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# REARRANGEMENT DURING CYCLISATION OF SOME 3-(2-PYRROLYL) PROPIONIC ACIDS AND RELATED COMPOUNDS

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**Abstract**—Cyclisation of the title compounds leads to mixtures of the expected 4H-cyclopental[b]pyrrol-4-ones (**1**), the corresponding 6-ones (**3**) by a single rearrangement, and the cyclopenta[c]pyrrol-4-ones (**4**) by a double rearrangement, the proportions depending upon the substituents.

The $^1$H NMR spectra of 2-methyl-4H-cyclopenta[b]thiophen-6-one (**3f**) shows $^6$J long range $CH_3/CH_2$ coupling, but this is absent in the corresponding pyrroles (**3c,d**). The $^{13}$C spectra of **1** and **3** cannot be interpreted on the basis of substituent chemical shifts in pyrroles and thiophens, and are clearly –CH = CH–X (X = NMe, NPh, S) bridged derivatives of cyclopent-2-enone.

As part of another investigation into the electronic structure of heterocyclic molecules, we had occasion to attempt the synthesis of the unknown 4H-cyclopenta[b]pyrrol-4-one (**1**) system. An obvious route appeared to be cyclisation of the 2-pyrrolylpropionic acids (**2**), by analogy with earlier work based upon the corresponding 3-(3-propionic acids) of pyrroles[1–3] and thiophens.[4–7] The N-Me derivative (**2a**) gave a mixture of cyclic ketones (as described below), and this led us to study some related cases.

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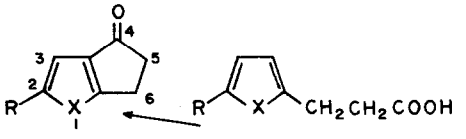
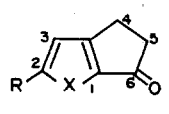
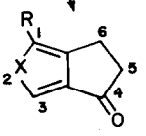


**1a**: R = H, X = NMe
**b**: R = H, X = NPh
**c**: R = Me, X = NMe
**d**: R = Me, X = NPh
**e**: R = H, X = S
**f**: R = Me, X = S

**2a**: R = H, X = NMe
**b**: R = H, X = NPh
**c**: R = Me, X = NMe
**d**: R = Me, X = NPh
**e**: R = H, X = S
**f**: R = Me, X = S
**g**: R = Me, X = O



**3a**: R = H, X = NMe
**b**: R = H, X = NPh
**c**: R = Me, X = NMe
**d**: R = Me, X = NPh
**e**: R = H, X = S
**f**: R = Me, X = S

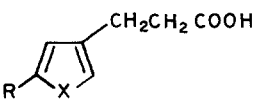


**4a**: R = H, X = NMe
**b**: R = H, X = NPh
**c**: R = Me, X = NMe
**d**: R = Me, X = NPh

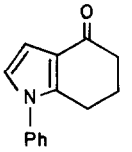
## RESULTS

Treatment of 3-(1-methyl-2-pyrrolyl)propionic acid (**2a**) with polyphosphoric acid (PPA) at 100° gave a nearly quantitative yield of isomeric neutral compounds $C_8H_9NO$ which were separated chromatographically. The compounds were clearly the expected ketone (**1a**) and its isomer (**3a**) in view of the $^1$H NMR spectra which showed adjacent pyrrolic protons (AB), but the assignment of the higher melting isomer to **1a** ($J_{A,B}$ 3.0 Hz) and the other ($J_{A,B}$ 2.5 Hz) to **3a** was non-trivial and followed from several pieces of information, in which a comparison of the $^1$H chemical shifts (Table 1) of the two compounds with 2- and 3-acylpyrroles was important.

Dipole moments,[8] a microwave study,[9] NMR studies[10] and theoretical calculations[11] all demonstrate that the preferred conformation of the 2-formyl- and 2-acetylpyrroles is the *syn* form (NCCO) analogous to **3a**; while similar studies have shown that the 3-acyl derivatives have the preferred rotamer in the *trans*-form (NCCCO) analogous to **1a**. Thus it is possible to compare the $^1$H chemical shifts of these acyl compounds with the cyclic



**5a**: R = H, X = NMe
**b**: R = H, X = NPh



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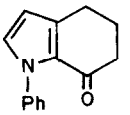

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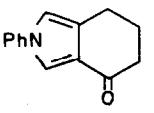


