Configuration of α-Hydroxyimino-ketones

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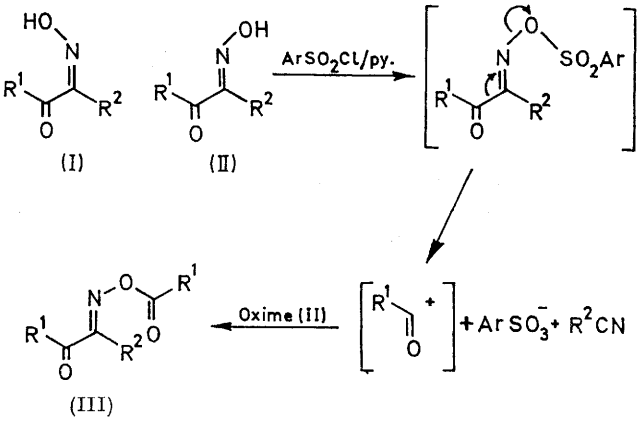
Four *syn*- and *anti*-isomeric pairs of acyclic α-hydroxyimino-ketones are studied. Some methods for determining their respective configurations are discussed and an additional procedure is described based on their reaction with toluene-*p*-sulphonyl chloride in pyridine. *anti*-Isomers are shown to undergo a second-order Beckmann cleavage, yielding acylium ions, which react with starting material to give oxime esters, whilst *syn*-isomers form stable toluene-*p*-sulphonates.

In a search for compounds having anti-hypertensive activity both *syn*- and *anti*-3′,4′-difluoro-2-hydroxyiminopropiophenone * (Ia) and (IIa) were prepared in these laboratories,[1] and since there was a difference in biological activity between the two it was necessary to define their respective configurations.

The *anti*-isomers of α-hydroxyimino-ketones readily form metal complexes whilst their *syn*-isomers do not. This property has been used to establish the configuration of α-hydroxyiminoketones [2-4] and the formation of a copper complex by the more active isomer tentatively led to its assignment of the *anti*-configuration (IIa).[5]

The configuration of *syn*- and *anti*-benzil monoxime (Ib) and (IIb) has been confirmed by an *X*-ray crystallographic study of *O*-(*p*-bromobenzoyl)-*anti*-benzil monoxime [6] and therefore this isomer pair can serve as a standard for comparison of physical properties in this compound class. It has been established by i.r. spectroscopy that neither isomer of benzil monoxime forms an intramolecular hydrogen bond.[7] This observation was also found to apply to compounds (Ia) and (IIa) and it is concluded that in this class of compound the hydroxyimino- and keto-groups adopt a transoid conformation. Compounds (Ia) and (IIa) were also examined by n.m.r. spectroscopy. In deuteriochloroform the methyl signals for the *syn*- and *anti*-isomer were observed at δ 2·12 and 2·15 p.p.m. but in benzene solution a much greater separation was noted, the signals appearing at δ 1·97 and 1·70 p.p.m. respectively. In dimethyl sulphoxide solution (concentration ⩽5 mole %), the hydroxy-proton of the *syn*-isomer (Ia) was observed at δ 11·12 p.p.m. whilst that of the *anti*-isomer (IIa) was observed at δ12·62 p.p.m. Under similar conditions the hydroxy-protons for *syn*- and *anti*-1-hydroxyimino-1-phenylacetone (Id) and (IId) were observed at δ 11·87 and 12·54 p.p.m. respectively and therefore these results, together with the figures of 11·73 and 12·44 published for *syn* and *anti*-benzil monoxime (Ib) and (IIb),[8] support the conclusion that the hydroxy-protons in *syn*-α-hydroxyimino-ketones resonate at higher field than those of their *anti*-isomers when examined in dimethyl sulphoxide. A number of *anti*-α-hydroxyimino-ketones have been examined [9] in this solvent and the protons under discussion resonated at δ 12·22—13·64 p.p.m.



a; R^1 = 3,4-difluorophenyl; R^2 = Me
b; R^1 = R^2 = Ph
c; R^1 = Ph, R^2 = Me
d; R^1 = Me, R^2 = Ph

Ferris has shown that *anti*-α-hydroxyimino-ketones, when treated with acid or an acylating agent in aqueous base, are cleaved, suffering a Beckmann rearrangement of the second order.[10] The configuration of α-hydroxyimino-ketones, therefore, cannot be determined by Beckmann's classical method. Both *syn*- and *anti*-3′,4′-difluoro-2-hydroxyiminopropiophenone yielded 3,4-difluorobenzoic acid with refluxing trifluoroacetic acid and, furthermore, the *syn*-isomer in cold trifluoroacetic acid or dry ethereal hydrogen chloride, was rapidly isomerised to the *anti*-form.

