6-(Substituted phenyl)-5-methyl-4,5-dihydropyridazin-3(2*H*)-ones of Medicinal Interest. The Synthesis of SK&F 94836 and SK&F 95654

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Two synthetic routes to the dihydropyridazinone-cyanoguanidine **4** (SK&F 94836) are described, both proceeding *via* the anilino compound **6**. An efficient synthesis of the dihydropyridazinone-pyridone **5** (SK&F 95654) is reported. This synthesis proceeds *via* the fluoro-keto-acid **24**, with subsequent displacement of the fluoro substituent by 4-pyridone. The surprising effectiveness of water as a solvent in this reaction has been highlighted.

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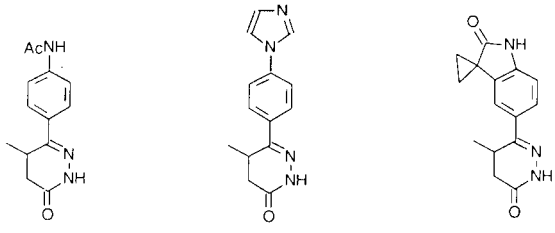
The 4,5-dihydropyridazin-3(2*H*)-one ring system has assumed considerable importance in recent years as the nucleus on which the structure of a number of compounds of potential therapeutic utility is founded.

Thus, the antihypertensive activity of various 6-substituted phenyl derivatives has been reported [1,2] and, for example, 6-(4-acetamidophenyl)-5-methyl-4,5-dihydropyridazin-3(2*H*)-one (**1**) was identified as exhibiting particularly potent and long-lasting antihypertensive activity [1]. More recently, compounds such as **2** [3] and **3** [4] have been shown to possess positive inotropic activity, and as such are of potential use in the treatment of congestive heart failure. The inotropic activity of both of these latter compounds is thought to be due to inhibtion of a cardiac c-AMP phosphodiesterase (PDE III) [3,4], an enzyme responsible for the hydrolysis of cyclic adenosine monophosphate to its ring-opened form [5]. Some years ago, a programme of research to identify positive inotropes of potential therapeutic utility was undertaken at Smith Kline and French Research Ltd., and this provided the two novel compounds SK&F 94836 **4** [6] and SK&F 95654 **5** [7] as development candidates. SK&F 94836 has now been shown to be a potent inotropic agent with a sustained duration of action [8]. The compounds **4** and **5** were initially prepared from the anilino-dihydropyridazinone **6**, prepared as described by McEvoy and Allen [9]. The synthesis of compound **6** involved a Mannich reaction on *p*-acetamidopropiophenone, quaternization, displacement by cyanide (*via* the unsaturated ketone) and hydrolysis to the anilino-keto acid **7**. Cyclization with hydrazine gave the required anilinodihydropyridazinone **6**. As part of our interest in the two compounds **4** and **5** referred to above, we investigated alternative routes suitable for large scale synthesis of these compounds. Reported in this paper are the results of this work [10].



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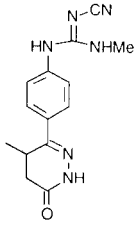

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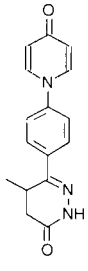

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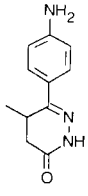

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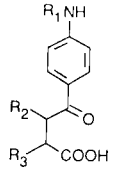


7 $R_1 = H$, $R_2 = Me$, $R_3 = H$

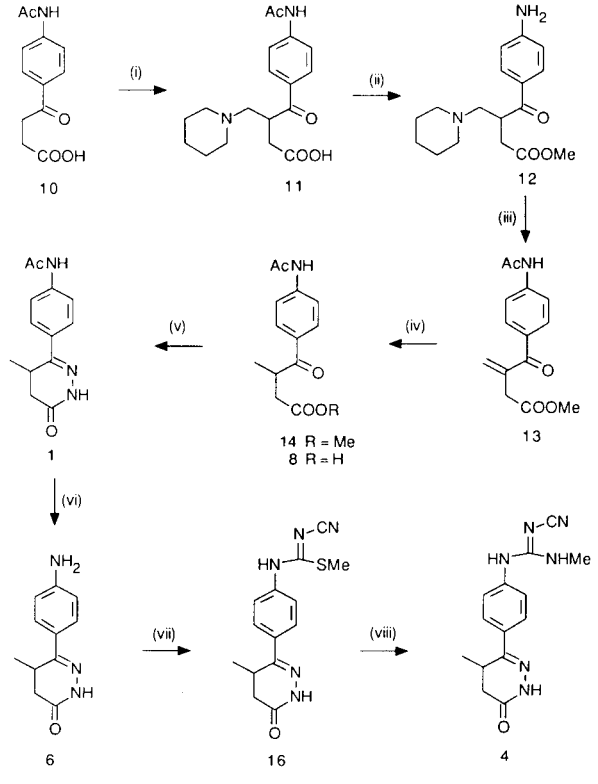
8 $R_1 = Ac$, $R_2 = Me$, $R_3 = H$

9 $R_1 = Ac$, $R_2 = H$, $R_3 = Me$

Friedel Crafts acylation of acetanilide with 2-methylsuccinic anhydride does not provide an efficient way of preparing the keto-acid **8**, as the other isomer **9** is also

formed [11]. Our first approach was based on the methylation of the readily available keto-acid **10**. To avoid the problem inherent in the direct methylation of a secondary carbon α to a carbonyl [12], the susceptibility of benzoylpropionic acid to undergo the Mannich reaction [13] was utilised (Scheme 1). Thus, the reaction of 3-(4-acetamidobenzoyl)propionic acid (**10**) with piperidine and formaldehyde gave the piperidinomethyl derivative **11** as a zwitterionic and easily isolable compound. However, attempts to quaternize this compound gave mixtures of products.