**8**

Table 1. NMR spectral characteristics of cyclised products

(a) $^1$H NMR

| Compound | Chemical Shifts (δ ppm) H-1 | H-2 | H-3 | H-4 | H-5 | H-6 | $J_{AB}$ |
|---|---|---|---|---|---|---|---|
| 4-Ones | | | | | | | |
| 1a | 3.55 | 6.64(A) | 6.21(B) | - | 2.81[a] | 2.81[a] | 3.0 |
| 1b | 7.43(m)[g] | 7.10(A) | 6.48(B) | - | 2.98[a] | 2.98[a] | 3.2 |
| 1f | - | 2.43(A)[b] | 6.70(B) | - | 3.08[c] | 2.83[c] | 1.2 |
| 6a | 3.53 | 6.51(A) | 6.51(B) | - | 2.70 | 2.20 | - |
| 6b | 7.42(m)[g] | 6.77(A) | 6.55(B) | - | 2.73 (2.50)[e] | 2.12 | 3.5 |
| 4b | 6.87(A) | 7.39(m)[g] | 7.34(B) | - | 2.92[a] | 2.92[a] | 1.60 |
| 8 | 6.86(A)[f] | 7.35(m)[g] | 7.60(B) | - | 2.58 (2.33)[e] | 1.93 | 2.1 |
| 1e | - | 7.08 | 7.33 | - | | | - |
| 6-Ones | | | | | | | |
| 3a | 3.75 | 6.92(A) | 5.98(B) | 2.77[a] | 2.77[a] | - | 2.5 |
| 3b | 7.40(m)[g] | 7.35(A) | 6.28(B) | 2.90[a] | 2.90[a] | - | 2.8 |
| 3c | 3.47 | 2.22(A) | 6.00(B) | 2.79[a] | 2.79[a] | - | 0.9 |
| 3d | 7.40(m)[g] | 2.12(A) | 6.13(B) | 2.77[a] | 2.77[a] | - | 1.05 |
| 3e | | | 7.02 | 2.95 | 2.95 | - | |
| 3f | - | 2.43(A) | 6.70(B) | 2.83 | 3.08 | - | 1.2,0.6 |
| 7-One | | | | | | | |
| 7 | 7.34(m)[g] | 6.92(A) | 6.15(B) | 2.48[h] | 2.13[h] | 2.80[h] | 2.8 |

(b) $^{13}$C NMR

| Compound | Chemical Shifts (δ ppm from TMS) $N\text{-}CH_3$ | C-2 | C-3 | C-4 | C-5 | C-6 | C-3a | C-6a | $C\text{-}CH_3$ |
|---|---|---|---|---|---|---|---|---|---|
| 4-Ones | | | | | | | | | |
| 1a | 33.5 | 129.1 | 102.8 | 196.1 | 41.5 | 19.8 | 126.6 | 159.7 | - |
| 1b | -[i] | 127.1 | 103.9 | 196.3 | 41.2 | 21.9 | 138.5 | 158.0 | - |
| 6-Ones | | | | | | | | | |
| 3b | -[j] | 133.1 | 106.6 | 20.0 | 41.8 | 189.0 | 155.5 | 137.9 | - |
| 3c | 30.8(Me) | 125.1 | 100.1 | 20.2 | 40.6 | 195.9 | 159.9 | 137.0 | 12.3 |
| 3d | -[k] | 136.8[l] | 100.2 | 20.2 | 39.9 | 195.3 | 159.4 | 136.2[l] | 12.4 |
| 3f | - | 145.5[l] | 116.5 | 24.3 | 40.7 | 197.8 | 168.9[l] | 145.7 | 15.8 |

(a) Totally degenerate AA'BB' case, single line.
(b) 1,2,2,2,1-Quintet, J = 1.2, 0.6 Hz
(c) $J_{5,6}$ 6.0 Hz; (d) 7-$CH_2$; $J_{5,6}$ 5.5 Hz; $J_{6,7}$ 6.0 Hz
(e) 7-$CH_2$; $J_{5,6} = J_{6,7}$ = 6.0 Hz; (f) Sextet, J = 2.1, 1.1 Hz
(g) 5-Proton multiplet; (h) $J_{4,5} = J_{5,6}$ = 6.0 Hz
(i) The 1-Ph group has $\delta_c$ 129.7(m), 122.0(o), 127.8(p); 128.8 ($C_1$-N).
(j) The 1-Ph group has $\delta_c$ 129.0 (m), 122.0(o), 126.4(p), 132.8(C-N).
(k) The 1-Ph group has $\delta_c$ 128.8(m), 125.5(o), 127.6(p);
C-1 not observed probably owing to intense neighbouring resonances (see Footnote j) and weak intensity.
(l) This pair of resonances could be reversed.

ketones, with pyrrole, and the starting propionic acids (**2a**).