Buehler [11] demonstrated that the ratio of *N*- and *O*-alkylated products obtained when *syn*- and *anti*-benzal dioximes are treated with alkyl halides in the presence of sodium ethoxide was determined by their configuration. Both *syn*- and *anti*-3′,4′-difluoro-2-hydroxyiminopropiophenone were treated in this manner with methyl

* The configurations of the *syn* and *anti*-isomers described in this study may also be defined by the descriptors *Z* and *E* respectively. J. E. Blackwood, C. L. Gladys, K. L. Loening, A. E. Petrarca, J. E. Rush, *J. Amer. Chem. Soc.*, 1968, **90**, 509.

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[4] T. W. J. Taylor and D. C. V. Roberts, *J. Chem. Soc.*, 1933, 1439.
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[7] P. C. Cherry, W. R. T. Cottrell, G. D. Meakins, and E. E. Richards, *J. Chem. Soc.* (*C*), 1968, 459.
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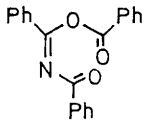
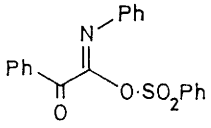
[9] J. Guetté, J. Armand, and L. Lacombe, *Compt. rend.*, 1967, *C*, **264**, 1509.
[10] A. F. Ferris, *J. Org. Chem.*, 1959, **24**, 580; 1960, **25**, 12; A. F. Ferris, G. S. Johnson, and F. E. Gould, *ibid.*, p. 1813.
[11] E. Buehler, *J. Org. Chem.*, 1967, **32**, 261.

iodide, but only their respective *O*-methyl ethers could be isolated.

The first correct assignment of the configuration of *syn*- and *anti*-benzil monoxime was made by Meisenheimer [12] who demonstrated that ozonolysis of triphenylisoxazole produced *O*-benzoyl-*syn*-benzil monoxime (m.p. 137·5—138·5°). In order to show that this compound was not formed by subsequent isomerisation but was the primary product of oxidation, he attempted the preparation of *O*-benzoyl-*anti*-benzil monoxime by treating *anti*-benzil monoxime (IIb) with benzoyl chloride in pyridine. However, the substance obtained (m.p. 95—96°), proved to be identical to that characterised by Werner and Piguet [13] who treated *anti*-benzil monoxime with benzenesulphonyl chloride. These authors had assigned structure (IV) to their product since, on alkaline hydrolysis, it afforded benzonitrile and two molar equivalents of benzoic acid. Initially, Meisenheimer [12] concurred with this assignment but later showed that the compound was, in fact, *O*-benzoyl-*anti*-benzil monoxime since, when treated with zinc and acetic acid, it afforded desoxybenzoin.[14] Werner and Piguet [13] also examined the reaction of benzenesulphonyl chloride with *syn*-benzil monoxime (Ib) and obtained a product to which they ascribed the structure (V), but a later



(IV)



(V)

investigation revealed that it was simply the benzenesulphonate of the oxime.[15] In summary then, *anti*-benzil monoxime, when treated with benzenesulphonyl chloride in pyridine gives its benzoate ester (IIIb) presumably by the mechanism shown earlier ($R^1 = R^2 =$ Ph) whilst *syn*-benzil monoxime gives its benzenesulphonate. As expected on mechanistic grounds, the benzenesulphonate of *syn*-benzil monoxime is more stable than that of the *anti*-isomer and this is shown by the fact that the former is stable in pyridine at 0° whilst the latter is not.

To establish whether this observation might be extended to other acyclic α-hydroxyimino-ketones, both *syn*- and *anti*-isomers of benzil monoxime, 2-hydroxyiminopropiophenone, 1-hydroxyimino-1-phenylacetone and 3′,4′-difluoro-2-hydroxyiminopropiophenone were treated with toluene-*p*-sulphonyl chloride in pyridine at 0°. All the *syn*-isomers afforded their respective toluene-*p*-sulphonates. *anti*-Benzil monoxime (IIb) and *anti*-2-hydroxyiminopropiophenone (IIc) afforded their respective benzoates (IIIb) and (IIIc). *anti*-1-Hydroxyimino-1-phenylacetone (IId) afforded its acetate (IIId) and *anti*-3′,4′-difluoro-2-hydroxyiminopropiophenone (IIa) its 3,4-difluorobenzoate (IIIa). These results show that the four pairs of isomers examined behaved similarly, and it is, therefore, concluded that the above procedure is of general applicability for confirming the configuration of acyclic α-hydroxyiminoketones.