Scheme 1

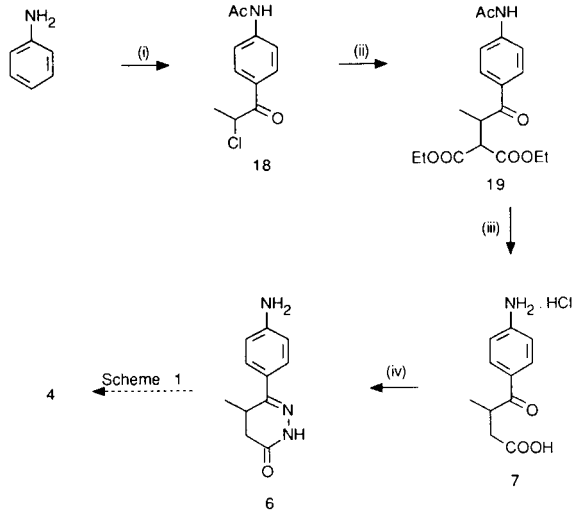


(I) piperidine / HCHO, (ii) MeOH / H_2SO_4, (iii) Ac_2O / pyridine, (iv) H_2 / Raney Ni, (v) $N_2H_4.H_2O$, (vi) aq. HCl, (vii) $(MeS)_2CNCN$, (viii) $MeNH_2$

Esterification of the carboxylic acid removed the acetyl functionality at the same time, giving the anilino-ester **12**. Treatment of the compound **12** with acetic anhydride and pyridine gave the unsaturated ketone **13**. Similar elimination reactions of β-amino-ketones are documented [14]. Reduction of the olefinic product **13** to give the saturated ketone **14** was cleanly effected using Raney Nickel and hydrogen, although a small amount of hydrolysis to the carboxylic acid **8** was observed. Cyclization with hydrazine gave the required ring system. Hydrolysis of the acetyl group gave the anilino-dihydropyridazinone **6**, which was converted into the cyanoguanidine **4** by reaction with dimethyl *N*-cyanodithioiminocarbonate (**15**) [15] to give the intermediate *S*-methylisothiourea **16**, followed by reaction with excess methylamine. These two reactions may be carried out in reverse order, but the poor nucleophilicity of aniline **6**, coupled with the fact that replacement of the first methylthio group (*e.g.* in **15**) by a nitrogen nucleophile is a great deal easier than displacement of the second (*e.g.* in **16**) [16], means that this is a much less efficient way of preparing the required cyanoguanidine **4**. The diphenyl *N*-cyanoiminocarbonate (**17**) [17] can be used instead of the bismethylthio-derivative **15**.

The above synthesis gave reasonable yields, easily isolable and crystalline intermediates, and all steps were amenable to large scale work. The overall yield of cyanoguanidine **4** from 3-(4-acetamidobenzoyl)propionic acid (**10**) was 13%. Optimisation of this route was not carried out however, because of the success of an alternative approach to the key anilino-dihydropyridazinone derivative **6**. This was based on the preparation of 1,4-keto-acids *via* reaction of α-haloketones with malonate esters. Thus, Friedel Crafts acylation of acetanilide with α-chloropropionyl chloride and aluminium trichloride gave the α-chloroketone **18** [18] (Scheme 2). Displacement with diethyl sodiomalonate [19] in DMF gave the required keto diester **19** [20]. This could be purified by column chromatography, or taken through to the hydrolysis product without purification.

Scheme 2

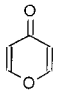


(i) $AlCl_3$ / MeCHClCOCl, (ii) $CH_2(COOEt)_2$ / NaH, (iii) EtOH / HCl ; aq. HCl, (iv) $N_2H_4.H_2O$

The hydrolysis was best effected in two steps, initial deacylation of the acetamido group using methanolic hydrogen chloride, followed by aqueous acid hydrolysis and decarboxylation to give the easily isolable anilino-keto-acid **7**. This cyclized readily on reaction with hydrazine to give 6-(4-aminophenyl)-5-methyl-4,5-dihydro-

pyridazin-3(2*H*)-one (**6**), identical to the material prepared *via* the previous route. The overall yield of the four-step synthesis of the anilino-dihydropyridazinone **6** from acetanilide was 23%, and this provided a very efficient route for the preparation of large quantities of the anilino compound **6**, which were converted to the required cyanoguanidine **4** as described above.

The pyridone **5** was initially prepared from the anilino compound **6** *via* the reaction with 4-pyrone (**20**). This is a clean, high yielding reaction but the cost of 4-pyrone (**20**) [21] makes it unattractive for the preparation of kilogram quantities of the pyridone **5**. *N*-Phenyl-4-pyridone has been prepared in 50% yield by refluxing aniline with chelidonic acid (**21**) in dimethyl sulphoxide [22]. Using a similar approach, pyridone **5** was formed by heating the anilino compound **6** in dimethyl sulphoxide or dimethylformamide with chelidonic acid (**21**), but only in low yields. Low yields of the product **5** were also obtained when the initial reaction with chelidonic acid (**21**) and the subsequent decarboxylation step were carried out separately [23]. Taylor prepared 1,5-bis(dimethylamino)-1,4-pentadien-3-one (**22**) for use in the preparation of 4-pyridones [24]. We were only able to prepare the reagent **22** in low yield (18%) using Taylor's method, and once again found that poor yields of the required product **5**, were obtained with the anilino compound **6** using the reagent **22** under a variety of conditions.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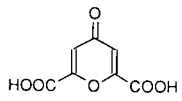

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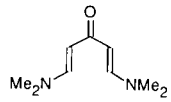

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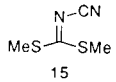

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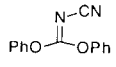

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Concurrently with the above work, an alternative route to the required pyridone **5** was investigated which did not go through **6**. The key step was the *N*-arylation of 4-pyridone (**23**) with an activated halobenzene.