In the $^1$H NMR spectrum of pyrrole itself (dilute $CDCl_3$ solution as in present work), the 2-H lies 0.6 ppm downfield of the 3-H.[12] In 2- and 3-acylpyrroles an adjacent (ortho) ring proton is deshielded by about 0.8 ppm, para (5-H in 2-acyl) by about 0.3 ppm, with meta (4-H in 2-acyl, 5-H in 3-acyl) largely unaffected.[12-14] Thus we expect the *separations* of the pyrrolic resonances in **1a** and **3a** to be respectively smaller and larger than in pyrrole itself, with the absolute values being shifted as above, relative to the starting pyrrolepropionic acid.

Finally we note that cyclisation of 4-(1-methyl-2-pyrrolyl)butyric acid gave the single expected ketone, 1-methyl-6,7-dihydroindol-4(5H)one, identical with that prepared unambiguously[15] by other routes. This compound has degenerate 2-H/3-H at $\delta$ 6.51 as expected by the above considerations.

Application of these principles to the cyclisation reaction products shows that **2a** cyclised largely with concommittant rearrangement (**1a**, 36%; **3a**, 64%), and this contrasts with the reaction of the corresponding butyric acid.

In a similar reaction, the 1-phenyl compound (**2b**) (which retains the chemical shift difference 0.6 ppm between 4-H and 5-H showing the 1-phenyl group to be unimportant) yielded a mixture of *three* isomeric ketones $C_{13}H_{11}NO$, which were separated by alumina chromatography. Two of the ketones again showed AB pyrrolic doublets similar to those of the 1-Me compounds (**1a**, **3a**); as previously these were assigned as (a) the 6-one (**3b**, 47%) having the larger 2-H/3-H chemical shift difference ($J_{AB}$ 2.8 Hz), and the other (b) as the 4-one (**1b**, 30%) having the smaller shift difference with $J_{AB}$ 3.2 Hz. The other cyclic ketone showed an approximately 1,2,2,2,1-quintet and a doublet (J 1.6 Hz); the quintet collapsed to a similar doublet (J 1.6 Hz) on irradiation of the nearly degenerate $CH_2CH_2$ resonances at $\delta$2.92. Thus removal of the sidechain to ring coupling showed the compound to be the 4H-cyclopenta[c]-pyrrol-4-one (**4b**), the remaining coupling being consistent with $J_{1,3}$ (cf. pyrrole[16] itself, which has the corresponding value $J_{2,5}$ 1.85 Hz). Again the rearranged products (**3b**, **4b**) predominated over the expected product (**1b**, 30%).

When the pair of 5-Me acids (**2c,d**) were treated with PPA similarly, only single products were obtained, and in each case these were the 6H-cyclopenta[b]pyrrol-6-ones (**3c,d**). Careful NMR analysis of the crude reaction products excluded the presence of more than trace amounts of the other products (**1c,d**; **4c,d**) on the basis of the previous chemical shifts, so that rearrangement had occurred exclusively.

3-(2-Thienyl)propionic acid (**2e**) has been shown[17] to cyclise directly to the thiophen-4-one (**1e**); in order to encourage rearrangement we treated the 5-methylthiophen derivative (**2f**) with PPA under the standard conditions and obtained a single bicyclic ketone. The product chemical shifts ($^1$H NMR) (Table 1) were as expected for **3f** when compared with the $^1$H shifts of 3-acetyl-2,5-dimethylthiophen ($\delta_{Me}$ 2.32, 2.56; $\delta_{4-H}$ 6.89) and 2-acetyl-3,5-dimethylthiophen ($\delta_{Me}$ 2.42, 2.43; $\delta_{4-H}$ 6.62), which clearly indicate a 6-one (**3f**) rather than 4-one structure. The unsubstituted compound **3e**[18a,b] and the 5-Me derivative of the 4-one (**1e**)[18a] show resonances (Table 1) consistent with these conclusions. Thus the cyclisation reaction had occurred with complete rearrangement to the 4,5-dihydro-2-methyl-6H-cyclopenta[b]thiophen-6-one (**3f**).

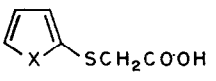
It is clear from the above that both a 1-phenyl- and a 5-methyl-substituent enhance rearrangement in the pyrrolylpropionic acids (**2**). In a final reaction to see whether cyclisation of a butyric acid would lead to rearrangement we attempted the synthesis of 1-phenylpyrrole-2-butyric acid from 1-phenylpyrrole and 3-methoxycarbonylpropionyl chloride; the product was a mixture of 2- and 3-($\gamma$-ketoesters) in the ratio 1 : 2. All attempts to separate these, the corresponding butyric esters or acids were unsuccessful. Since however, the absence of the normal product (**6**) from cyclisation of the 2-acid would be significant, the mixture of 1-phenylpyrrole-2- and -3-butyric acids were treated with PPA. Three cyclic ketones were obtained in the ratios 40% (**6**): 30% (**7**): 30% (**8**); only **6** and **7** were isolated in a pure state. It is clear that (unless the 3-acid had isomerised to the 2-acid) the 2-acid had cyclised quantitatively to the normal ketone (**6**), while the two other products **7** and **8** were derived from the 3-acid or each other.

