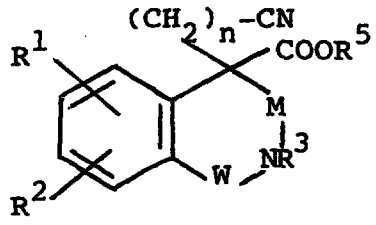
The present invention relates to a process for the preparation of spiro[isoquinoline-4(1H),3′-pyrrolidine]-1,2′,3,5′(2H)-tetrones which are useful as aldose reductase inhibitors. The invention also relates to novel intermediates useful in the process.

EP 0 365 324A discloses a class of nitriles having the general formula I



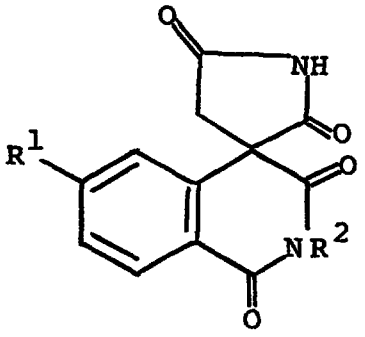
(I)

in which R^1 and R^2 represent hydrogen or various substituents, R^3 represents hydrogen or various substituents, M and W are independently carbonyl, thiocarbonyl, sulfonyl, sulfoxo or C_1 or C_2 lower alkylene and n is 1 to 3. The nitriles are disclosed for the purpose of preparing thioamides by reaction with $HSP(=S)(OEt)_2/HCl$. The present invention includes a selected novel subgenus of compounds falling within the said class. The novel compounds have the advantage of being useful in an improved method of preparing spiro[isoquinoline-4(1H),3′-pyrrolidine]-1,2′,3,5′(2H)-tetrones from 1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolinecarboxylic acid esters.

dioxo-4-isoquinolinecarboxylic acid esters. The method comprises 4 steps. The starting compound is reacted with t-butyl bromacetate in the presence of K_2CO_3 to introduce $-CH_2COO^tBu$ at the 4-position. The second step comprises removal of the tertiary butyl group with trifluoroacetic acid to produce the 4-(carboxymethyl) derivative of the starting compound. The third step comprises reacting the carboxylic acid with a coupling agent followed by ammonia to prepare the 4-(2-amino-2-oxoethyl) derivative of the starting compound. The fourth step comprises cyclization of this amide in the presence of a suitable base.

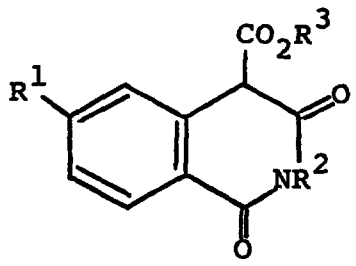
The prior art method employs three steps for the conversion of the starting compound into its 4-(2-amino-2-oxoethyl) derivative. The present invention provides a process in which this conversion is carried out in fewer steps, namely two steps. Each of these steps can be performed in very high yield. Thus the invention has the advantage that it can be carried out in higher yields than the prior art method.

The present invention provides a process for the preparation of a compound having the formula II



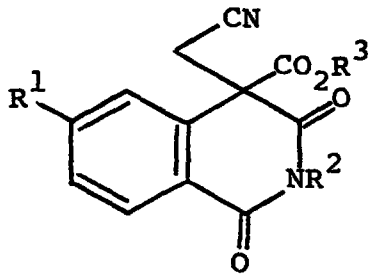
(II)

(1) a compound having the formula III



(III)

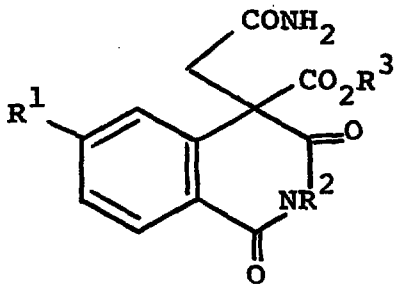
in which R^1 and R^2 are as defined above and $-CO_2R^3$ is an ester group preferably $-CO_2Me$, is cyanomethylated to prepare a compound having the formula IV



(IV)

in which R^1, R^2 and $-CO_2R^3$ are as defined above;

(2) the compound having formula IV is hydrated to prepare an amide having the formula V



(V)

(3) the amide having the formula V is cyclized with a base to form the compound having formula II. The invention also provides the nitriles having formula IV as new compounds.

R^1 is preferably halogen, more preferably fluorine. R^2 is preferably dihalogen- substituted benzyl, more preferably (4-bromo-2-fluorophenyl) methyl. R^3 is preferably methyl.

The compounds having formula III can be prepared in manner known per se. Our preferred compounds of formula III, the methyl esters, are preferably prepared by the steps designated (a) and (b) below.

The cyanomethylation reaction can be carried out by reaction of the compound having formula III with a cyanomethylating agent, i.e. a compound having the formula $CNCH_2X$ where X is a leaving group, preferably bromine, in the presence of a base such as potassium carbonate. The reaction can be performed in a conventional solvent. We prefer to carry out the reaction at about 0°C in a a combination of DMF and acetone. The cyanomethylation can be carried out in yields of around 94% and 95%.

