# Unusual Base-induced Transformations of 2',6'-Dihydroxyacetophenone Oxime

By **P. Crabbé,***† **A. Villarino,** and **J. M. Muchowski,** Research Laboratories, Syntex S.A., Apartado Postal 10-820, Mexico 10, D.F., Mexico

The formation of 4-hydroxy-3-methylbenzisoxazole and/or 4-hydroxy-2-methylbenzoxazole from 2',6'-dihydroxyacetophenone oxime in aqueous methanol containing potassium hydroxide is described.

*o*-HYDROXYPHENYL ALKYL (or ARYL) KETONE *O*-ACYLOXIMES undergo a number of base-induced transformations [1-5] to give products whose nature depends on the oxime configuration, the type of base used, and characteristics of the ester leaving group. For example, the (*E*)-oxime esters (1a and b) underwent a Beckmann rearrangement with cyclization, to give the benzoxazole (3) in the presence of aqueous sodium carbonate, but were cleaved to the starting oxime with an excess of aqueous sodium hydroxide.[2-4]. Furthermore, whereas the sulphonate ester (1c) yielded the benzoxazole (3) in pyridine, cyclization occurred [to (4)] without rearrangement when aqueous potassium hydroxide was used. In contrast, the action of bases on the (*Z*)-oxime esters (2a and b) only regenerated the original oxime.

In all the base-promoted reactions described above, the formation of the products was facilitated by the

† *Present address:* Laboratoire de Chimie Organique, C.E.R.M.O., Université Scientifique et Médicale, Boite Postale 53, Grenoble—38.041, France.

[1] H. Lindemann and W. Pickert, *Annalen*, 1927, **456**, 275; H. Lindemann, H. Konitzer and S. Romanoff, *ibid.*, p. 284.

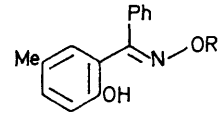
[2] A. H. Blatt and L. A. Russel, *J. Amer. Chem. Soc.*, 1936, **58**, 1903.

[3] A. H. Blatt, *J. Amer. Chem. Soc.*, 1938, **60**, 205.

[4] A. H. Blatt, *J. Org. Chem.*, 1955, **20**, 591.

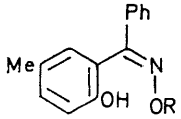
[5] P. Crabbé, L. A. Maldonado, and I. Sánchez, *Tetrahedron*, 1971, **27**, 711.

presence of a good leaving group on the oxime oxygen atom. This paper shows that, in one case, analogous reactions can occur with an unsubstituted oxime.



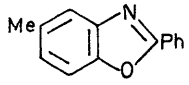
(1)

a; R = COMe
b; R = COPh
c; R = $SO_2Ph$

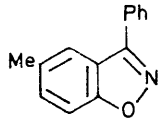


(2)

a; R = COMe
b; R = COPh



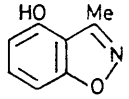
(3)



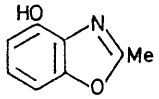
(4)

When 2′,6′-dihydroxyacetophenone oxime (5) * was heated under reflux in aqueous methanol containing 0·5 equiv. of potassium hydroxide, loss of the elements of water occurred with concomitant formation of 4-hydroxy-3-methylbenzisoxazole (6). If the hydroxide : oxime molar ratio was increased to 1, a small amount (see Table) of the isomeric 4-hydroxy-2-methylbenzoxazole (7) was formed. Further increase of

(5)



(6)



(7)

the hydroxide : oxime ratio (or the reaction temperature) resulted in formation of increasing amounts of the benzoxazole, until at a hydroxide : oxime ratio of 12, it constituted about 80% of the product mixture. Both (6) and (7) were recovered unchanged after 24 h at 140—150° in the presence of 1·7 equiv. of potassium hydroxide. In addition, although (6) and (7) were formed on pyrolysis of the oxime at temperatures greater than (or equal to) 200°, the latter substance was stable at 150° in aqueous methanol.

The transformation, under basic conditions, of the oxime (5) into the hydroxybenzisoxazole (6) can be considered analogous to reactions reported previously.[6,7] The formation of the benzoxazole (7) from the free oxime, in highly concentrated alkaline solutions, is however, to our knowledge, unprecedented. The reactions described here are apparently limited to 2′,6′-dihydroxyphenyl ketone oximes, since 2′-hydroxy-4′-methoxyacetophenone oxime and 2′,4′-dihydroxyacetophenone oxime failed to give cyclic products at reflux temperature in the presence of 8 and 12 equiv. of potassium hydroxide, respectively.