4-Pyridones usually alkylate on nitrogen under basic conditions, and, for example, the *N*-arylation of 4-pyridone (**23**) with 4-nitro and 2,4-dinitrochlorobenzene has been reported [25]. The substrate chosen was 3-(4-fluorobenzoyl)butanoic acid (**24**). This compound had been prepared by McEvoy and Allen [9] *via* an analogous route to that used by them for the preparation of the anilino-keto-acid **7** (*vide supra*). However, in view of the success of the malonate route to compound **7** reported above, the same approach was applied to the preparation of the fluoro analogue **24**. Thus fluorobenzene was readily acylated under Friedel Crafts conditions with 2-chloropropionyl chloride to give the corresponding propiophenone **25** (Scheme 3). Reaction with diethyl sodiomalonate in DMF [18] gave the crude fluoro-keto-diester **26**. This could be isolated by chromatography but it was simpler to hydrolyse the crude product in aqueous hydrochloric acid/1,4-dioxan. This gave the fluoro-keto-acid **24** as a solid in 72% yield from the propiophenone **25**.

The displacement reaction, **24** to **27**, was initially attempted using the sodium salt of both the 4-pyridone (**23**) and the fluoro-keto-acid **24** in *N*-methylpyrrolidin-2-one. Heating the reaction mixture to 105° for 4.5 hours gave the required compound **27** but the polar product was very difficult to isolate from aqueous *N*-methylpyrrolidin-2-one solutions after work-up, and evaporation of the solvent prior to work-up was not practical on a large scale. Significant quantities of impurities were also produced in this reaction, as observed by hplc.

Use of the sodium salts of 4-pyridone (**23**) and the fluoro-keto-acid **24** in other aprotic solvents (*e.g.*, 1,4-dioxan) to simplify the work-up were unsuccessful, presumably because of the insolubility of the starting materials in these solvents. Using the fluoro-keto-ester **28** in place of the acid **24** in DMF gave a low yield of the corresponding ester **29**, which could be isolated reasonably easily, but hplc analysis of the reaction mixture revealed the formation of considerable quantities of the corresponding acids **24** and **27**. This was initially assumed to be due to hydrolysis by residual water contained in the 4-pyridone (which was supplied as a hydrate and was dried before use). However, even with rigorous drying of the 4-pyridone before use large amounts of the acids **24** and **27** were still formed in the reaction of the fluoro-keto-ester **28** with 4-pyridone sodium salt, prepared with sodium hydride in DMF. This suggests an alternative explanation, that conversion to the acids **24** and **27** occurs *via* attack of the 4-pyridone anion on the methyl group of the corresponding esters **28** and **29**. However, the water solubility of *N*-methyl-4-pyridone precluded its isolation and confirmation of its formation was not obtained.

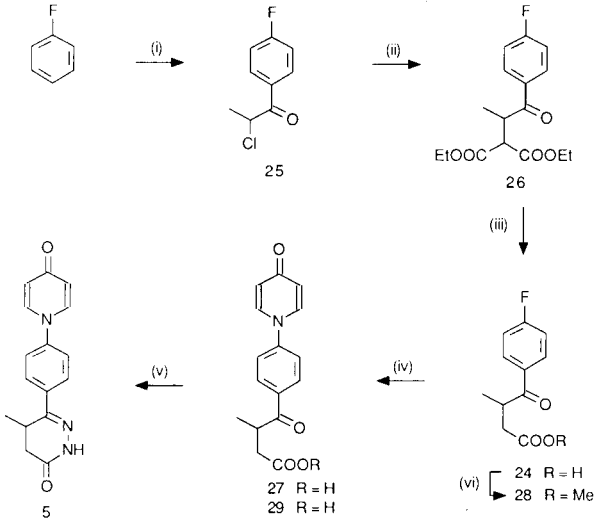
The use of protic solvents was investigated next. Using sodium ethoxide in ethanol to generate the sodium salts of 4-pyridone (**23**) and the fluoro-keto-acid **24**, and refluxing the reaction mixture, gave a slow reaction and formation of the required pyridone **27** and 3-(4-ethoxybenzoyl)-butanoic acid (**30**) occurred in approximately equal amounts. A similar result was obtained in refluxing 1-butanol, although the reaction was faster. However, carrying out the reaction in water in an autoclave at 140° resulted, to our surprise, in a very clean reaction to give the required product **27**, essentially free from side products (as assessed by hplc), in contrast to the reaction in DMF. In particular, formation of the 3-(4-hydroxybenzoyl)-

butanoic acid **31** was not observed. Acidification of the crude reaction mixture gave the required product **27** in high yield and purity. The use of an autoclave was a disadvantage, but this was overcome by working with higher concentrations of reactants (2 *M* in the fluoro-keto-acid **24**). Thus, refluxing **24** in water with 4-pyridone **23** (1.5 equivalents) and sodium hydroxide (2.5 equivalents) for 23 hours gave, after acidification, a 94% isolated yield of analytically pure pyridone-keto-acid **27**. The displacement reaction was also attempted on the crude fluoro-keto-diester **26** (sodium hydride/DMF), but a complex mixture was obtained. The reaction of 4-pyridone sodium salt with the cyclized compound 6-(4-fluorophenyl)-5-methyl-4,5-dihydropyridazin-3(2*H*)-one (**32**) gave inferior yields.

