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The Synthesis and Reactions of Homonuclear Ferrocene Acid Anhydrides and their use in the Preparation of Ferrocenyl-penicillins and -cephalosporins[+]

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Summary

1,1'-Ferrocenediacetic acid anhydride and o-[1'-(carboxymethylferrocene]benzoic acid anhydride have been prepared and their reactions with amines investigated. These anhydrides have been shown to be useful for the preparation of heteroannularly substituted ferrocenyl-penicillins and -cephalosporins.

Introduction

Recently we reported the synthesis of a series of ferrocenyl-penicillins and -cephalosporins, for example (I and II; R^1 = H, R^2 = Na) [2]. Almost all these molecules exhibited antibiotic activity and some behaved as β-lactamase inhibitors. These compounds were prepared from ferrocenyl carboxylic acids which were condensed via their acid chlorides or in the presence of N,N'-dicyclohexylcarbodiimide with either 6-aminopenicillanic acid (6-APA) or 7-amino-cephalosporanic acid (7-ACA). In all

[+] Some of these results have been presented in a preliminary form [1].

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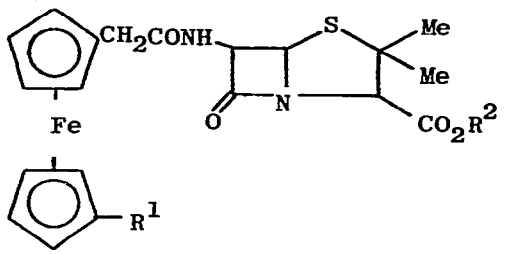
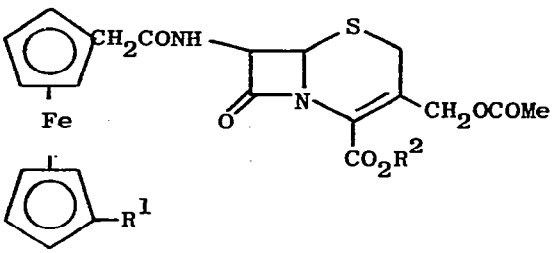


(I)



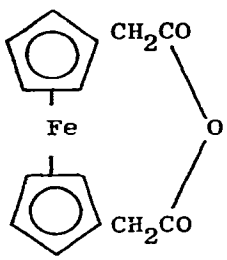
(II)

these molecules only one η-cyclopentadienyl ring of the ferrocene moiety was substituted. Most commercially available semi-synthetic penicillins and cephalosporins possess a side chain that includes a phenyl or heteroaromatic group and the introduction of substituents into these nuclei effects changes in their antibiotic activity and β-lactamase susceptibility. The introduction of substituents into the ferrocenyl group should modify the pharmacological activity of the ferrocene compounds. In this report we describe the preparation of some heteroannularly substituted ferrocenyl-penicillins and -cephalosporins.

Results and discussion

The reaction of acid anhydrides with 6-aminopenicillanic acid or 7-aminocephalosporanic acid has been used to introduce substituents into the side chains of these molecules and this route seemed ideal for the preparation of heteroannularly substituted ferrocene derivatives [3].

1,1'-Ferrocenediacetic acid anhydride (III) was prepared by the treatment of 1,1'-ferrocenediacetic acid with dicyclohexylcarbodiimide. Treatment of the anhydride (III) with cyclohexylamine gave the amide (IV;R = $C_6H_{13}N$). Similar reactions with ammonium hydroxide, morpholine and benzylamine gave the corresponding amides (IV; R = NH_2, C_4H_9NO and $PhCH_2NH$) respectively. Similarly, the anhydride was treated with



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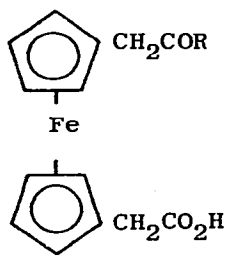


(IV)