## DISCUSSION

There is a strong analogy between the behaviour of the present 3-(2-pyrrolyl)propionic acids (**2a-2d**) and the 2-thioacetic acids of pyrrole[19a-c] and thiophen (**9a,b**)[20a,b] which cyclise to the thieno[3,2-b]pyrrol - 3 - one and thieno[3,2-b]thiophen - 3 - one respectively. We note that no similar rearrangements have been observed with the corresponding 3-pyrrolyl or 3-thienyl- thioacetic acids,[20c] and it is normally an implicit[21] assumption that arylpropionic acids of this present type cyclise without rearrangement. Clearly this is not so.

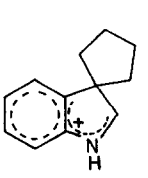
Gronowitz *et al*, considered the two possibilities (a) rearrangement of the 2-side chain to the 3-isomer followed by normal cyclisation and (b) a mechanism in which the spirocyclic intermediate (**10a**) is involved and concluded that the latter was the more probable.[12c] A similar mechanism (via **10 b,c**) seems probable for the present propionic acid rearrangement reactions, but there seems no reason to insist that the sequence of changes surrounding the formation and breakdown of **10 b,c** should be synchronous or concerted. Spirocyclic intermediates are well established in the indole series (e.g. **11**),[22] whilst stable $\alpha$-protonated pyrrole nuclei have long been known.[23] The formation of the normal ketones (**1a,b**) in conjunction with the rearranged ketones (**3a,b**) contrasts with the thioacetic acids which lead to single products[19,20] (although not with some (2-thienylthio)propan-2-ones[20c] which also lead to mixtures of normal and rearranged thieno-thiophenes). A reasonable explanation of the present lower selectivity could be the presence of strong $H_\alpha$ $H_\beta$ non-bonded interactions when the propionyl side-chain (**12a,b**) cyclises to the ion (**10b,c**) (these are absent in the thioacetyl ion), as well as the electron-dense sulphur atom attracting the acylium ion to the cyclisation site.

The protonation of pyrrole has been the subject of various theoretical studies[24] by semi-empirical molecular orbital methods; $\alpha$-protonation is calculated for the lowest energy cation, in agreement with experiment.[25] We have carried out a small number of CNDO/2



**9a**: X = NH
**b**: X = S

**10a**: R = H, X = S = Y
**b**: R = H, X = NMe, Y = $CH_2$
**c**: R = H, X = NPh, Y = $CH_2$
**d**: R = Me, X = NMe, NPh; Y = $CH_2$



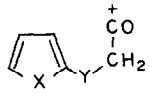
**11**

calculations[26,27] on the monocyclic acylium ions (e.g. **12a**) of the N-methylpyrrolepropionic acids (**2a**,**5a**), the spirocyclic intermediates (**10b** and **13**) and the bicyclic ketones (**1a**, **3a** and **4a**). For the neutral compounds and the acylium ions the pyrrole ring geometry was as in pyrrole itself,[28] which seems a reasonable assumption in the absence of experimental data, while the remaining portions of the molecules are shown (**14–17**) (all CH = 1.09 Å, $CH_3$–N 1.479 Å, angles HCH 110°). Although none of these geometries are optimised, the constraints of the fused [5,5] bicyclic system angles lead to little possible variation, such that the present structures are a result of various tests with angles in the range 108–115°. Cleghorn[24a] performed a partial optimisation of the geometry in protonated pyrroles by the MINDO/2 method, and this showed the systems to be largely in accord with classical azabutadiene type systems; ones similar to these were used for the spirocyclic ketones. The results (Table 2) show that the singly and doubly rearranged ketones (**3a** and **4a**) are approximately 200 kJ $mol^{-1}$ more stable than the normal ketone (**1a**). The pair of spirocyclic compounds (**10b** and **13**) are approximately equal in energy and more stable than the pair of open chain acylium ions (cf. **12a**) by about 500 kJ $mol^{-1}$. This is smaller than the difference in energy between pyrrole and its protonated forms (~ 800 kJ $mol^{-1}$) and this can be attributed (in part) to the additional strain in the spirocyclic compounds, but none the less is indicative of the ease of formation of the latter and hence their plausibility as rearrangement intermediates.