Cyclization of the pyridone-keto-acid **27** to give the final compound **5** was accomplished in 90% yield by refluxing with aqueous hydrazine hydrate. Thus the pyridone **5** was prepared in an overall 55% yield from fluorobenzene, avoiding the use of the commercially expensive 4-pyrone (**20**).

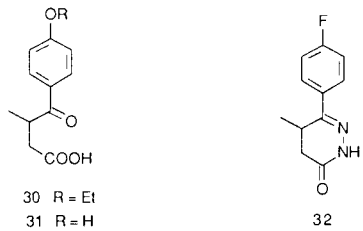
In summary, two routes to the dihydropyridazinone-cyanoguanidine **4** have been described, both going *via* the anilino compound **6**, the malonate route being the shorter and giving **6** in an overall 23% yield from acetanilide. Attempts to find an alternative to 4-pyrone (**20**) for preparation of the pyridone-dihydropyridazinone **5** from the anilino compound **6** have been detailed, and an alternative synthesis of this compound has been reported. This synthesis goes through the fluoro-keto-acid **24**, prepared *via* the analogous malonate route used to prepare the anilino-dihydropyridazinone **6**, followed by displacement of the fluoro substituent by 4-pyridone. The surprising effectiveness of water as solvent in this reaction has been highlighted. The overall yield of pyridone **5** from fluorobenzene is 55%.

Scheme 3



(i) $AlCl_3$ / MeCHClCOCl, (ii) $CH_2(COOEt)_2$ / NaH, (iii) dioxan / HCl,

(iv) 4-hydroxypyridine / aq. NaOH, (v) $N_2H_4.H_2O$, (vi) MeOH / H_2SO_4.



EXPERIMENTAL

The ^{1}H nmr spectra were recorded on a Bruker 250 MHz spectrometer in deuteriochloroform with tetramethylsilane as internal standard unless otherwise stated. The 100 MHz ^{1}H nmr spectra were recorded on a Jeol PFT 100P instrument. Infra-red spectra were recorded as nujol mulls on a Perkin Elmer 781 instrument unless otherwise stated. Mass spectra were recorded on a VG7070F spectrometer. Melting points were recorded on an Electrothermal IA6304 instrument and are uncorrected. Silica gel (230-400 mesh) was used for column chromatography. 95% IMS is a mixture of approximately 90% ethanol, 5% methanol, and 5% water.

3-(4-Acetamidobenzoyl)-4-(*N*-piperidinyl)butanoic Acid (**11**).

3-(4-Acetamidobenzoyl)propionic acid (**10**) [26] (253 g, 1.08 moles) was combined with piperidine (170 g, 2.0 moles) to give a semisolid mass. Aqueous formaldehyde solution (37% w/v, 75 ml, 2.0 moles) was added slowly, and the slurry was stirred at room temperature overnight. The reaction mixture was heated on a steam bath for 2 hours to complete the reaction, after one hour a crystalline solid began to separate from the solution. The reaction mixture was left to cool to room temperature, diluted with 95% IMS (500 ml), filtered, and the solid was washed with IMS and dried to give 222 g (62%) of **11** mp 191-194° dec; ir: ν 1685 and 1667 (amide I), 1626 (H-bonded ketone), 1601 (carboxylate and aryl), 1535 (amide II) cm^{-1}; ^{1}H nmr (DMSO-d_6): 100 MHz δ, 1.4 (br m, 6H, C3, C4, C5 protons of piperidine ring), 2.08 (s, 3H, Me), 2.45 (m, 8H, C2, C6 protons of piperidine ring, NCH_2CH and CH_2CO), 4.04 (m, 1H, CH), 7.80 (m, 4H, aryl), 10.17 ppm (s, 1H, NH).

Anal. Calcd. for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.28; N, 8.43. Found: C, 64.97; 7.40; N, 8.38.

Methyl 3-(4-Acetamidobenzoyl)-3-butenoate (**13**).

The amino acid **11** (200 g, 0.60 mole) was suspended in methanol (2.0 l) and concentrated sulphuric acid (200 ml) was added slowly. The solution was heated under reflux for 1 hour, left to cool overnight and poured onto ice (4 kg). The aqueous solution was basified to *p*H 8 (50% aqueous sodium hydroxide) and extracted with dichloromethane (2 x 1 l). The combined extracts were dried (magnesium sulfate) and filtered to give the crude ester **12**. Acetic anhydride (250 ml, 2.65 moles) was added to the filtrate, followed by pyridine (100 ml, 1.24 moles). The contents of the flask were distilled until a still head temperature of 80° was reached. The residue was cooled and poured into water with vigorous stirring. This gave 103 g (66%) of the pale yellow crystalline olefinic ester **13** mp 113-115°; ir: ν 3300 (NH), 1738 (ester), 1670 and 1648 (amide I + α,β-unsaturated ketone) 1628, 1608, 1591 (aryl and olefinic) and 1523 (amide II) cm^{-1}; ^{1}H nmr: 100 MHz δ 2.15 (s, 3H, MeCO), 3.53 (s, 2H, CH_2CO), 3.64 (s, 3H, OMe), 5.73 and 5.93 (s, s, 1H, 1H, olefinic CH_2), 7.65 (m, 4H, aryl), 8.10 ppm (br s, 1H, NH).