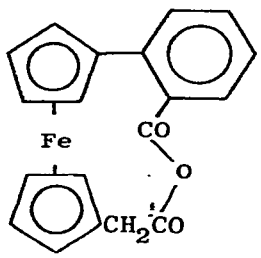
6-aminopenicillanic acid (6-APA) or 7-aminocephalosporanic acid (7-ACA) in the presence of two molar equivalents of triethylamine. Acidification of the triethylamine salts gave the ferrocenyl-penicillin (I; $R^1 = CH_2CO_2H$, R^2= H) or -cephalosporin (II; $R^1 = CH_2CO_2H$, R^2 = H) which were isolated as their disodium salts (I; $R^1 = CH_2CO_2Na$, R^2 = Na) and (II; $R^1 = CH_2CO_2Na$, R^2 = Na) by the addition of sodium 2-ethylhexanoate. The infrared spectrum of the ferrocenylpenicillin (I; $R^1 = CH_2CO_2Na$, R^2 = Na) exhibited a strong absorption at 1765 cm^{-1} characteristic of a carbonyl group in the β-lactam ring of a penicillin. Absorptions at 1660 cm^{-1} and 1600 cm^{-1} indicated the presence of an amide carbonyl group and ionized carboxylic acid groups respectively. The spectrum of the ferrocenyl-cephalosporin (II, $R^1 = CH_2CO_2Na$, R^2 = Na) showed similar absorptions at

1760, 1660 and 1610 cm^{-1} together with a peak at 1735 cm^{-1} characteristic of an ester carbonyl group.

An interesting feature of the reaction of an anhydride with amines is that it can be adapted to give disubstituted ferrocenes in which one cyclopentadienyl ring is part of the side-chain of a penicillin and the other is part of the side-chain of a cephalosporin. Compounds of this type have been described by Perella and Dolfini and shown to be useful broad spectrum antibiotics [4]. The anhydride (III) was condensed with a molar equivalent of the trimethylsilyl ester of 6-aminopenicillanic acid in the presence of triethylamine to give the trimethylsilyl ester of 1-(6-acetamidopenicillanic acid)-1'-(carboxymethyl)ferrocene (I; $R^1 = CH_2CO_2H$, $R^2 = SiMe_3$). The carboxylic acid group on the second η-cyclopentadienyl of the compound (I; $R^1 = CH_2CO_2H$, $R^2 = SiMe_3$) was activated with ethyl chloroformate and coupled with 7-aminocephalosporanic acid to give the mixed antibiotic (I; $R^1 = CH_2CO$-7-ACA, $R^2 = H$). The trimethylsilyl group was readily removed under the acid conditions used in the reaction work up.

o-[1'-(Carboxymethyl)ferrocenyl]benzoic acid anhydride (V) was prepared as part of the study of acid anhydrides that were suitable for coupling with 6-APA and 7-ACA. The anhydride (V) was formed readily in high yield by the treatment of o-[1'-(carboxymethyl)ferrocene]benzoic acid with N,N'-dicyclohexylcarbodiimide. Treatment of the anhydride (V) with 6-APA followed by sodium 2-ethylhexanoate gave the ferrocenyl-penicillin (VI; $R^1 = CO_2Na$, $R^2 = Na$) as the major product which was formed by nucleophilic attack on the aliphatic carbonyl group. This structure was supported by the infrared spectrum which exhibited an absorption at 1670 cm^{-1} for the amide carbonyl group which was at the same position as that found with 6-(2-ferrocenyl-

acetamido)penicillanic acid (I; R^1 = H, R^2 = Na) [2]. In contrast the absorption for the carbonyl group of the conjugated amide in the ferrocenyl-penicillin (VII) occurred at 1655 cm^{-1} [5]. The spectrum of the ferrocenyl-penicillin (VI; R^1= CO_2Na, R^2 = Na) also had absorptions at 1765 cm^{-1} and 1605 cm^{-1} consistent with there being a β-lactam carbonyl group and ionized carboxylic acid groups in the molecule. Similarly, treatment of the anhydride (V) with 7-ACA followed by sodium 2-ethylhexanoate gave the ferrocenyl-cephalosporin (VIII; R^1 = CO_2Na, R^2 = Na) as the major product since the infrared spectrum of this molecule possessed a carbonyl absorption at 1670 cm^{-1}.



