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Note

Use of ^{1}H NMR spectroscopy in the selection of the mobile phase for high-performance liquid chromatographic monitoring of the synthesis of ibuproxam

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A convenient method for the synthesis of ibuproxam, 2-(4-isobutylphenyl)-propiohydroxamic acid (**3**), which has analgesic, antipyretic and anti-inflammatory properties[1–3], from ibuprofen (**4**)[4] via the corresponding anhydride (**2**) (Fig. 1) has been developed[5].

The developement of such a synthetic method must be supported by appropriate analytical methods capable of determining all the reactants and products quantitatively over a wide range of concentrations (even less than 1% relative). However, the instability of **2** towards solvolysis is a crucial problem for the development of a suitable high-performance liquid chromatographic (HPLC) method. Therefore, we first studied its stability by ^{1}H NMR spectroscopy.

EXPERIMENTAL

Melting points were measured on a Kofler micro hot-stage. IR, mass, UV and ^{1}H NMR spectra were obtained on a Perkin-Elmer 727B IR spectrometer, a CEC 21-110B mass spectrometer, a Hewlett-Packard 8451A diode-array UV spectrometer and Varian EM-360 60 Hz NMR spectrometer at 25°C with tetramethylsilane (TMS) as internal standard, respectively.

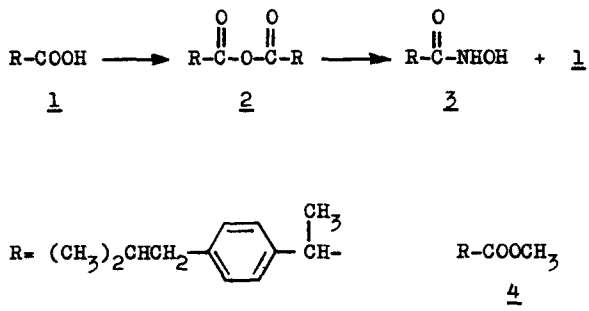

Fig. 1. Synthesis of ibuproxam.

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HPLC was carried out using an LDC/Milton Roy Constametric III pumping system with a Rheodyne 7125 sampling valve.

^{1}H NMR determinations of the stability of **2** were based on chemical shift differences for CH–CH_3 in anhydride **2** (τ 8.58), ibuprofen (**1**) and the methyl ester **4** (τ 8.53) and $COOCH_3$ in **4** (τ 6.4) in methanol (Fig. 2). The same differences were used for determinations of the stability of **2** in the presence of methanol in deuterated aprotic solvents such as chloroform, dichoromethane, carbon tetrachloride and acetonitrile, and CH–CH_3 chemical shift differences for **1** (τ 8.53) and **2** (τ 8.58) were used for studies in the same solvents in the presence of water.

Standards of **1**[4], **2**[5], **3**[1] and **4**[6] were prepared according to the literature. The UV absorption maxima obtained were 222 nm for **1** and **2** and 210 nm for **3**.

RESULTS AND DISCUSSION

Stability studies of **2** in different aprotic and protic solvents and in mixtures by ^{1}H NMR spectroscopy showed that solvolysis in methanol at 25°C is relatively fast and is completed in about 24 h, whereas **2** is stable in aprotic solvents such as chloroform, dichloromethane, carbon tetrachloride and acetonitrile when less than 5% of a protic solvent such as methanol or water is present. However, the presence of 10% of a protic solvent causes significant solvolysis.

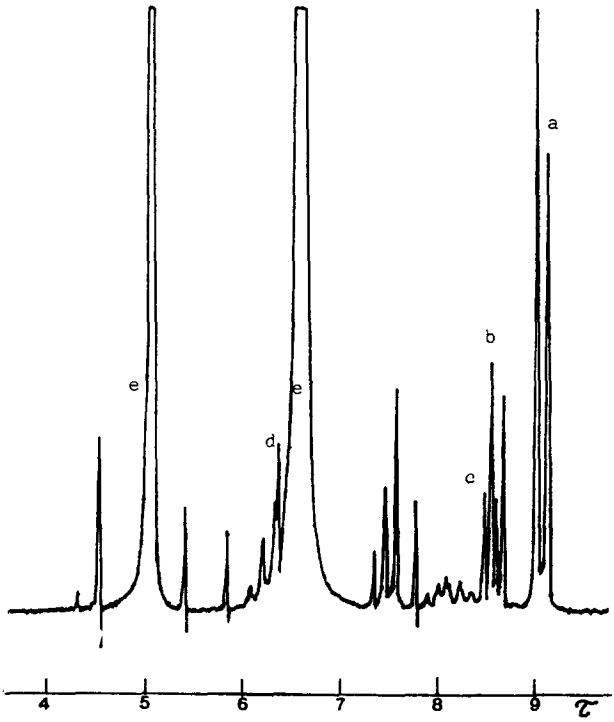

Fig. 2. ^{1}H NMR spectrum of **2** in methanol after 80 min. Signals for (a) $(CH_3)_2CHCH_2$ in **1**, **2** and **4**; (b) CH_3CH in **2**; (c) CH_3 in **1** and **4**; (d) CH_3O in **4**; (e) methanol.

Fig. 3. Chromatogram of 0.1 mg/ml of **2** (retention time 2.11 min), ibuprofen (**1**) (3.17 min) and ibuproxam **3** (5.35 min) standards.

As shown by independent experiments, hydrolysis was catalysed by addition of $Eu(fod)_3$, to increase the chemical shift differences. Although $Eu(fod)_3$ significantly influences the chemical shifts, particularly those of the isopropionic acid part of the molecules, we were unable to use ^1H NMR as a simple and direct tool to follow the reaction course quantitatively.

From the stability of two indifferent solvents and mixtures it was clear which solvent or mixture could be used and the appropriate phase was chosen. The HPLC method developed on the basis of these results is as follows: metal column (150 × 4.6 mm I.D.), LiChrosorb NH_2 (5 μm) as stationary phase, acetonitrile–0.01 *M* tartaric acid (100:1.5) as eluent, flow-rate 1 ml/min and UV detection at 220 nm.

With the above mobile phase **2** is stable and good resolution is achieved (Fig. 3). The method shows good reproducibility (relative standard deviation = 0.5%), a wide range of linearity (from below 1 ng/ml to 0.1 mg/ml for **1**, **2** and **3**) and low detection limits (1 ng/ml for **1** and 0.1 ng/ml for **2**).

This HPLC method has been used successfully not only for the developement of the synthetic method but also for in-process control on a production scale and for the final product quality control.

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