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 63.2; H, 5.68; N, 5.28.

Methyl 3-(4-Acetamidobenzoyl)butanoate (**14**).

The olefin **13** (10.0 g, 38 mmoles) was suspended in methanol (100 ml) and hydrogenated at 20 psi using Raney Nickel (1.0 g, wet) as catalyst. After the theoretical uptake of hydrogen (20 minutes) the catalyst was removed by filtration and evaporation of the filtrate gave 10.1 g (100%) of the crude acetamido-ester **14**, mp 100-103°. This material was used as described below without further purification. However, an analytical sample could be prepared by chromatography on silica (chloroform/-methanol) and crystallization mp 122-124°; ir: ν 3310 (NH), 1733 (ester), 1676 (ketone and amide I), 1599 and 1590 (aryl), 1539 (amide II) cm^{-1}; ^1H nmr: δ 1.22 (d, J = 7 Hz, 3H, CHC*H*$_3$), 2.17 (s, 3H, C*H*$_3$CO), 2.45 (d of d, J = 4, 16 Hz, 1H, CHC*H*H'), 2.96 (d of d, J = 9, 16 Hz, 1H, CHCH*H'*), 3.63 (s, 3H, OCH$_3$), 3.86 (m, 1H, C*H*), 7.60 (m, 2H, aryl), 7.93 (m, 2H, aryl), 8.21 ppm (br s, 1H, NH); ms: (m/e) spectrum 263 (M^+), 232 (M^+-OMe), 162 ($CH_3CONHC_6H_4CO^+$), 120 (162-CH_2CO), 92 (162-CH_2CO-CO).

Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.77; H, 6.40; N, 5.27.

6-(4-Acetamidophenyl)-5-methyl-4,5-dihydropyridazin-3(2*H*)-one (**1**).

The acetamido-ester **14** (3.95 g, 15.0 mmoles) was suspended in a mixture of water (16 ml) and ethanol (4 ml), hydrazine hydrate (2.0 ml, 40 mmoles) was added and the reaction mixture was heated under reflux for 2 hours to give a clear solution. The solution was cooled to room temperature, and the solid was filtered off, washed and dried to give 3.50 g (90%) of **1** as a hydrate mp 238-241°, (lit mp 235-236° [1]); ir: ν 3445 (water OH), 3213 (NH), 1668 (2 x amide I), 1612 and 1591 (aryl), 1541 (amide II), 1517 (aryl) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.06 (d, J = 7 Hz, 3H, C*H*$_3$CH), 2.06 (s, 3H, CH$_3$CO), 2.22 (m, 1H, CHC*H*H'), 2.67 (m, 1H, CHCH*H'*), 3.35 (m, 1H, C*H*), 7.63 (m, 2H, aryl), 7.72 (m, 2H, aryl), 10.10 (s, 1H, NH), 10.89 (ppm (s, 1H, NH).

Anal. Calcd. for $C_{13}H_{15}N_3O_2.0.7H_2O$: C, 60.4; H, 6.40; N, 16.29. Found: C, 60.41; H, 6.55; N, 16.18.

6-(4-Aminophenyl)-5-methyl-4,5-dihydropyridazin-3(2*H*)-one (**6**).

The acetanilide **1** (2.45 g, 10.0 mmoles) was suspended in 1*M* hydrochloric acid (20 ml) and the mixture was heated under reflux for 75 minutes. The clear solution was cooled, neutralized with concentrated ammonium hydroxide (2 ml) and filtered to give 1.55 g (76%) of **6** mp 194-196° (lit mp 195-197° [1]). The spectroscopic and chromatographic characteristics of this product were identical to those of a sample of the above compound **6** prepared by the alternative route described below.

N-[4-(2-Chloropropionyl)phenyl]acetamide (**18**).

Aluminium trichloride (19.95 g, 15.0 mmoles) was suspended in dichloromethane (50 ml), acetanilide (6.75 g, 5.0 mmoles) was added, and the mixture was cooled to 5°. A solution of 2-chloropropionyl chloride (7.62 g, 5.82 ml, 6.0 mmoles) in dichloromethane (5 ml) was added dropwise over 10 minutes, and the mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with dichloromethane (150 ml) and added to ice (200 g) slowly, with stirring. The organic layer was washed with water (2 x 100 ml), dried (magnesium sulfate) and evaporated to give the crude product (10.1 g) as a light brown solid. This was slurried in diethyl ether (100 ml) for 2 hours, filtered and the solid dried to give 6.87 g (61%) of **18** as a yellow solid, mp 116-117°. The tlc and ^1H nmr spectrum of this product showed the presence of only trace impurities, and the material was suitable for use in the subsequent reaction. Recrystallization from ethanol/water gave **18** mp 119-120°; ir: ν 1670 (amide I and ketone), 1586 (aryl), 1537 (amide II) cm^{-1}; ^1H nmr: δ 1.73 (d, J = 7 Hz, 3H, C*H*$_3$CH), 2.22 (s, 3H, CH$_3$CO), 5.23 (q, J = 7 Hz, 1H, CH), 7.66 (m, 2H, aryl), 7.98 ppm (m, 2H, aryl); ms: m/e 225 (M^+), 162 (M^+-CH_3CHCl), 120 ($H_2NC_6H_4CO^+$), 92 ($H_2NC_6H_4^+$).