Dependence of product composition on reaction conditions

| Molar ratio, KOH: oxime [a] | Temp. (°C) | Time (h) [b] | Yield (%) Benzisoxazole(6) [c] | Yield (%) Benzoxazole(7) |
|---|---|---|---|---|
| 0·5 | 65 [d] | 69 | 100 | |
| 1·0 | 65 | 22·5 | 97·9 | 2·1 |
| 1·7 | 65 | 17 | 77·0 | 23·0 |
| 1·7 | 140—150 | 24 | 66·8 | 33·2 |
| 6·0 | 65 | 45 | 50·4 | 49·6 |
| 12·0 | 65 | 47 | 16·8 | 83·2 |
| 0·0 | 140—150 | 24 | *e* | |
| 0·0 | 200 [f] | 0·4 | 77·5 | 22·5 |
| 0·0 | 290 [g] | | 70·1 | 29·9 |

[a] In all cases a solution of the oxime (1 mmol) in 50% (v/v) aqueous methanol (10 ml) was used. Duplicate runs were made for reactions containing potassium hydroxide. [b] This indicates the time that the reaction was maintained at the indicated temperature, and is not, in general, representative of the reaction rate. [c] Determined by g.l.c. on a 6 ft × 1/8 in column packed with 10% Silicone Gum rubber on Chromosorb W at a column temperature of 250 °C and a nitrogen pressure of 11 lb $in^{-2}$. The retention times were 3·0 and 7·1 min for the benzoxazole (7) and the benzisoxazole (6), respectively. The reproducibility in duplicate runs was better than ±1%. Reflux temperature. [e] The oxime was recovered. [f] This pryolysis was carried out at 200 mmHg. [g] Injection port temperature of the g.l.c. apparatus.

## EXPERIMENTAL

M.p.s were determined in a Mel-temp apparatus and are corrected. I.r. spectral data refer to dispersions in potassium bromide discs and were measured with a Perkin-Elmer model 21 spectrophotometer. U.v. spectra were determined with a Beckmann model DU spectrophotometer for solutions in methanol. N.m.r. spectra were measured with Varian T-60 spectrometer for solutions in [$^2H_6$]acetone (unless stated otherwise) containing tetramethylsilane as internal standard. The mass spectrometric data were obtained with an Atlas CH-4 spectrometer.

*2′,6′-Dihydroxyacetophenone Oxime* (5).—The oxime, prepared from 2,6-dihydroxyacetophenone and hydroxylamine hydrochloride in hot aqueous methanol containing sodium acetate and crystallized from aqueous methanol, had m.p. 177°, $\nu_{max.}$ 3230, 1621, and 1602 $cm^{-1}$, $\lambda_{max.}$ 218 and 262 nm (ε 18,600 and 7240), δ [$(CD_3)_2SO$] 2·16 (3H, s), 6·37 (2H, d, d, *J* 7·5 Hz), 6·95 and 7·08 (1H, 2d, *J* 7·5 Hz), 9·82 (2H, s, $W_{\frac{1}{2}}$ 5 Hz), and 11·00 (1H, s, $W_{\frac{1}{2}}$ 6 Hz). Grammaticakis [8] has reported two isomeric forms, m.p. 186° and m.p. 189°, of this oxime. We are unable to explain the discrepancy between his and our observations.

*Reaction of 2′,6′-Dihydroxyacetophenone Oxime with Alkali.*—(a) 1 *Equiv. of Potassium Hydroxide.* A solution of the oxime (2·00 g) in 50% aqueous methanol (120 ml) containing 85% potassium hydroxide (0·786 g) was boiled under reflux until the oxime was no longer present (*ca.* 24 h) (t.l.c.). The methanol was removed *in vacuo*, and the residual solution was made strongly basic by addition of an excess of aqueous alkali and extracted with ethyl acetate. The aqueous phase was made acidic with hydrochloric acid, the product was extracted into ethyl acetate,

* The configuration of this oxime is unknown, but, since its toluene-*p*-sulphonate readily undergoes the Beckmann rearrangement to give (7) (see Experimental section) it is probably in the hydrogen-bonded (*E*)-form.

[6] T. Zincke and P. Schwarz, *Annalen*, 1899, **307**, 28; L. Wolff, *Ber.*, 1895, **28**, 69.

[7] A. R. Gagneux and R. Meier, *Helv. Chim. Acta*, 1970, **53**, 1883.