anti-3′,4′-Difluoro-2-hydroxyiminopropiophenone has been the subject of an *X*-ray crystallographic study and it was found to have the proposed configuration.[16]

EXPERIMENTAL

M.p.s were determined on a Kofler block and are corrected. T.l.c. was carried out on Merck silica gel $HF_{254-366}$ and unless otherwise stated 10% ether in benzene was used as the mobile phase. N.m.r. spectra were taken in deuteriochloroform with a Varian A60 n.m.r. spectrophotometer and i.r. spectra were taken in Nujol with a Perkin-Elmer Infracord spectrophotometer. I.r. spectra taken in carbon tetrachloride to assess hydrogen bonding were recorded with a Perkin-Elmer 237 grating spectrophotometer.

anti-3′,4′-*Difluoro*-2-*hydroxyiminopropiophenone*.— This compound [1] prepared from 3′,4′-difluoropropiophenone by Hartung's method,[17] had m.p. 118°, t.l.c., $R_F = 0·6$; $\nu_{max.}$ (CCl_4, 0·001M) 3580 cm.$^{-1}$ (OH); n.m.r., δ 9·00 (s, OH), 7·79 (m, 2′,6′-H_2), 7·20 (m, 5′-H), and 2·15 (*s*, CH_3).

1-(3,4-*Difluorophenyl*)-*propane*-1,2-*dione*.— *anti*-3′,4′-Difluoro-2-oximinopropiophenone (60·0 g.) was heated under reflux with 5N-sulphuric acid (500 ml.) for 5 min.; the suspension was then steam distilled. The distillate was extracted with ether and the organic phase was dried ($MgSO_4$). The solvent was evaporated off and the residue, when distilled gave the *dione* as a bright yellow liquid (48·0 g., 87%) b.p. 42—50°/0·05—0·2 mm.; n_D^{23} 1·4960. An analytical sample had b.p. 46°/0·07 mm. (Found: C, 58·45; H, 3·05. $C_9H_6F_2O_2$ requires C, 58·7; H, 3·3%).

syn-3′,4′-*Difluoro*-2-*hydroxyiminopropiophenone*.—*Method A*. Hydroxylamine hydrochloride (1·66 g.) and anhydrous sodium acetate (2·67 g.) were dissolved in water (10 ml.). Ethanol (50 ml.) was added to the solution and the precipitated sodium chloride was filtered off. 1-(3,4-Difluorophenyl)-propane-1,2-dione (4·0 g.) was added to the filtrate followed by water (30 ml.) and the mixture was set aside at room temperature; after 30 min. a solid began to crystallise out. The mixture was cooled in ice for 2 hr. and the product was filtered off, washed with water, and dried. This was found to be pure *anti*-isomer, m.p. 117·5° (2·4 g., 56%). The filtrate was diluted with an equal volume of water and was set aside at 0° overnight. A second crop of material m.p. 79—97° (0·5 g.) was thus obtained which, when recrystallized from benzene–light petroleum (b.p. 40—60°) afforded syn-3′,4′-*difluoro*-2-*hydroxyiminopropiophenone* as needles m.p. 102—103° (100 mg., 4·6%). An analytical sample had m.p. 103—104°; t.l.c., $R_F = 0·4$; $\nu_{max.}$ (CCl_4, 0·001M) 3608 cm.$^{-1}$ (OH); n.m.r., δ 9·01 (s, OH), 7·79 (m, 2′,6′-H_2), 7·30 (m, 5′-H), and 2·12 (s, CH_3) (Found: C, 54·6; H, 3·45; N, 7·1. $C_9H_7F_2NO_2$ requires C, 54·3; H, 3·55; N, 7·05%).