Anal. Accurate mass: Calcd. for $C_{11}H_{12}ClNO_2$: 225.0557. Found: 225.054.

Ethyl 3-(4-Acetamidobenzoyl)-2-ethoxycarbonylbutanoate (**19**).

Diethyl malonate (17.8 g, 0.111 mole) was added dropwise to a suspension of sodium hydride (50% in oil, 4.89 g, 0.102 mole) in dry DMF (90 ml), keeping the temperature below 30°. The mixture was stirred overnight at room temperature, the chloro-ketone **18** (25 g, 0.116 mole) was added and the reaction mixture was heated at 110° for 3 hours, cooled and extracted with petroleum ether (bp 40°-60°). The residual DMF solution was evaporated to dryness and purified on silica gel by medium pressure liquid chromatography using chloroform as eluant. The appropriate fractions were combined to give 31.6 g (88%) of the required product **19** as a light yellow oil which crystallized on standing. Recrystallization from 2-propanol-water gave 23.2 g (65%) of **19** mp 102-104°; ir: ν 3330 (NH), 1755 and 1730 (esters), 1675 (ketone and amide I), 1590 (aryl), 1530 (amide II) cm^{-1}; ^1H nmr: δ 1.18-1.33 (m, 9H, CHC*H*$_3$ and 2 x CH_2CH_3), 2.19 (s, 3H, CH_3CO), 3.97 (d, J = 10.5 Hz 1H, COC*H*CO), 4.13-4.27 (m, 5H, CH_3CH and 2 x CH_2), 7.60 (m, 2H, aryl), 7.94 (m, 2H, aryl), 8.04 ppm (s, 1H, NH).

Anal. Calcd. for $C_{18}H_{23}NO_6$: C, 61.88; H, 6.63; N, 4.01. Found: C, 62.01; H, 6.73; N, 3.95.

3-(4-Aminobenzoyl)butanoic Acid Hydrochloride (**7**).

The acetamido-diester **19** (10.0 g, 28.6 mmoles) was dissolved in ethanolic hydrogen chloride solution (400 ml) and the mixture was heated under reflux for two hours and evaporated to dryness. The residual oil was dissolved in 6 *N* hydrochloric acid (200 ml) and the solution was heated under reflux for 2 hours, evaporated to low volume, 9 *M* hydrochloric acid (20 ml) was added and the solid was filtered off and washed with 9 *M* hydrochloric acid followed by 1-propanol to give 4.50 g (65%) of **7** mp 189° dec; ir: ν 3500-2300 ($^+NH_3$, OH), 1710 (ester), 1690 (ketone), 1605, 1563 (aryl) cm^{-1}; ^1H nmr (deuterium oxide): δ 1.20 (d, J = 7 Hz, 3H, CH$_3$), 2.67 (dd, J = 17, 5 Hz, 1H, C*H*H'), 2.91 (dd, J = 17, 8 Hz, 1H, CH*H'*), 4.03 (m, 1H, CH), 7.50 (m, 2H, aryl), 8.13 ppm (m, 2H, aryl).

Anal. Calcd. for $C_{11}H_{14}ClNO_3$: C, 54.21; H, 5.79; N, 5.75; Cl, 14.55. Found: C, 53.97; H, 5.71; N, 5.41; Cl, 14.23.

6-(4-Aminophenyl)-5-methyl-4,5-dihydropyridazin-3(2*H*)-one (**6**).

3-(4-Aminophenyl)butanoic acid hydrochloride **7** (170 g, 0.70 mole) was dissolved in water (800 ml) with warming, hydrazine hydrate (70 g, 1.40 moles) was added, and the solution was heated under reflux. After 1.5 hours the reaction mixture was cooled, filtered, and the residue was washed with water and 1-propanol and dried to give 167 g (87%) of **6** mp 201-203° (lit mp 195-197° [1]); ^1H nmr (DMSO-d_6): δ 1.03 (d, J = 7 Hz, 3H, CH$_3$), 2.17 (1H, d, J = 17 Hz, CHCH*H'*), 2.59 (d of d, J = 17, 7 Hz, 1H), 3.27 (d of q, J = 7 Hz, 1H, C*H*CH$_3$), 5.50 (2H, s, NH_2), 6.57 (2H, d, J = 8 Hz, aryl), 7.48 ppm (d, J = 8 Hz, 2H, aryl).

Anal. Calcd. for $C_{11}H_{13}N_3O$: C, 65.00; H, 6.45; N, 20.68. Found: C, 65.14; H, 6.45; N, 20.83.

6-[4-*N'*-Cyano-*S*-methylisothioureido)phenyl]-5-methyl-4,5-dihydropyridazin-3(2*H*)-one (**16**).

The aniline **6** (32.8 g, 0.161 mole) was dissolved in pyridine (250 ml) and *N*-cyano-*S,S*-dimethyldithioiminocarbonate **15** (47.9 g, 0.336 mole) was added. The mixture was heated under reflux for 3.5 hours, cooled and the solid was filtered off and washed with 95% IMS and diethyl ether to give 31.3 g (65%) of **16** mp 231-234° ir: ν 3220, 3100 (NH), 2170 (C=N), 1680 (amide), 1605, 1585 (aryl), 1520 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): 100 MHz δ 1.09 (d, J = 7 Hz, 3H, CHC*H*$_3$), 2.22 (d, J = 18 Hz, 1H, C*H*H'), 2.67 (d of d, J = 18, 7 Hz, 1H, CH*H'*), 2.73 (s, 3H, SCH_3), 3.38 (d of q, J = 7, 7 Hz, 1H, C*H*CH$_3$), 7.54 (m, 2H, aryl), 7.81 (m, 2H, aryl), 10.15 (s, 1H, NH), 10.85 ppm (s, 1H, NH).

