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Preliminary communication

THE FERROCENE ANALOGUES OF SALICYLIC ACID AND ASPIRIN

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Summary

The reaction of hydroxyferrocene with 2,3-dihydropyran gave (ferrocenyloxy)-2-tetrahydropyran which on lithiation gave the corresponding 2-lithiated ferrocene which was used to prepare 1-carboxy-2-hydroxyferrocene and 1-carboxy-2-acetoferrocene.

Currently, there is much interest in the possible technological applications of metallocenes, especially ferrocene, for use in the design of drugs [1]. We have reported the preparation of some ferrocene derivatives of penicillins and cephalosporins. Several of these compounds exhibited high antibiotic activity and others behaved as potent β-lactamase inhibitors [2]. The activity of these ferrocene compounds prompted us to attempt the preparation of ferrocene analogues of other pharmacologically active compounds. In this report we describe the preparation of the ferrocene analogues of salicylic acid and aspirin.

Recently a high yield route to ferrocenylboron dibromide was reported [3] and we utilized this to prepare ferrocenylboronic acid via base hydrolysis [4]. The ferrocenylboronic acid was converted to the oxidatively unstable hydroxyferrocene [5]. Treatment of hydroxyferrocene with 2,3-dihydropyran in the presence of acid gave the crystalline air stable pyran II m.p. 58°C (yield 83%) [6]. The hydroxyferrocene was regenerated easily from the pyran in good yield (94%) by treatment with hydrochloric acid at room temperature but the pyran II was stable in the presence of base.

Lithiation of the ferrocenyloxypyran II with n-butyllithium in ether gave the 2-lithiated intermediate III which was condensed with carbon dioxide to give (1-carboxyferrocenyl-2-oxy)-2-tetrahydropyran (88%) (Scheme 1). Treatment of this ether with acid, under mild conditions, gave the hydroxyferrocene IV (78%) which is the analogue of salicylic acid.

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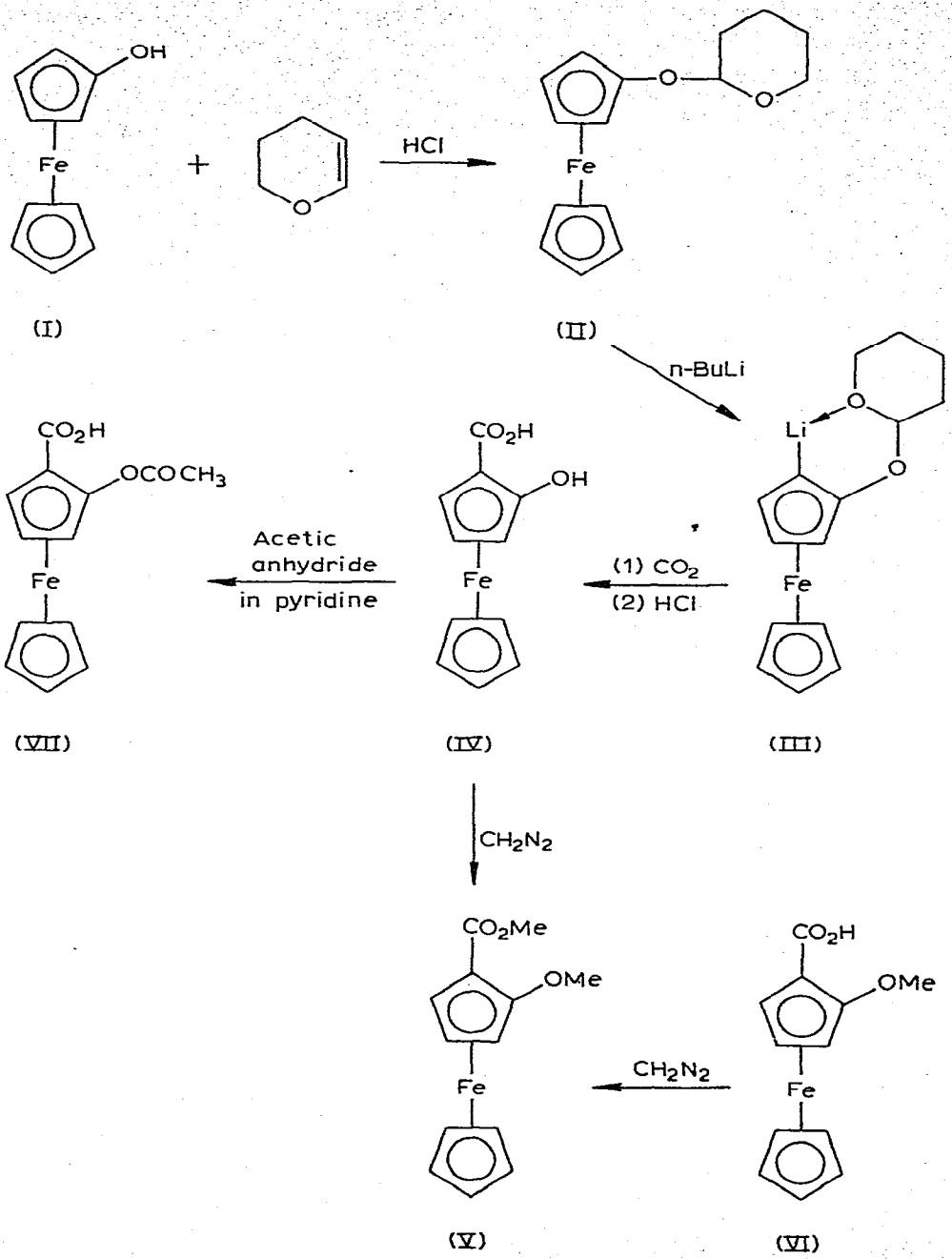