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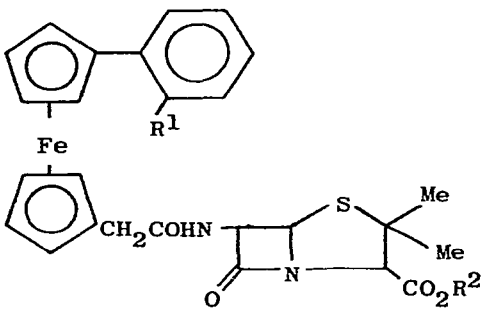

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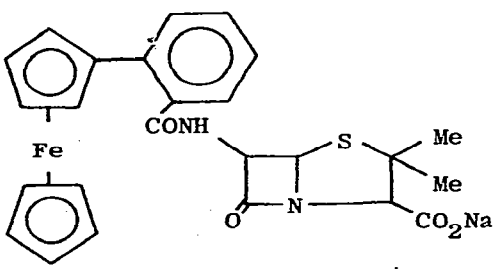

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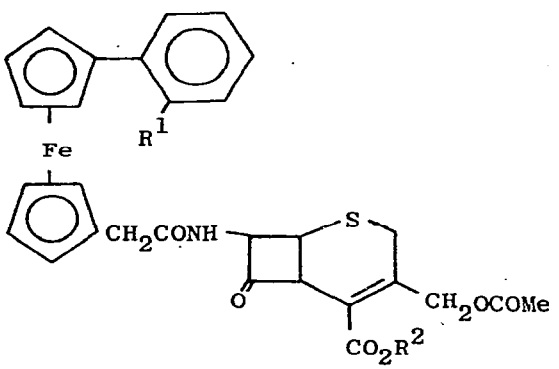

(VIII)

Using the same preparative procedure as that employed to prepare the mixed ferrocene antibiotic (I; R^1 = CH_2CO-7-ACA, R^2 = Na) treatment of the anhydride (V) with two consecutive molar equivalents of 6-APA or 7-ACA gave the disubstituted derivatives (VI; R^1 = CO-6-APA-Na, R^2= Na) and (VIII; R^1 = CO-7-ACA-Na, R^2 = Na) respectively. Compound VI is of interest because it incorporates an aromatic system analogous to that found in biphenyl penicillin (β-lactamase resistant) and an aromatic system analogous to classical benzyl penicillin (penicillin G).

All the ferrocenyl-penicillins and -cephalosporins prepared in this investigation were characterised by the preparation of at least one amine salt. Initially the sodium and triethylamine salts were prepared for elemental analysis in the traditional manner. However, many of the sodium salts decomposed during recrystallization and the triethylamine salts did not crystallize satisfactorily. In most cases the benzylamine or cyclohexylamine salts were prepared but, if the isolation of these salts also proved difficult, the ferrocenyl-penicillins and cephalosporins were characterised as their adamantanamine salts. We found that adamantanamine was useful for preparing crystalline derivatives of many β-lactam antibiotics.

Experimental

1,1'-Ferrocenediacetic acid anhydride III

A mixture of 1,1'-ferrocenediacetic acid (5.4 g, 0.0178 mol) and N,N'-dicyclohexylcarbodiimide (3.66 g, 0.0178 mol) in dichloromethane (200 cm^3) was stirred at room temperature for 6 h. The precipitated N,N'-dicyclohexylurea was removed by filtration and the solvent evaporated. The residue was extracted with ether. Evaporation of the ether gave the product as a yellow solid. Recrystallisation from light

petroleum afforded 1,1'-ferrocenediacetic acid anhydride (3.23 g, 64%) as yellow platelets, m.p. 91-92.5°. (Found: C, 58.94; H, 4.40; O, 16.77%; M^+ 284. $C_{14}H_{12}O_3Fe$ requires C, 59.18; H, 4.26; O, 16.90%; M, 284.10) . PMR (60 MHz) (δ, CCl_4); 4.12 (8H, s, ferrocene) and 3.32 (4H, s, $2xCH_2$).

Reactions of 1,1'-ferrocenediacetic acid anhydride

(a) Reaction with cyclohexylamine

Cyclohexylamine (0.5 cm^3) in ether (10 cm^3) was added dropwise to 1,1'-ferrocenediacetic acid anhydride (0.57 g, 0.002 mol) in ether (25 cm^3) and the mixture was stirred for 0.25 h. Aqueous 2MNaOH (25 cm^3) was added, and the mixture was stirred for 0.5 h. The ether layer was separated and extracted with 2M NaOH. The combined alkaline extracts were adjusted to pH 4 with 2M HCl and an oil was deposited which was extracted with dichloromethane. Evaporation of the dried ($MgSO_4$) organic extracts gave the product as a yellow solid. Recrystallisation from acetone-light petroleum afforded N-cyclohexyl-(1'-carboxymethylferrocenyl)acetamide (0.467 g, 61%) as yellow needles, m.p. 132.5 - 133.5°. (Found: C, 62.85; H, 6.57; O, 12.74%; M^+ 383. $C_{20}H_{25}O_3Fe$ requires C, 62.67; H, 6.58; O, 12.52%; M 383.28) PMR (60 MHz) (δ, CD_2Cl_2): 6.17 (1H, s, OH), 5.48 (1H, s, NH), 4.04 (8H, s, ferrocene), 3.28 and 3.21 (4H, s and s, $2xCH_2$) and 1.98 - 0.93 [11H, m (broad), cyclohexyl].