Anal. Calcd. for $C_{14}H_{15}N_5OS$: C, 55.79; H, 5.02; N, 23.24; S, 10.64. Found: C, 55.39; H, 4.99; N, 22.72; S, 10.81.

6-[4-(*N'*-cyano-*N''*-methylguanidino)phenyl]-5-methyl-4,5-dihydropyridazin-3(2*H*)-one (**4**).

The methylthio derivative **16** (37.2 g, 0.123 mole) was added to 33%

methylamine in ethanol (465 ml) and the mixture was heated under reflux for 2 hours, cooled and the solid was filtered off and washed with 95% IMS to give the required product **4** (31.5 g). Recrystallization from water-DMF gave 25.3 g (72%) of **4** mp 267-270°; ir: ν 3300-2600 (NH), 2170 (C=N), 1670 (amide), 1615, 1585, 1560 (aryl and C=N) cm^{-1}; ^1H nmr (DMSO-d_6): 100 MHz δ 1.09 (d, J = 7 Hz, 3H, $CHCH_3$), 2.23 (d of d, J = 17, 1.5 Hz, 1H, CHH'), 2.67 (d of d, J = 17, 7 Hz, 1H, CHH'), 2.82 (s, 3H, $NHCH_3$), 3.38 (d of d of q, J = 7, 7, 1.5 Hz, CH_3CH), 7.2 (br s, 1H, NH), 7.35 (m, 2H, aryl), 7.74 (m, 2H, aryl), 8.90 (br s, 1H, NH), 10.79 ppm (s, 1H, NH).

Anal. Calcd. for $C_{14}H_{16}N_6O$: C, 59.14; H, 5.67; N, 29.56. Found: C, 59.11; H, 5.68; N, 29.66.

2-Chloro-*p*-fluoropropiophenone (**25**).

Aluminium trichloride (884 g, 6.30 moles) was suspended in dichloromethane (1600 ml), cooled to 15° and a solution of 2-chloropropionyl chloride (1.00 kg, 765 ml, 7.86 moles) in dichloromethane (800 ml) was added over 30 minutes, keeping the temperature below 20°. A solution of fluorobenzene (610 g, 596 ml, 6.34 moles) in dichloromethane (600 ml) was then added over 30 minutes, keeping the temperature below 25°. The reaction was stirred at room temperature for 3 hours and carefully poured into a stirred mixture of ice (3 kg) and concentrated hydrochloric acid (250 ml, 3.0 moles). The organic phase was separated and the aqueous phase was extracted with dichloromethane (1 x 600 ml), and the combined extracts were washed with aqueous sodium hydroxide (3 *M*, 1 x 1 l) and brine (1 x 500 ml), dried, filtered and the solvent evaporated to give 1085 g (92%) of **25** as a lachrymatory and vesicant oil; ir: ν 1695 (ketone), 1598 (aryl); ^1H nmr: δ 1.73 (d, J = 7 Hz, 3H, CH_3), 5.19 (q, J = 7 Hz, 1H, CH), 7.17 (dd, J_{HH} = 8 Hz, J_{HF} = 8 Hz, 2H, aryl), 8.05 (dd, J_{HH} = 8 Hz, J_{HF} = 5 Hz, 2H, aryl); ms: (m/e) 186 (M^+), 123 ($FC_6H_4CO^+$), 95 ($FC_6H_4^+$).

Anal. Calcd. for C_9H_8ClFO: C, 57.92; H, 4.32. Found: C, 57.28; H, 4.25. Accurate mass: Calcd. for C_9H_8ClFO: 186.0248. Found: 186.026.

Ethyl 2-Ethoxycarbonyl-3-(4-fluorobenzoyl)butanoate (**26**).

Sodium hydride (50% suspension in oil, 340 g, 7.1 moles) was suspended in DMF (2.0 l) and cooled to 10°. Diethyl malonate (1.22 kg, 7.6 moles) was added dropwise over 90 minutes, keeping the temperature below 30°, and the mixture was stirred for a further 30 minutes. A solution of the α-chloroketone **25** (1.18 kg, 6.33 moles) in DMF (2.0 l) was added over 75 minutes, keeping the temperature at 20-25°. The reaction mixture was stirred at room temperature overnight, ammonium chloride (150 g, 2.8 moles) in water (3.0 l) was added and the mixture was extracted with toluene (2 x 2.0 l). The combined extracts were washed with water (2 x 2 l), dried (magnesium sulfate), filtered and the solvent removed by rotary evaporation to give the crude product **26** as an oil (2.2 kg). This was used in the next step without further purification. However an analytical sample was obtained by chromatography on silica (ethyl acetate:hexane) and distillation (bulb to bulb, 160°, 0.3 mm Hg) ir: ν 1749 and 1733 (esters), 1686 (ketone), 1599 (aryl) cm^{-1}; ^1H nmr: δ 1.18 (t, J = 7 Hz, 3H, CH_3CH_2), 1.19 (d, J = 7 Hz, 2H, CH_3CH), 1.33 (t, J = 7 Hz, 3H, CH_3CH_2), 3.98 (d, J = 10 Hz, 1H, COCHCO), 4.11 (m, 3H, CH_3CH_2 + CH_3CH), 4.28 (q, J = 7 Hz, 2H, CH_3CH_2), 7.16 (dd, J_{HH} = 8 Hz, J_{HF} = 8 Hz, 2H, aryl), 8.05 ppm (dd, J_{HH} = 8 Hz, J_{HF} = 5 Hz, 2H, aryl); ms: (m/e) 310 (M^+), 123 ($FC_6H_4CO^+$).