[8] P. Grammaticakis, *Compt. rend.*, 1969, **268**, 730.

and the extract was dried ($Na_2SO_4$) and evaporated *in vacuo*. The residue was sublimed at 130° and 0·005 mmHg to give *4-hydroxy-3-methylbenzisoxazole* (6) (1·30 g), m.p. 219—221° (from acetone–hexane) (Found: C, 64·55; H, 4·85; N, 9·2. $C_8H_7NO_2$ requires C, 64·4; H, 4·75; N, 9·4%), $\nu_{max.}$ 3195, 1613, 787, and 747 $cm^{-1}$, $\lambda_{max.}$ 213, 242, and 292 nm (ε 26,300, 2450, and 2270), δ 2·65 (3H, s), 6·74 (1H, q, $J_o$ 8, $J_m$ 1 Hz), 7·04 (1H, q, $J_o$ 8, $J_m$ 1 Hz), 7·42 (1H, t, $J_o$ 8 Hz), and 9·43 (1H, s, $W_{\frac{1}{2}}$ 5 Hz).

(b) 12 *Equiv. of Potassium Hydroxide.* A solution of the oxime (1·67 g) in 50% aqueous methanol containing potassium hydroxide (7·90 g) was boiled under reflux (48 h) and then worked up in the usual way. The crude product was separated into two fractions by preparative t.l.c. on silica gel (hexane–ethyl acetate; 9 : 1). Sublimation of the more polar fraction at 90° and 0·005 mmHg gave 4-hydroxy-2-methylbenzoxazole (7) (0·352 g), m.p. 139—140° (lit.,[9] 143°) (from dichloromethane–hexane), $\nu_{max.}$ 3077, 1631, 1613, 1577, 760, and 734 $cm^{-1}$, $\lambda_{max.}$ 209, 242, and 274 nm (ε 25,700, 10,200, and 1780), δ 2·60 (3H, s), 6·83 (1H, q, $J_o$ 7, $J_m$ 2 Hz), 7·07 (1H, q, $J_o$ 7, $J_m$ 2 Hz), 7·23 (1H, t, $J_o$ 7 Hz), and 9·33 (1H, s, $W_{\frac{1}{2}}$ 1 Hz), *m/e* 149 ($M^+$). Sublimation of the less polar fraction, first at 90° and 0·005 mmHg gave more of the benzoxazole (7) (0·137 g; m.p. 133—138°), and then at 130° and 0·005 mmHg gave the benzisoxazole (6) (0·177 g; m.p. 220—221°) identical with the material described in (a).

*Reaction of 2′,6′-Dihydroxyacetophenone Oxime with Toluene-p-sulphonyl Chloride in Pyridine.*—To a solution of 2′,6′-dihydroxyacetophenone oxime (10·0 g) in pyridine (50 ml) maintained at −25°, was added dropwise a solution of toluene-*p*-sulphonyl chloride (12·0 g) in pyridine (50 ml). The solution was allowed to warm to room temperature and was then boiled under reflux for 24 h. The mixture was cooled to room temperature, an additional portion (3·0 g) of toluene-*p*-sulphonyl chloride in pyridine (5 ml) was added, and reflux was resumed for a further 4 h. The mixture was cooled, poured into cold water, and extracted with ethyl acetate. The extract was washed with water, then with 10% hydrochloric acid, and then dried ($Na_2SO_4$). The solvent was removed *in vacuo* and the crude product was purified by column chromatography on silica gel. Elution with hexane–ethyl acetate (4 : 1) gave *3-methyl-4-tosyloxybenzoxazole* (2·54 g), m.p. 127—129° (from dichloromethane–hexane) (Found: C, 59·6; H, 4·45; N, 4·5; S, 10·2. $C_{15}H_{12}NO_4S$ requires C, 59·6; H, 4·0; N, 4·55; S, 10·6%), $\nu_{max.}$ 1600, 1344, and 1047 $cm^{-1}$, $\lambda_{max.}$ 228, 268, and 276 nm (ε 21,900, 3800, and 3240), δ ($CDCl_3$) 2·44 (3H, s), 2·56 (3H, s), and 7·00—8·06 (7H, m). Elution with hexane–ethyl acetate (7 : 3) afforded 4-hydroxy-2-methylbenzoxazole (7) (5·09 g) which after several crystallizations from dichloromethane–hexane had m.p. 139—140° and was identical with the major product from reaction (6) above.

We thank Dr. L. Throop, Dr. L. Tökés, and associates, Syntex Research, Palo Alto, California, for the mass spectrum of 4-hydroxy-2-methylbenzoxazole, and Mr. E. Avila and collaborators, Analytical Department, Syntex S.A., who provided all the other physical data. We are grateful to Mr. V. Ridaura for technical assistance.

[3/241 *Received*, 16*th January*, 1973]

[9] E. S. Lane and C. Williams, *J. Chem. Soc.*, 1965, 569.