(b) Reaction with benzylamine

Benzylamine (0.5 cm^3) in ether (10 cm^3) was added to 1,1'-ferrocenediacetic acid anhydride (0.57 g, 0.002 mol) in ether (25 cm^3). The work up was as described previously. Recrystallisation of the product from acetone-light petroleum

gave N-benzyl(1'-carboxymethylferrocenyl)acetamide (0.501 g, 64%) as yellow needles, m.p. 91-92°. (Found: C, 64.36; H, 5.29%; M^+ 391. $C_{21}H_{21}O_3Fe$ requires C, 64.45; H, 5.41% M 391.26). PMR (60 MHz) (δ, CD_2Cl_2): 10.70 (1H, s, OH), 7.14 (5H, s, phenyl), 6.23 (1H, s, NH), 4.24 and 4.08 (10H, s and s, CH_2 and ferrocene) and 3.31 (4H, s, 2xCH_2).

(c) Reaction with morpholine

Morpholine (0.5 cm^3) in ether (10 cm^3) was added dropwise to 1,1'-ferrocenediacetic acid anhydride (0.57 g, 0.002 mol) in ether (25 cm^3). The work up was as described previously. Recrystallisation from acetone-light petroleum gave N-[(1'-carboxymethyl)ferrocenylacetyl]morpholine (0.422 g, 57%) as yellow needles, m.p. 132-133.5°. (Found: C, 58.02; H, 5.62; O, 18.30%; M^+ 371. $C_{18}H_{21}O_4NFe$ requires C, 58.25; H, 5.71; O, 17.25%; M 371.23). PMR (60 MHz) (δ, CD_2Cl_2): 7.25 (1H, s, OH), 4.19 and 4.09 (8H, s and s, ferrocene), 3.57, 3.44 and 3.38 (12H, s, s and s, 6xCH_2).

(d) Reaction with aqueous ammonia

28% Aqueous ammonia (2 cm^3) was added to 1,1'-ferrocenediacetic acid anhydride (0.57 g, 0.002 mol). There was an immediate reaction accompanied by a rise in temperature. The mixture was diluted with water (10 cm^3), washed with ether and adjusted to pH 4 with 6M HCl. Fine yellow crystals were deposited. The crystals were collected, dissolved in 28% aqueous ammonia (5 cm^3) and the product redeposited by acidification of the solution. The product 1'-(carboxymethyl)-ferrocenylacetamide was collected by filtration (0.422 g, 70%) as yellow needles, m.p. 162-164° (decomp). (Found: C, 56.11; H, 5.19%; M^+ 301. $C_{14}H_{15}O_3NFe$ requires C, 55.84; H, 5.02%; M 301.13).

1-(6-Acetamidopenicillanic acid)-1'-(carboxymethyl)ferrocene (disodium salt) (I; $R^1 = CH_2CO_2Na$, $R^2 = Na$)