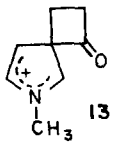
In the light of these calculations we tested the normal and singly rearranged products (**1a** and **3b**) for thermodynamic stability under the reaction conditions. In fact the 1-phenyl-6-one (**3b**) was partially rearranged (19%) to the cyclopenta[c]-4-one (**4b**) during 1.5 times the original cyclisation period; thus it seems clear that some or all of the latter was formed by the sequence **2b**→**3b**→**18** (R = Ph)→**4b** rather than **2b**→**5b**→**4b** (or the corresponding acylium ions for **2b** and **5b**). The failure of the 5-Me compound (**2d**) to yield a doubly rearranged ketone (**4d**) is presumably at least attributable to a steric effect. Curiously the 1-phenyl compound of the unrearranged 4-one series (**1b**) failed to rearrange to **3b** or **4b** over an even more extended period (3.5 times the original reaction of the acid **2b**).

The enhancement of the tendency to rearrangement in the 5-Me series (**2c**,**d**) can be interpreted as inductive and hyperconjugative release from the 5-Me group in **10d**; the 5-Me group leads to a substantial enhancement in rate of 2-acylation in pyrroles, furans and thiophens.[25] None of the "normal" ketone (**1c**,**d**) was observed in the reactions of these 5-Me compounds (**2c**,**d**), so that it was not possible to test their stability.

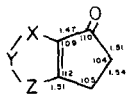
In conclusion, it is clear from the present work that rearrangement reactions during the cyclisation of heteroaromatic-alkanoic acids are to be expected, and that the behaviour of the 2-pyrrolyl- and 2-thienylthioacetic acids is not atypical. This suggests that reinvestigation of some of the related cyclisations[21] would be



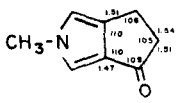
**12a**: X = NMe, Y = $CH_2$
**b**: X = NPh, Y = $CH_2$
**c**: X = Y = S



**13**



**14**: XYZ = MeN–CH=CH
**15**: XYZ = CH=CH–NMe



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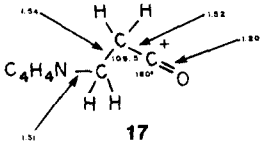

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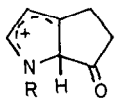

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Table 2. Calculated binding energies and dipole moments for the cyclic ketones and precursors

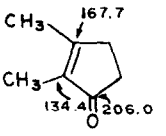
| Compound | Binding Energy (a.u.) | Dipole Moment/D |
|---|---|---|
| (a) Ketones | | |
| 1a | -9.5300 | 4.712 |
| 3a | -9.6100 | 2.065 |
| 4a | -9.6136 | 4.027 |
| (b) Acids | | |
| 2a | -10.1800 | 0.317 |
| 5a | -10.1754 | 3.310 |
| (c) Acylium Ions | | |
| 13a (2-$CH_2CH_2CO^+$) | -9.2200 | - |
| (3-$CH_2CH_2CO^+$) | -9.2242 | - |
| (d) Spirocyclic Ions | | |
| 10b | -9.4213 | - |
| 14 | -9.4233 | - |

worthwhile. This lay outside the scope of the present investigation.

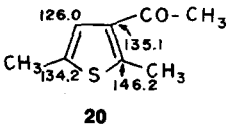
*$^1H$ and $^{13}C$ NMR spectra of the products.* The adjacent methylene groups ($A_2B_2$) of the 3-(2-pyrrolyl)-propionic acids occur as almost completely degenerate multiplets; it is interesting to note that the cyclisation process leading to the ketones **1a**, **3a**, **3c** increases this degeneracy, with $CH_2CH_2$ occuring as a single line in all three cases. Although coupling to the 2-Me group ($J_{H,CH_3} = 0.9$, 1.05 Hz) is observed in **3c** and **3d** respectively, there is no evidence of coupling to the $CH_2CH_2$ group in any of these cases. The cyclopenta[c]pyrrolone (**4b**) shows a more complex pattern of coupling in the pyrrolic protons, the high field 3H-proton ($\delta$ 6.87) appearing as an apparent quintet. Irradiation of the $CH_2CH_2$ broad band ($\delta$ 2.92) collapses the quintet to a doublet J 1.6 Hz also observed on the 1-H at $\delta$ 7.34. In view of the degeneracy of the $CH_2CH_2$ groups the coupling to the ring (J 0.8 Hz) is an averaged rather than single coupling.

