_3$], 217 [$M^+ - CH_2C(NOH)C_6H_5$], and 78 (C_6H_6) (Found: C, 69.4; H, 6.35; N, 11.1. $C_{20}H_{20}N_3O_3,0.25C_6H_6$: C, 69.6; H, 6.1; N, 11.35%).

4-*Methoxycarbonylmethylene*-2,6-*diphenylpyran* (4e).—A solution of phenacylidenetriphenylphosphorane (10.4 g) and dimethyl malonate (1.9 g) in *p*-xylene (170 ml) was heated under reflux for 45 h in the absence of light.[3,17] The mixture was cooled, the unchanged Wittig reagent was filtered off, concentrated hydrochloric acid was added, and the organic layer was separated, dried, and concentrated *in vacuo*. The crude product in benzene was filtered through a column of Florisil (100 g) to give the crude *pyran* (4e) (2.74 g), which was purified by preparative t.l.c.; m.p. 125—126° (from hexane); $\lambda_{max.}$ 215 (log ε 4.33), 254—256sh (4.29), 298 (4.38), and 363 nm (4.52); $\nu_{max.}$ 1 682, 1 635, and 1 585 cm^{-1}; δ 3.71 (CO_2Me), 5.25 (vinylic H), 6.45 (d, *J* 2 Hz, 5-H), *ca.* 7.5 (m, 10 aromatic H), and 8.22 (d, *J* 2 Hz, 3-H) (Found: C, 78.7; H, 5.2; O, 15.9. $C_{20}H_{16}O_3$ requires C, 78.95; H, 5.3, O, 15.75%).

Reaction of 4-*Methoxycarbonylmethylene*-2,6-*diphenylpyran* (4e) *with Hydroxylamine.*—(a) A solution containing the ester (4e) (153 mg) and hydroxylamine hydrochloride (350 mg) in ethanol (12 ml) and pyridine (6 ml) was gently refluxed for 90 min. The solvents were removed *in vacuo*. Water was added to the residue. The crystalline precipitate was filtered off and dried, furnishing 5-(β-*hydroxyiminophenethyl*)-5-*methoxycarbonylmethyl*-3-*phenyl*-Δ^2-*isoxazoline* (6d) (167 mg), m.p. 108—110° (from ether–hexane); $\lambda_{max.}$ 211 (log ε 4.28) and 258 nm (4.23); $\nu_{max.}$ 3 400, 1 745, 1 635, 1 580, 1 170, and 1 035 cm^{-1}; δ 2.86 (4-H_2), 3.48 (2 × CH_2), 3.62 (CO_2Me), and *ca.* 7.4 (m, 10 aromatic H); *m/e* 352 (M^+), 218 [$M^+ - CH{\cdot}C(:NOH)Ph$], and 135 [$CH_2{\cdot}C(:NOH)Ph$ + H, base peak] (Found: C, 68.1; H, 5.8; N, 7.8. $C_{20}H_{20}N_2O_4$ requires C, 68.15; H, 5.7; N, 7.95%).

(*b*) Treatment of a solution of the ester (4e) (50 mg) and hydroxylamine hydrochloride (190 mg) in dimethyl sulphoxide (20 ml) and pyridine (2 ml) at 114 °C for 3 h, followed by the usual extraction procedure, afforded the isoxazoline (6d) (53 mg), m.p. 108—109°, identical with the above material (mixed m.p., i.r. spectrum, and t.l.c.).

4-*Methoxycarbonylmethylene*-2,6-*dimethylpyran* (4f).—A solution of acetonylidenetriphenylphosphorane (10 g) and dimethyl malonate (2 g) in *p*-xylene (150 ml) was gently refluxed for 15 h in the absence of light. After cooling, the unchanged reagent was filtered off and the filtrate was concentrated *in vacuo*. Hexane was added to the residue and the organic solution was evaporated, giving the crude *pyran* (4f), which was purified by t.l.c.; this formed slightly pink crystals (862 mg), m.p. 92—93° (from hexane); $\lambda_{max.}$ 247 (log ε 3.86) and 362 nm (4.42); $\nu_{max.}$ 1 685, 1 640, and 1 600 cm^{-1}; δ 2.04 (d, *J* 1 Hz, 2-Me), 2.08 (d, *J* 1 Hz, 6-Me), 3.64 (CO_2Me), 4.92 (vinylic H), 5.72 (m, *J* 1 and 2 Hz, 5-H), and 7.38 (m, *J* 1 and 2 Hz, 3-H); *m/e* 180 (M^+) and

[17] See H. Strzelecka, M. Dupré, and M. Simalty, *Tetrahedron Letters*, 1971, 617.

149 (M^+ − OMe, base peak) (Found: C, 66.5; H, 6.75; O, 26.75. $C_{10}H_{12}O_3$ requires C, 66.65; H, 6.7; O, 26.65%).

Reaction of 4-*Methoxycarbonylmethylene*-2,6-*dimethylpyran* (4f) *with Hydroxylamine*.—(*a*) A solution of the ester (4f) (394 mg) and hydroxylamine hydrochloride (1.97 g) in ethanol (25 ml) and pyridine (20 ml) was kept under reflux for 90 min. The solvents were then removed *in vacuo*. Chloroform was added and the solution was stirred with potassium hydrogen sulphite (10 g) for 15 min. After filtration and removal of the solvent the crude product, which appeared (n.m.r.) to be a mixture of (7c) and (6e), was purified by t.l.c.

The less polar compound (188 mg) was recyrstallized from benzene–hexane yielding the pyridine oxide (7c), m.p. 106—108°; $\lambda_{max.}$ 216 (log ε 4.42) and 262 nm (4.17); $\nu_{max.}$ 1 735, 1 560, 1 245, and 1 220 cm^{-1}; δ 2.52 (2- and 6-Me), 3.58 ($CH_2{\cdot}CO_2Me$), 3.73 (CO_2Me), and 7.13 (3- and 5-H); *m/e* 195 (M^+, base peak), 179 (M^+ − 16), and 136 (M^+ − CO_2Me).

The more polar substance (168 mg) was the isoxazoline (6e), which was purified by t.l.c.; m.p. 156—160°; $\nu_{max.}$ 3 500, 1 735, and 1 640 cm^{-1}; δ 1.92 (Me), 1.94 (Me), 3.01 (4-H_2), 3.64 (CO_2Me), and 7.9 (NOH, exchanged with D_2O); *m/e* 228 (M^+), 197 (M^+ − OMe), 170 [M^+ − C·(:NOH)Me], and 156 [M^+ − $CH_2{\cdot}C$(:NOH)Me, major peak].

(*b*) When the above reaction was conducted in ethanol in the presence of equimolar amounts of sodium acetate and hydroxylamine hydrochloride, the *N*-oxide (7c) : isoxazoline (6e) ratio was 3 : 1.

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