1,1'-Ferrocenyldiacetic acid anhydride (0.4 g, 0.0014 mol) in dichloromethane (10 cm^3) was added to a mixture of 6-aminopenicillanic acid (0.3 g, 0.0014 mol) and triethylamine (0.28 g, 0.0028 mol) in dichloromethane (15 cm^3). The mixture was stirred at 0° for 0.25 h and at 15° for 1 h, and the solvent evaporated under vacuum at room temperature. The residue was dissolved in a mixture of water (50 cm^3) and ethyl acetate (25 cm^3) and the aqueous phase was adjusted to pH 2.5 with 2M HCl. The layers were separated and the organic phase was washed with water and dried ($MgSO_4$). A 40% solution of sodium 2-ethylhexanoate in 4-methylpentan-2-one (1.16 cm^3) was added to the dried ($MgSO_4$) ethyl acetate solution. The mixture was concentrated under vacuum and added dropwise to ether (300 cm^3). A pale yellow solid separated which was washed by decantation with ether, collected by filtration and dried to give the disodium salt of 1-(6-acetamidopenicillanic acid)-1'-(carboxymethyl)ferrocene (0.478 g, 61%), m.p. 248-253° (decomp.). (Found: C, 47.42; H, 4.97; N, 4.41%. $C_{22}H_{22}O_6N_2FeSNa_2 . H_2O$ requires C, 47.01; H, 4.30; N, 4.99%). Principal infrared absorption frequencies (cm^{-1}) at:- 3120s, 3095w, 2980w, 1765s, 1660s, 1595s, 1530s, 1405s, 1330m. PMR (60 MHz) (δ, D_2O): 5.48 and 5.43 (2H, d and d, 2xCH), 4.20 and 4.16 (9H, s and s, ferrocene and CH), 3.38 and 3.22 (4H, s and s, $2xCH_2$), 1.58 and 1.49 (6H, s and s, $2xCH_3$). T.L.C. showed that the compound was pure and the dicyclohexylamine salt (I; $R^1 = CH_2CO_2^-C_6H_{11}^+NH_3$, $R^2 = C_6H_{11}^+NH_3$), m.p. 129-132° (decomp) was prepared. (Found: C, 58.05; H, 7.40; N, 8.16%. $C_{34}H_{50}O_6N_4SFe$ requires C, 58.44; H, 7.22; N, 8.03%). PMR (60 MHz) (δ, D_2O): 5.45 and 5.38 (2H, d and d, 2xCH), 4.18 (8H, s, ferrocene), 3.97 (1H, s, CH), 3.37 and 3.20 (4H, s and

s, 2xCH_2), 1.96 to 1.14, 1.56 and 1.48 [28H, m (broad), s and s, cyclohexyl and 2xCH_3].

1-(7-Acetamidocephalosporanic acid)-1'-(carboxymethyl)-ferrocene (disodium salt) (II; $R^1 = CH_2CO_2Na$, $R^2 = Na$)

1,1'-Ferrocenyldiacetic acid anhydride (0.84 g, 0.003 mol) in dichloromethane (15 cm^3) was added to a mixture of 7-aminocephalosporanic acid (0.82 g, 0.003 mol) and triethylamine (0.61 g, 0.006 mol) in dichloromethane (25 cm^3) at 0^o. The work up was as described previously and this gave the disodium salt of 1-(7-acetamidocephalosporanic acid)-1'-(carboxymethyl)-ferrocene (0.882 g, 53%) as a yellow solid, m.p. 154-159° (decomp). Principal infrared absorption frequencies (cm^{-1}) at:- 3440s, 3100w, 2970w, 1760s, 1665s, 1605s, 1400s, 1235s, 1045m, 815m. PMR (60 MHz) (δ, D_2O): 5.62 and 5.07 (2H, d and d, 2xCH), 4.76 (2H, s, CH_2), 4.19 (8H, s, ferrocene), 3.53, 3.39 and 3.23 (6H, s, s and s, 3xCH_3) and 2.10 (3H, s, O$C\underline{H}_3$). T.L.C. showed the compound to be pure and it was characterised as the diadamantanamine salt (II; $R^1 = CH_2CO_2C_{10}H_{15}^+NH_3$, $R^2 = C_{10}H_{15}^+NH_3$ obtained as brown crystals; m.p. 178-182° (decomp.). (Found: C, 60.32; H, 7.02; N, 5.85%. $C_{44}H_{58}O_8N_4SFe$: H_2O requires C, 60.27; H, 6.90; N, 6.34%).

1-(6-Acetamidopenicillanic acid)-1'-(7-acetamidocephalosporanic acid)ferrocene (disodium salt)