The $\alpha,\beta$-$CH_2$ groups of the 3-(5-methyl-2-thienyl)propionic acid (**2f**) are well separated ($\delta$ 2.97 and 2.68) and this also occurs in the cyclised product (**3f**); however whilst the downfield ($\delta$ 3.08) resonance of **3f** is a triplet, the upfield is a complex multiplet arising from further splitting of the corresponding AA'XX' triplet. The latter arises from coupling to the methyl group which occurs as a 1,2,2,2,1-quintet, collapsed to a 1,2,1-triplet (J 0.6 Hz) by irradiation of the thienyl 3-H; this in turn is unchanged by double or triple irradiation of the $CH_2$ groups but is coupled to the Me group ($J_{H.Me}$ 1.2 Hz). This last coupling is typical[12] of Me-$^1$C=CH-coupling in 5-membered ring heterocycles, but the Me/$CH_2$ coupling ($^6$J or $^7$J depending upon the route through the thiophen ring) is much less frequently observed, although Me/Me coupling is observed in some dimethylthiophens.[29,30] Since the normal ketones (**1c,d**) were not obtained from the corresponding pyrrolepropionic acids, we prepared 3-acetyl-2,5-dimethylthiophen; this does show a similar complex spectrum; the methyl resonances occur at $\delta$ 2.58 (2-Me, multiplet), $\delta$ 2.36 ($CH_3CO$, singlet) and $\delta$ 2.33 (5-Me, septet). Irradiation of the low field Me collapses the quintet to a doublet (J = 1.2 Hz), the latter arising from coupling to the 4-H (quartet). Thus the $CH_3/CH_3$ coupling is 0.6 Hz approximately.

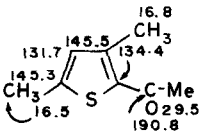
*The $^{13}C$ spectra.* The $^{13}C$ spectra of typical members of the 4- and 6-ones (**1a, b**; **3b,c,d**) have been obtained, there being insufficient material from the third series (**4**) to obtain spectra. Basically these systems consist of a fused cyclopent-2-enone (**19**) with either a pyrrole or thiophen ring. Analyses of the former spectrum,[31] and many derivatives of the heterocyclic ring systems are available,[32,33] and in the latter cases substituent chemical shifts (SCS) were obtained. Comparison of the SCS predictions[32] for 2,5-dimethyl-3-acetylthiophen and the isomer 3,5-dimethyl-2-acetylthiophen showed that the two agreed to within 7 ppm (**20** and **21**), whilst similar studies of the dihydrocyclopenta[b]-pyrrol-4- and -6-ones (Table 1, and **22,23**) showed that no assignments of the pyrrolic -C were possible to within 20 ppm based upon the SCS results.[33] Indeed it is clear that the highly polar C=C–C=O group dominates the spectra of the bicyclic compounds and that the observed shifts can be readily interpreted on the basis of C=C–X (X = S,NR) bridging of the latter system (**19**). The shifts within the $C_\beta = C_\alpha$–X group show the same trends for X = NMe, NPh, S, with $C_\beta$ to high field of $C_\alpha$, and with the $C_\alpha/C_\beta$ separation much larger than in thiophen (1.8 ppm) and pyrrole



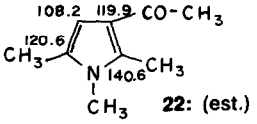

19



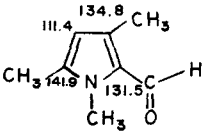

20



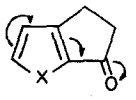

21




22: (est.)




23: (est.)




24

(9.7 ppm), even when the SCS data is used (**20**, **22**, **23**). Using the now well-defined connections between $^{13}C$ shift and electron density[34,35] this implies a much more enhanced $C^{\delta-} = C^{\delta+}$–X polarisation than in the parent ring systems; clearly this is attributable in part to the polarisation produced by changes as in **24** for the 6-ones, but that similar changes for the 4-ones cannot be drawn in classical terms. We conclude therefore that these changes are in part a result of loss of aromatic character in the fused [5,5] system, probably as a result of ring strain. The polarisation of the C=C–X part in aliphatic rather than the weakly aromatic pyrrole and thiophen systems can be expected to be larger, for the cyclic nature of the latter, and different symmetry, will tend to reduce the polarity of the bonds, through both push-pull type effects and also C-3/C-4 electrostatic effects.

## EXPERIMENTAL

M.ps were recorded using a Koffler hot-stage apparatus. PMR spectra (dilute soln. in $CDCl_3$) were obtained at 100 MHz (Varian HA100) and 60 MHz (Perkin–Elmer R10). $^{13}C$ NMR spectra were obtained at 20 MHz (Varian CFT-20) under $^{13}C\{^1H\}$ noise decoupled conditions using TMS as standard ($CDCl_3$ soln).