Anal. Calcd. for $C_{16}H_{19}FO_5$: C, 61.93; H, 6.17. Found: C, 61.63; H, 6.12.

3-(4-Fluorobenzoyl)butanoic Acid (**24**).

The crude keto-diester **26** (2.2 kg) was refluxed in a mixture of concentrated hydrochloric acid (4.0 l), water (4.0 l) and dioxan (4.0 l) for 4.5 days, the layers were separated and the aqueous layer was extracted with dichloromethane (2 x 2.5 l). The combined organic extracts were washed with water (2 x 2.0 l) and evaporated to give an oil. This was redissolved in dichloromethane (1.0 l), extracted with aqueous sodium hydroxide (2 *M*, 1 x 2.0 l; 1 *M*, 1 x 2.0 l), and the aqueous extracts were washed with dichloromethane, acidified to *p*H 1 with concentrated hydrochloric acid and extracted with dichloromethane (1 x 3 l). The organic extract was washed with water, dried (magnesium sulfate), filtered and evaporated to give a solid. This was warmed in cyclohexane (3.5 l), stirred vigorously and left to cool. The solid was filtered off, washed with cyclohexane and petroleum ether (bp 40-60°) to give 947 g (71% from **25**) of **24** mp 75-78° (lit mp 57-58° [9], 71-73° [10c]); ir: ν 3300-2300 (OH), 1705 (acid), 1665 (ketone), 1590 (aryl) cm^{-1}; ^1H nmr: δ 1.21 (d, J = 7 Hz, 3H, CH_3), 2.48 (dd, J = 17, 7 Hz, 1H, $CHCHH'$), 2.99 (dd, J = 17, 9 Hz, 1H, $CHCHH'$), 3.86 (m, C*H*), 7.23 (dd, J_{HH} = 9 Hz, J_{HF} = 9 Hz, H, aryl), 8.00 ppm (dd, J_{HH} = 9 Hz, J_{HF} = 5 Hz, 2H, aryl); ms: (m/e) 210 (M^+), 193 (M^+-OH), 192 (M^+-H_2O), 123 ($FC_6H_4CO^+$), 95 ($FC_6H_4^+$).

Anal. Calcd. for $C_{11}H_{11}FO_3$: C, 62.85; H, 5.27. Found: C, 62.73; H, 5.23.

3-[4-(4-Oxo-1,4-dihydropyridin-1-yl)benzoyl]butanoic Acid (**27**).

Sodium hydroxide (453 g, 11.3 moles) was dissolved in water (2.2 l) and the fluoro-keto-acid **24** (885 g, 4.21 moles) and 4-hydroxypyridine **23** (663 g, 6.97 moles) were added. The reaction mixture was heated under reflux for 24 hours, cooled, diluted with water (10 l), filtered through celite and the *p*H of the filtrate was adjusted to 3 with concentrated hydrochloric acid. The resulting solid was collected, washed with water and dried to give 1127 g (94%) of **27** mp 251-254°; ir: ν 2925, 2855, 2515 (OH), 1705 (acid), 1675 (ketone), 1635 and 1550 (pyridone), 1600 and 1510 (aryl), 1280, 1190, 980, 850 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.14 (d, J = 7 Hz, 2H, CH_3), 2.48 (d of d, J = 4, 17 Hz, 1H, $CHCHH'$), 2.79 (d of d, J = 8, 17 Hz, 1H, $CHCHH'$), 3.96 (m, 1H, CH), 6.30 (m, 2H, pyridone), 7.75 (2H, m, aryl), 8.15 ppm (m, 4H, aryl and pyridone).

Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.49; H, 5.37; N, 4.81.

5-Methyl-6-[4-(4-oxo-1,4-dihydropyridin-1-yl)phenyl]-4,5-dihydropyridazin-3(2*H*)-one (**5**).

The pyridone-keto-acid **27** (5.00 g, 17.5 mmoles) was suspended in water (60 ml) and hydrazine hydrate (1.80 g, 1.75 ml, 36 mmoles) was added. The solution was heated under reflux for 2 hours, cooled and the solid was filtered off, washed with water and dried to give 4.45 g (90%) of **5** as a partial hydrate mp 255-258°; ir: ν 1675 (amide), 1635 and 1560 (pyridone), 1610, 1580, 1510 (aryl) cm^{-1}; ^1H nmr: δ 1.09 (d, J = 7 Hz, 3H, $CHCH_3$), 2.27 (d, J = 17 Hz, 1H, CHH'), 2.73 (d of d, J = 17, 7 Hz, 1H, CHH'), 3.46 (d of q, J = 1H, $CHCH_3$), 6.25 (m, 2H, pyridone), 7.62 (m, 2H, aryl), 7.94 (m, 2H, aryl), 8.05 ppm (m, 2H, pyridone).

Anal. Calcd. for $C_{16}H_{15}N_3O_2.0.7H_2O$: C, 65.38; H, 5.62; N, 14.29. Found: C, 65.53; H, 5.43; N, 14.31.

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