Chlorotrimethylsilane (0.22 g, 0.002 mol) was added to a mixture of 6-aminopenicillanic acid (0.43 g, 0.002 mol) and triethylamine (0.41 g, 0.004 mol) in dichloromethane (40 cm^3) and the mixture was stirred for 1 h. 1,1'-Ferrocenyldiacetic acid anhydride (0.2 g, 0.002 mol) in dichloromethane (10 cm^3) was added. The mixture was stirred for 1 h, cooled to 0^o,

ethyl chloroformate (0.22 g, 0.002 mol) added and then stirred at 0^{o} for 0.25 h. A solution of 7-aminocephalosporanic acid (0.54 g, 0.002 mol) and triethylamine (0.41 g, 0.002 mol) in dichloromethane (10 cm^3) was added. The coolant was removed and the reaction allowed to proceed for 1 h. The mixture was diluted with an equal volume of dichloromethane extracted three times with 0.1M HCl, washed with water, dried ($MgSO_4$) and the solvent evaporated under vacuum at room temperature. The residue was dissolved in a mixture of phosphate buffer pH 7.5 (100 cm^3) and ethyl acetate (50 cm^3) and the aqueous phase adjusted to pH 2.5 with 2M HCl. The organic layer was separated, washed with water and dried ($MgSO_4$). A solution of sodium 2-ethylhexanoate in 4-methylpentan-2-one (1.8 cm^3) was added to the dried ($MgSO_4$) ethyl acetate solution. The mixture was concentrated under vacuum and added dropwise to ether (300 cm^3). The yellow-brown solid which separated was washed by decantation with ether, collected by filtration and dried to give the disodium salt of 1-(6-acetamidopenicillanic acid)-1'-(7-acetamidocephalosporanic acid)ferrocene, as a brown solid (0.656, 29%). Principal infrared absorption frequencies (cm^{-1}) at:- 3470s, 2990m, 1770s, 1740m, 1665s, 1615s, 1575s, 1525m, 1420s, 1330m, 1240m, 1155m, 1040m, 820m. T.L.C. showed a single compound and it was characterised as the diadamantanamine salt (I; $R^1 = CH_2CO\text{-}7\text{-}ACA\text{-}C_{10}H_{15}^{+}NH_3$, $R^2 = C_{10}H_{15}^{+}NH_3$) obtained as orange crystals, m.p. 132-136^{o} (decomp.). (Found: C, 56.78; H, 6.23; N, 6.43%. $C_{52}H_{68}N_6O_{10}S_2Fe$. H_2O requires C, 57.13; H, 6.63; N, 7.67%).

Preparation of o-[1'-(Carboxymethyl)ferrocene] benzoic acid anhydride (V)

N,N'-Dicyclohexylcarbodiimide (3.2 g, 0.015 mol) in dichloromethane (20 cm^3) was added dropwise to a solution of

o-[1'-(carboxymethyl)ferrocene]benzoic acid (5.33 g, 0.015 mol) in dichloromethane (100 cm^3) at 0°. The coolant was removed and the mixture was stirred for 1 h at room temperature. The precipitated N,N'-dicyclohexylurea was removed by filtration and evaporation of the solvent gave the product as an orange solid. Recrystallisation from dichloromethane-light petroleum afforded o-[1'-(carboxymethyl)ferrocenyl]benzoic acid anhydride (4.10 g, 81%) as orange needles, m.p. 140-143° (decomp.). (Found: C, 66.31; H, 4.27; O, 13.86%; M^+ 346. $C_{19}H_{14}O_3Fe$ requires C, 65.92; H, 4.08; O, 13.86% M 346.17). PMR (60 MHz) (δ, $CDCl_3$): 7.71-7.20 [4H, m (broad), phenyl], 4.40, 4.16 and 4.01 (8H, m, m and m, ferrocene) and 3.32 (2H, s, CH_2).

o-[1'-(6-Acetamidopenicillanic acid)ferrocene]benzoic acid (disodium salt) (VI; $R^1 = CO_2Na$, $R^2 = Na$)

o-[1'-(Carboxymethyl)ferrocene]benzoic acid anhydride (0.69 g, 0.002 mol) in dichloromethane (10 cm^3) was added to a mixture of 6-aminopenicillanic acid (0.43 g, 0.002 mol) and triethylamine (0.4 g, 0.004 mol) in dichloromethane (20 cm^3) at 0°. The mixture was stirred at 0° for 0.25 h and at 15° for 1 h, and the solvent was evaporated under vacuum at room temperature. The work up was as previously described and the disodium salt of o-[1'-(6-acetamidopenicillanic acid)-ferrocene]benzoic acid (0.608 g, 60%) was isolated as a pale yellow solid, m.p. 226-232°. Principal infrared absorption frequencies (cm^{-1}) at:- 3440s, 3110w, 2990m, 1765s, 1670s, 1605s, 1585s, 1415s, 1330m, 770m. This compound was characterised as the dicyclohexylamine salt (VI; $R^1 = CO_2C_6H_{11}^+NH_3$, $R^2 = C_6H_{11}^+NH_3$ obtained as deep orange crystals, m.p. 179-184° (decomp.). (Found: C, 61.00; H, 7.06; N, 6.43%. $C_{39}H_{52}N_4O_6SFe$ requires C, 61.57; H, 6.89; N, 7.47%).