Method B. *anti*-3′,4′-Difluoro-2-oximinopropiophenone (40·0 g.) dissolved in methanol (1·5 l.) was irradiated through quartz with a 100-w medium-pressure mercury lamp for 13 hr. under pure nitrogen. The solution was evaporated

[12] J. Meisenheimer, *Ber.*, 1921, **54**, 3206.
[13] A. Werner and A. Piguet, *Ber.*, 1904, **37**, 4295.
[14] J. Meisenheimer and W. Lamparter, *Ber.*, 1924, **57**, 276.
[15] E. B. Ayres, M. Patterson, R. D. Bright, and C. R. Hauser, *J. Org. Chem.*, 1941, **6**, 804.
[16] F. H. Allen and J. Trotter, to be submitted for publication in *J. Chem. Soc.* (*B*).
[17] H. K. Iwamoto and W. H. Hartung, *J. Org. Chem.*, 1944, **9**, 513.

to dryness at room temperature and the residue was chromatographed on Florisil (500 g.). Benzene eluted *anti*-isomer first; the *syn*-isomer was eluted with ether–benzene. The fractions containing mainly the *syn*-isomer, as judged by t.l.c., were combined (14·3 g.) and recrystallised from benzene–light petroleum to give pure *syn*-3′,4′-difluoro-2-hydroxyiminopropiophenone, m.p. 103—104° (9·5 g., 24%), identical to the product described above.

anti-2-*Hydroxyiminopropiophenone*.—Propiophenone was nitrosated by Hartung's method [17] to give the required product as needles (60%), m.p. 113—115·5° (lit.,[18] m.p. 115°), t.l.c., $R_F = 0·75$; $\nu_{max.}$ 1660 and 1590 cm.$^{-1}$; n.m.r., δ 9·27 (s, OH), 8·02 (m, 2′,6′-H_2), 7·58 (m, 3′,4′,5′-H_3), and 2·19 (s, CH_3).

syn-2-*Hydroxyiminopropiophenone*.— The *anti*-isomer (14·2 g.) was irradiated and chromatographed on Florisil as described in method B. Recrystallisation of the product from benzene–light petroleum gave needles m.p. 57—58·5° (1·11 g., 7·7%); t.l.c., $R_F = 0·4$; $\nu_{max.}$ 1670 and 1590 cm.$^{-1}$; n.m.r., δ 8·70 (s, OH), 8·08 (m, 2′,6′-H_2), 7·60 (m, 3′,4′,5′-H_3), and 2·12 (s, CH_3) (Found: C, 66·45; H, 5·45; N, 8·3. $C_9H_9NO_2$ requires C, 66·25; H, 5·55; N, 8·6%).

anti-1-*Hydroxyimino*-1-*phenylacetone*.— Phenylacetone was nitrosated by Hartungs method,[17] and the product was obtained as rectangular plates, m.p. 172—173° (from ethanol-water) (lit.,[18] m.p. 166—167°), t.l.c., $R_F = 0·64$; $\nu_{max.}$ 1660, 1185, 1075, 1040, 1020, 990, 945, 910, 764, and 730 cm.$^{-1}$; n.m.r., δ 8·20 (s, OH), 7·55 (m, aromatic-H_5), and 2·57 (s, CH_3).

syn-1-*Hydroxyimino*-1-*phenylacetone*.—The *anti*-isomer (14·5 g.) was irradiated as described above in method B and the resulting mixture fractionally recrystallised from benzene–light petroleum. The more soluble *syn-isomer* was isolated as needles, m.p. 51—53° (740 mg., 5·1%); t.l.c., $R_F = 0·64$; $\nu_{max.}$ 1690, 1190, 1040, 970, 920, and 770 cm.$^{-1}$; n.m.r., δ 9·12 (s, OH), 7·59 (m, aromatic-H_5), and 2·56 (s, CH_3) (Found: C, 66·25; H, 5·6; N, 8·65. $C_9H_9NO_2$ requires C, 66·25; H, 5·55; N, 8·6%).

Treatment of Oximes with Toluene-p-*sulphonyl Chloride in Pyridine: General Method*.—The oxime and toluene-*p*-sulphonyl chloride (1·1 mol.) dissolved in a minimum amount of pyridine at 0°, were set aside overnight at 0°; the mixture was then poured onto ice chips.

Procedure A. The resulting suspension was extracted with ether and the organic phase was washed with dilute hydrochloric acid, 5% aqueous sodium hydrogen carbonate and water; it was then dried ($MgSO_4$). The solvent was evaporated off and the residue, dissolved in benzene, was filtered through Florisil. The filtrate was then evaporated to dryness.