*Cyclisation reactions-general method*

(a) 1-Phenylpyrrole-2-propionic acid (0.95 g) and polyphosphoric acid (100 g) were heated and stirred at 100° for 3 hrs. After decomposition with water, extraction with chloroform (3 × 50 ml), back extraction with $NaHCO_3$ and drying, the crude evaporated material was investigated by PMR and then separated by chromatography on alumina. Elution with toluene gave 4,5-*dihydro*-1-*phenyl*-6H-*cyclopenta*[*b*]*pyrrol*-6-*one*, m.p. 88.5–89.5° (0.30 g); C Found: C, 79.25; H, 5.74; N, 7.04. $C_{13}H_{11}NO$ requires: C, 79.17; H, 5.62; N, 7.10%); Elution with chloroform (20%) in toluene gave (i) 5,6-*dihydro*-2-*phenyl*-4*H*-*cyclopenta*[*c*]*pyrrol*-4-*one*, m.p. 126.8° (0.05 g); Found: C, 78.9; H, 5.4; N, 6.9%; then (ii) 5,6-*dihydro*-1-*phenyl*-4*H*-*cyclopenta*[*b*]*pyrrol*-4-*one*, m.p. 87–88.5°; (Found: C, 79.22; H, 5.76; N, 7.03%).

(b) 3-(1-*Methyl*-2-*pyrrolyl*)*propionic acid* was treated with PPA and worked-up as in (a) above. Chromatography ($SiO_2$) gave (i) (eluent 60% $CHCl_3$/40% PhMe) 4,5-*dihydro*-1-*methyl*-6*H*-*cyclopenta*[b]*pyrrol*-6-*one*, m.p. 57–8°; (Found: C, 71.17; H, 6.78; N, 10.31. $C_8H_9NO$ requires: C, 71.09; H, 6.71; N, 10.36%). (ii) (eluent $CHCl_3$) 5,6-*dihydro*-1-*methyl*-4*H*-*cyclopenta*[*b*]*pyrrol*-4-

*one*, m.p. 140–1° (from light petroleum, b.p. 100–120°). (Found: C, 71.14; H, 6.82; N, 10.29%).

(c) 3-(5-*Methyl*-1-*phenyl*-2-*pyrrolyl*)*propionic acid* was treated with PPA and worked up as in (a) above and gave 4,5-*Dihydro*-2-*methyl*-1-*phenyl*-6*H*-*cyclopenta*[*b*]*pyrrol*-6-*one*, m.p. 103.5–105.5° (from petroleum b.p. 80–100°) (Found: C, 79.81; H, 6.17; N, 6.92. $C_{14}H_{13}NO$ requires: C, 79.59; H, 6.20; N, 6.63%).

(d) 3-(1,5-*Dimethyl*-2-*pyrrolyl*) *pyropionic acid* treated as in (a) above gave 4,5-*dihydro*-1,2-*dimethyl*-6*H*-*cyclopenta*[*b*]*pyrrol*-6-*one*, m.p. 145–7° (from petroleum b.p. 80–100°). (Found: C, 72.58; H, 7.61; N, 9.18. $C_9H_{11}NO$ requires: C, 72.46; H, 7.43; N, 9.39%).

(e) 3-(5-*Methyl*-2-*thienyl*) *propionic acid* treated with PPA as in (a) above gave 5,6-*dihydro*-2-*methyl*-6*H*-*cyclopenta*[*b*]*thiophen*-6-*one*, m.p. 65.5–66.5° (from light petroleum, b.p. 60–80°). (Found: C, 62.7; H, 5.1. $C_8H_8OS$ requires: C, 63.15; H, 5.30%).

(f) 4-(1-*Methyl*-2-*pyrrolyl*) *butyric acid* treated with PPA as in (a) above gave 6,7-*dihydro*-1-*methylindol*-4(5*H*) *one* m.p. 83–85° (lit.[15] m.p. 85°) (Found: C, 72.28; H, 7.31; N, 9.17. $C_9H_{11}NO$ requires: C, 72.46; H, 7.43; N, 9.39%).

(g) *The mixture of* (1-*phenyl*-2- *and* 3-*pyrrolyl*) *butyric acids.* The mixture containing 41% of the 2-acid, was treated with PPA as in (a) above. Chromatography on alumina gave three fractions (using toluene).

(h) 4,5-*dihydro*-1-*phenylindol*-7 (6*H*) *one*, m.p. 100–100.5° (from light petroleum, b.p. 100–120°). (Found: C, 79.57; H, 6.13 N, 6.66. $C_{14}H_{13}NO$ requires: C, 79.54; H, 6.20; N, 6.63%); (ii) 4,5,6,7-tetrahydro-2-phenylbenzo[c]pyrrol-4-one, slightly contaminated by (i); (iii) 6,7-*dihydro*-1-*phenylindol*-4 (5*H*) *one*, m.p. 65–66° (from light petroleum, b.p. 100–120°). (Found: C, 79.57; H, 6.13; N, 6.32. $C_{14}H_{13}NO$ requires: C, 79.59; H, 6.20; N, 6.63%).