o-[1'-(7-Acetamidocephalosporanic acid)ferrocene]benzoic acid (disodium salt) (VIII; $R^1 = CO_2Na$, $R^2 = Na$)

o-[1'-Carboxymethyl)ferrocene]benzoic acid anhydride (1.04 g, 0.003 mol) in dichloromethane (10 cm^3) was added to a mixture of 7-aminocephalosporanic acid (0.82 g, 0.003 mol) and triethylamine (0.61 g, 0.006 mol) in dichloromethane (25 cm^3) at 0^o. The work up was as described previously and this gave the disodium salt of o-[1'-(7-acetamidocephalosporanic acid)-ferrocene]benzoic acid (1.05 g, 58%) as a pale yellow solid, m.p. 169-174^o (decomp.). Principal infrared absorption frequencies (cm^{-1}) at:- 3450s, 3110w, 2960m, 1755s, 1720s, 1670s, 1610s, 1585s, 1565m, 1405s, 1230s, 1030m, 765m. This compound was characterised as the diadamantanamine salt (VIII; $R^1 = CO_2C_{10}H_{15}^+NH_3$, $R^2 = C_{10}H_{15}^+NH_3$) obtained as brown crystals m.p. 157-162^o (decomp.). (Found: C, 62.90; H, 6.88; N, 4.98%. $C_{49}H_{60}N_4O_8SFe.H_2O$ requires C, 62.68; H, 6.66; N, 5.96%).

o-[1'-(6-Acetamidopenicillanic acid)ferrocene]benzoyl-N-(6-aminopenicillanic acid) (disodium salt)

This compound was prepared from the anhydride (V) (104 g, 0.003 mol) by the route described for the mixed antibiotic (I; $R^1 = CH_2CO$-7-ACA-Na, $R^2 = Na$). The disodium salt (VI; $R^1 = CO$-6-APA-Na, $R^2 = Na$) (1.146 g, 48%) was obtained as a yellow solid, m.p. 178-182^o (decomp). Principal infrared absorption frequencies (cm^{-1}) at:- 3420s, 3100w, 2970m, 1765s, 1665s, 1610s, 1580s, 1410s, 1325m, 765m. T.L.C. showed that the compound was pure and it was characterised as the dicyclohexylamine salt (VI; CO-6-APA-$C_6H_{11}^+NH_3$, $C_6H_{11}^+NH_3$) obtained as orange crystals m.p. 149-153^o. (Found: C, 58.71; H, 6.84; N, 7.20% $C_{47}H_{62}N_6O_8S_2Fe$ requires C, 58.86; H, 6.52; N, 8.76%).

o-[1'-(7-Acetamidocephalosporanic acid)ferrocene]benzoyl-N-(7-aminocephalosporanic acid) (disodium salt)

This compound was prepared from the anhydride (V) (1.04 g, 0.003 mol) by the route described for the mixed antibiotic (I; R^1 = CH_2CO-7-ACA-Na, R^2 = Na). The disodium salt (VIII; R^1 = CO-7-ACA-Na, R^2 = Na) (0.997 g, 36%) was obtained as a yellow solid, m.p. 141-145° (decomp.). Principal infrared absorption frequencies (cm^{-1}) at:- 3420s, 2965m, 1775s, 1745s, 1675s, 1605s, 1575s, 1415s, 1235s, 1035m, 770m. TL.C. showed that the compound was pure and it was characterised as the diadamantanamine salt (VIII; R^1 = CO-7-ACA-$C_{10}H_{15}^+NH_3$, R^2 = $C_{10}H_{15}^+NH_3$) obtained as brown crystals, m.p. 156-161° (decomp). (Found: C, 58.42; H, 6.84; N, 6.02%. $C_{59}H_{70}N_6O_{12}S_2Fe$. $2H_2O$ requires C, 58.50; H, 6.16; N, 6.93%).

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