Procedure B. The resulting suspension was filtered and the solid obtained was washed with water and dried *in vacuo*.

anti-*Benzil Monoxime*.—The oxime (2·25 g.) was treated with toluene-*p*-sulphonyl chloride and the product, isolated by procedure A, when recrystallised from benzene–light petroleum and then from methanol–water gave *O*-benzoyl-*anti*-benzil monoxime (0·7 g.), m.p. 95—96·5° (lit.,[12] m.p. 95—96°); t.l.c., $R_F = 0·3$; $\nu_{max.}$ 1750, 1680, and 1605 cm.$^{-1}$ This product was identical to that obtained in 70% yield when the oxime was treated with benzoyl chloride in pyridine.

syn-*Benzil Monoxime*.—The oxime (1·12 g.) was treated with toluene-*p*-sulphonyl chloride and the product, isolated by procedure A, when recrystallised from aqueous methanol and then ethanol gave O-*toluene*-p-*sulphonyl*-syn-*benzil Monoxime* (0·93 g., 49%) as needles, m.p. 113—115°; $\nu_{max.}$ 1695, and 1600 cm.$^{-1}$; n.m.r., δ ~7·7 (m, aromatic-H_{14}), and 2·48 (s, aryl-CH_3) (Found: C, 66·45; H, 4·8; N, 3·6. $C_{21}H_{17}NO_4S$ requires C, 66·45; H, 4·5; N, 3·7%).

anti-2-*Hydroxyiminopropiophenone*.—The oxime (2·1 g.) was treated with toluene-*p*-sulphonyl chloride and the product, isolated by procedure A, when recrystallised from aqueous methanol gave O-*benzoyl*-anti-2-*hydroxyiminopropiophenone*, m.p. 71—72° (1·01 g., 58%) which was identical to the product obtained in 83% yield by treating the oxime with benzoyl chloride in pyridine. An analytical sample had m.p. 72—73°; $\nu_{max.}$ 1760, and 1680 cm.$^{-1}$; n.m.r., δ 8·3 (m, aromatic-H_4), 7·7 (m, aromatic-H_6), and 2·45 (s, CH_3) (Found: C, 72·15; H, 5·1; N, 5·3. $C_{16}H_{13}NO_3$ requires C, 71·9; H, 4·9; N, 5·25%).

syn-2-*Hydroxyiminopropiophenone*.—The oxime (400 mg.) was treated with toluene-*p*-sulphonyl chloride and the solid obtained by procedure B, when recrystallised from ethanol afforded O-*toluene*-p-*sulphonyl*-syn-2-*hydroxyiminopropiophenone* as diamond-shaped crystals (300 mg., 40%), which on heating sublimed to long needles, m.p. 74—77°. An analytical sample had m.p. 75—77°; $\nu_{max.}$ 1680, and 1600 cm.$^{-1}$; n.m.r., δ ~7·8 (m, aromatic-H_9), 2·50 (s, aryl-CH_3), and 2·20 (s, CH_3) (Found: C, 60·65; H, 4·85; N, 4·4. $C_{16}H_{15}NO_4S$ requires C, 60·55; H, 4·75; N, 4·4%).

anti-1-*Hydroxyimino*-1-*phenylacetone*.—The oxime (9·0 g.) was treated with toluene-*p*-sulphonyl chloride, and the mobile liquid, obtained by procedure A, was distilled. The first fraction collected had b.p. 74—77°/14 mm. and was shown to be pure benzonitrile (2·51 g., 99·5%). The pressure was reduced and a second fraction b.p. 101—103°/0·05 mm. was collected. This product (4·10 g.) solidified and when recrystallised from benzene–light petroleum gave *O*-acetyl-*anti*-1-hydroxyimino-1-phenylacetone (2·77 g., 47%) m.p. 57—59° (lit.,[18] m.p. 61—62°); $\nu_{max.}$ 1780, 1705, and 1615 cm.$^{-1}$; n.m.r., δ ~7·5 (m, aromatic-H_5), 2·65 (s, $OCO{\cdot}CH_3$), and 2·12 (s, CH_3). This product was identical to that obtained in 76% yield when the oxime was treated with acetic anhydride in pyridine.

syn-1-*Hydroxyimino*-1-*phenylacetone*.—The oxime (450 mg.) was treated with toluene-*p*-sulphonyl chloride and the solid obtained by procedure A, when recrystallised from ether–light petroleum, gave O-*toluene*-p-*sulphonyl*-syn-1-*hydroxyimino*-1-*phenylacetone*, m.p. 61—63° (280 mg., 32%), n.m.r., δ 8·8 (*d*, toluene-*p*-sulphonate-3,5-H_2), δ 7·6 (m, aromatic-H_7), 2·49 and 2·45 (two s, two-CH_3) (Found: C, 60·65; H, 4·9; N, 4·44. $C_{16}H_{15}NO_4S$ requires C, 60·55; H, 4·75; N, 4·4%). This compound decomposed to a black oil within one week.