*The propionic and butyric acids*

(a) *The* 5-*methyl series.* All of these compounds were prepared from 4,7-dioxooctanoic acid[36] by reaction with the appropriate amine (leading to the pyrroles), $P_2S_5$ (thiophens) by standard methods. The physical properties of the products are:

3-(1,5-*Dimethyl*-2-*pyrrolyl*) *propionic acid* **2c** (using 25% aqueous methylamine, yield 40%), m.p. 105.5–106.5° (from light petroleum, b.p. 80–100°). PMR ($CDCl_3$): δ11.2(s,1H; OH), δ5.76(s, 2H; H-3, H-4), δ3.35 (s, 3H, N-Me), δ2.75(AA'BB' multiplet, 4H; $CH_2CH_2$), δ1.17(s, 3H; C-Me). (Found: C, 64.84; H, 7.81; N, 8.50. $C_9H_{13}NO_2$ requires: C, 64.65; H, 7.84; N, 8.38%).

3-(5-*Methyl*-1-*phenyl*-2-*pyrrolyl*) *propionic acid* **2d** (using 1 mol in AcOH acid, yield 63%), m.p. 109-110° (from light petroleum, b.p. 80–100°). PMR ($CDCl_3$): δ11.3(s, 1H; OH), δ7.0–7.5 (multiplet, 5H, $C_6H_5$), δ5.87 (s, 2H; 3-H, 4-H), δ2.55(multiplet, 4H, $CH_2CH_2$), δ1.95(s, 3H; C-Me). (Found: C, 73.5; H, 6.7; N, 6.02. $C_{14}H_{15}NO_2$ requires: C, 73.34; H, 6.59; N, 6.11%).

3-(5-*Methyl*-2-*thienyl*) *propionic acid* **2f** (using $P_2S_5$ in toluene, 40%), m.p. 37–8° (from light petroleum, b.p. 60–80°). PMR ($CDCl_3$): δ10.4 (s, 1H; OH), δ6.55(s, 2H; H-3, H-4), δ3.0(AA'BB', 4H; $CH_2CH_2$), δ2.38(s, 3H; C-Me). (Found: C, 55.9; H, 5.69. $C_8H_{10}O_2S$ requires: C, 56.47; H, 5.92%).

(b) *The* 5-*unsubstituted series.* These were prepared from the N-substituted pyrrole by reaction with β-propiolactone (2 mole) under reflux.[37]

3(1-*Phenyl*-2-*pyrrolyl*) *propionic acid* **2** (yield 13%), m.p. 87–89° (from light petroleum, b.p. 80–100°). PMR ($CDCl_3$): δ10.2 (s, 1H; OH), δ7.34(s, 5H; $C_6H_5$), δ6.9(m, 1H; H-5), δ6.2(m,2H; H-4, H-5), δ2.8 (m, 4H; $CH_2CH_2$). (Found: C, 72.35; H, 5.94; N, 6.4. $C_{13}H_{13}NO_2$ requires: C, 72.54; H, 6.09; N, 6.51%).

3(1-*Methyl*-2-*pyrrolyl*) *propionic acid* **2** (yield 5%), m.p. 80–82° (from light petroleum, b.p. 80–100°). PMR ($CDCl_3$): δ12.0(s, 1H; OH), δ6.50 (m, 1H; H-5), δ5.95(m, 2H; H-3, H-4), δ3.53((s, 3H; N-Me), δ2.75 (m, 4H; $CH_2CH_2$). (Found: C, 62.80; H, 7.31; N, 9.08. $C_8H_{11}NO_2$ requires: C, 62.73; H, 7.24: N, 9.14%).

1-*Phenylpyrrole*-2- *and* -3-*butyric acids.* 3-Methoxycarbonylpropionic acid was prepared from succinic acid and excess MeOH after boiling for 12 h and evaporation; treatment of the crude acid (4.62 g) with excess thionyl chloride gave the acid chloride which was used without further purification. The acid chloride in tetrachloroethane (TCE) (20 ml) was added slowly to N-phenylpyrrole (5.00 g) in TCE (20 ml) with simultaneous addition of stannic chloride (10.95 g) in TCE (20 ml) at 5°. After 3 h, hydrolysis with ice, steam distillation, extraction ($CHCl_3$) and evaporation gave a mixture of γ-keto esters (6.03 g), containing 41% of the 2-ester. Chromatography failed to separate the mixture which was therefore directly reduced to the free butyric *acids* by treatment with KOH (4.7 g) and 85% hydrazine hydrate (4 ml) in digol (35 ml). $^1H$ NMR spectroscopy showed the mixture to contain 41% of the 2-acid as in the ketoesters above. Again chromatography failed to separate the mixture which was used directly as in cyclisation (*g*) above.

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