The 1,2-orientation of the substituents was confirmed by conversion of the acid IV, with diazomethane, to the methoxy ester V. This ester V (identical m.p. 39°C, IR spectrum and R_F value from TLC) was prepared also from methoxyferrocene by treatment with n-butyllithium condensation with carbon dioxide, to give the acid VI followed by diazomethane [7]. The

hydroxyferrocene IV was air-stable and this is probably due to the presence of the electron-withdrawing carboxylic acid group and also due to intramolecular hydrogen bonding between the two adjacent groups, as indicated by the infrared spectrum IR absorption frequencies (KBr) 1650vs (characteristic of H-bonded carboxylic acid) 3380m cm^{-1} (characteristic of H-bonded phenolic OH).

The hydroxyferrocene IV underwent facile conversion to the ferrocenylacetate VII on treatment with acetic anhydride in pyridine. The ferrocene analogue of aspirin was an air stable solid, m.p. 136°C, the ^1H NMR spectrum exhibited signals at δ (ppm, CCl_4), —1.62 (1H, s, OH; this signal disappeared on the addition of D_2O) 6.39 and 5.70 (8H, m and s, ferrocene), 7.79 (3H, s, CH_3).

The tetrahydropyranyl system is an effective protecting group for hydroxyferrocene and provides also for directed lithiation in the 2-position. It is possible that the lithiated intermediate III could be used to synthesise a number of hitherto unobtainable 2-substituted hydroxyferrocenes. Further work is in progress to explore this possibility.

All new compounds exhibited the requisite analytical and spectral properties.

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References

1 J.C. Johnson, Metallocene Technology, Noyes Data Corporation, Park Ridge, New Jersey, 1973; R. Kalish, T.V. Steppe and A. Walser, J. Med. Chem., 18 (1975) 224.
2 E.I. Edwards, R. Epton and G. Marr, J. Organometal. Chem., 85 (1975) C23.
3 W. Rut, M. Fueller and W. Siebert, J. Organometal. Chem., 64 (1974) C45.
4 S. McVey, I.G. Morrison and P.L. Pauson, J. Chem. Soc., C, (1967) 1847.
5 A.N. Nesmeyanov, V.A. Sazonova and V.N. Drozd, Tetrahedron Lett., (1959) 13; A.N. Nesmeyanov, V.A. Sazonova and V.N. Drozd, Doklady Akad. Nauk SSSR, 129 (1959) 1867.
6 G.F. Woods and D.N. Kramer, J. Amer. Chem. Soc., 67 (1947) 2246.
7 A.N. Nesmeyanov, T.V. Baukova and K.I. Grandberg, Izv. Akad. Nauk SSSR, Ser. Khim., (1967) 1867.