anti-3′,4′-*Difluoro*-2-*hydroxyiminopropiophenone*.— The oxime (10 g.) was treated with toluene-*p*-sulphonyl chloride and the solid obtained by procedure B, when recrystallised from aqueous methanol afforded O-(3,4-*difluorobenzoyl*)-anti-3′,4′-*difluoro*-2-*hydroxyiminopropiophenone* (4·9 g., 57%), m.p. 151—152°; t.l.c. (benzene), $R_F = 0·3$; $\nu_{max.}$ 1780, 1700, and 1625 cm.$^{-1}$; n.m.r., δ ~7·7 (m, aromatic-H_6) and 2·45 (s, CH_3) (Found: C, 57·1; H, 2·9; N, 4·15. $C_{16}H_9F_4NO_3$ requires C, 56·9; H, 2·65; N, 4·1%). This product was identical to that obtained by treating the oxime with 3,4-difluorobenzoyl chloride in pyridine and afforded

[18] Beilstein, ' Handbuch der Organischen Chemie,' Bond VII, p. 677.

two mole equivalents of 3,4-difluorobenzoic acid in 90% yield when hydrolysed with refluxing 10% aqueous sodium carbonate.

syn-3′,4′-*Difluoro*-2-*oximinopropiophenone*.—The oxime (0·8 g.) was treated toluene-*p*-sulphonyl chloride and the solid, obtained by procedure B, when recrystallised from methanol–water and then from benzene–light petroleum gave O-*toluene*-p-*sulphonyl*-syn-3′,4′-*difluoro*-2-*hydroxyiminopropiophenone* as plates (390 mg., 26% yield), which sublimed when heated to give needles, m.p. 119—123°, t.l.c. R_F = 0·7; $\nu_{max.}$ 1700, 1620, and 1195 cm.$^{-1}$; n.m.r., δ ~7·6 (m, aromatic-H_2), 2·50 (s, aryl-CH_3), and 2·18 (s, CH_3) (Found: C, 54·3; H; 3·5; N, 4·0. $C_{16}H_{13}F_2NO_4S$ requires C, 54·4; H, 3·7; N, 3·95%).

O-*Methyl*-anti-3′,4′-*difluoro*-2-*hydroxyiminopropiophenone*.—*anti*-3′,4′-Difluoro-2-hydroxyiminopropiophenone (5·0 g., 0·025 mole) was added to a solution of sodium ethoxide (0·025 mole) in methanol (30 ml.). Methyl iodide was added to the mixture which was then set aside at room temperature for one week. The mixture was evaporated to dryness and the residue was triturated with chloroform and filtered. The filtrate was evaporated to dryness and chromatographed on Florisil. Benzene eluted the O-*methyl* derivative, which was a mobile liquid (1·7 g., 32%) b.p. 58—60°/0·2 mm.; $\nu_{max.}$ (film) 1670, 1620, and 1520 cm.$^{-1}$,; n.m.r., δ ~ 7·8 (m, 2′,6′-H_2), ~7·2; (m, 5′-H), 4·06 (s, OCH_3), and 2·10 (s, CH_3) (Found: C, 56·35; H, 4·55; N, 6·75. $C_{10}H_9F_2NO_2$ requires C, 56·35; H, 4·25; N, 6·55%). Later fractions eluted with ether–benzene contained a large proportion of unchanged starting material.

O-*Methyl*-syn-3′,4′-*difluoro*-2-*hydroxyiminopropiophenone*.—*syn*-3′,4′-Difluoro-2-hydroxyiminopropiophenone (3·0 g.) was treated with sodium ethoxide and methyl iodide as described for the *anti*-isomer but with a reaction time of only 24 hr. The O-*methyl* derivative was obtained as a liquid (640 mg., 20%), b.p. 64—65°/0·5 mm., $\nu_{max.}$ 1700, 1625, and 1520 cm.$^{-1}$; n.m.r., δ ~7·7 (m-2′,6′-H_2), ~7·3 (m, 5′-H), 3·79 (s, OCH_3), and 2·12 (s, CH_3) (Found: C, 56·3; H, 3·95; N, 6·1. $C_{10}H_9F_2NO_2$ requires C, 56·35; H, 4·25; N, 6·55%).

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