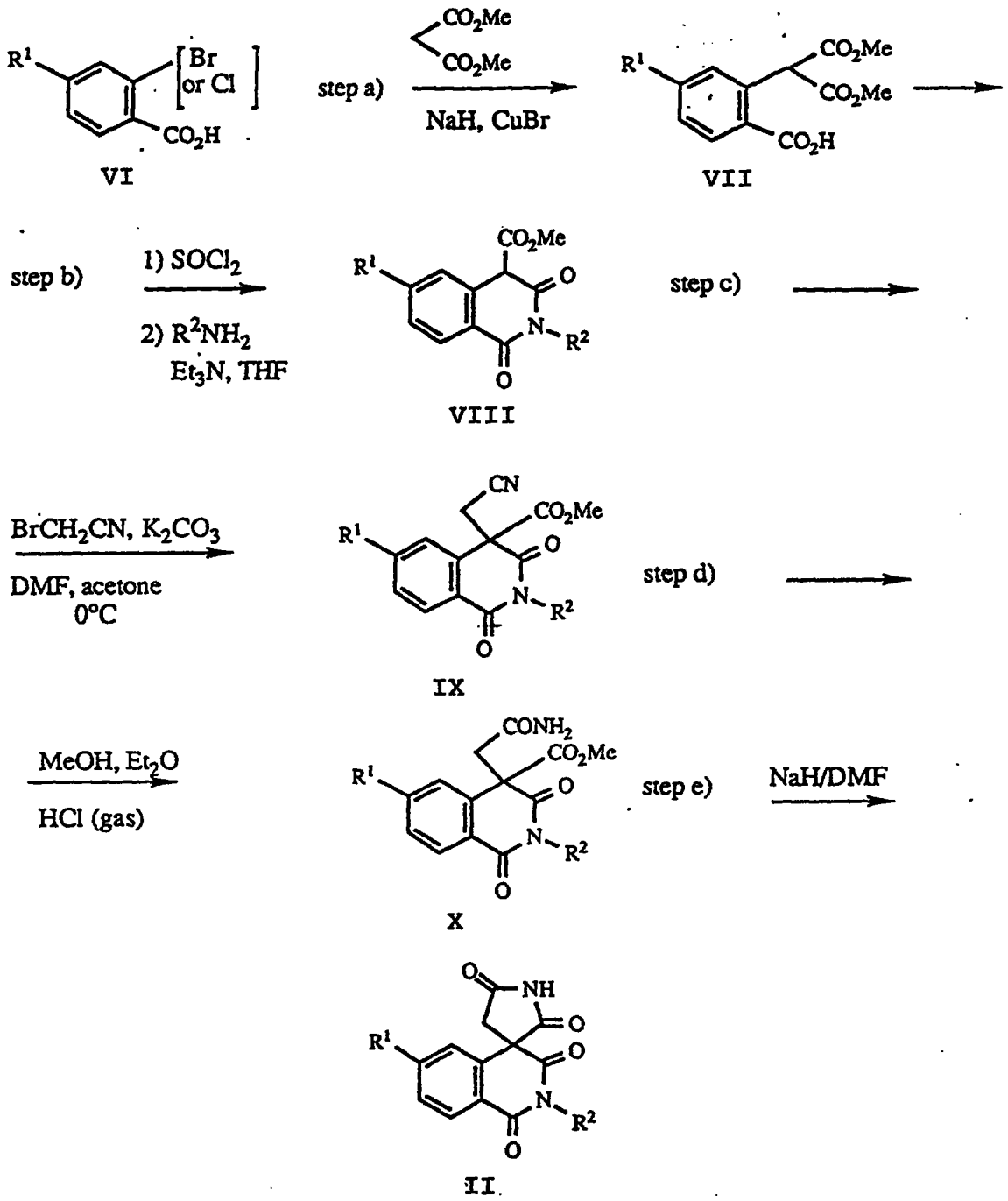
The conversion of the nitrile (IV) into the amide (V) is preferably carried out in a manner avoiding aqueous base or aqueous acid in order to avoid hydrolysis of the ester group $-CO_2R^3$. Thus the hydration of the nitrile (IV) is suitably performed under non-hydrolytic conditions. We prefer to carry out the hydration by reaction of the nitrile with an

conditions. The reaction is preferably carried out in the presence of diethyl ether as solvent. Excess of the alcohol may also serve as additional solvent. As preferred reactants one may use by hydrogen chloride gas and methanol. These reactants are believed to produce an imido ester salt which readily decomposes to form methyl chloride and the desired amide (V). The conversion of the nitrile (IV) into the amide (V) can be carried out in yields of about 92% to 95%.

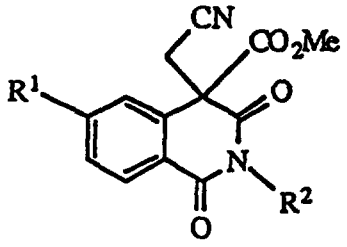
The cyclization of the amide (V) is preferably carried out in the presence of NaH in DMF.

If R3 in formula III is homochiral then the intermediate compounds of formulae IV and V will be a mixture of diastereoisomers which may be separated by means known in the art, e.g crystallisation and chromotography. In this case cyclization of compound V will give a single enantiomer of formula II.

The process of the present invention is illustrated by the following process:



wherein R^1 and R^2 are as defined above.



(IX)

wherein R^1 and R^2 are as defined above.

(IX) is useful as an intermediate for preparing spiro[isoquinoline]-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrones of formula (I) which have strong aldose reductase inhibiting activity and are expected useful as remedies for diabetic complications.

The following examples further illustrate this invention.

Example 1

2-[(4-Bromo-2-fluorophenyl)methyl]-6-fluorospiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone

Step a)

(2-Carboxy-6-fluorophenyl)propanedioic Acid Dimethyl Ester

To a rapidly stirred cold suspension (0°C) of 2-chloro-4-fluorobenzoic acid (20.0 g, 114.6 mmol), cuprous bromide (1.64 g, 11.46 mmol) and dimethyl malonate (250 g) was added NaH (80% in mineral oil, 8.25 g, 275.04 mmol) over a 30 minute period, while a stream of dry N_2 was passed over the mixture. After the addition of the NaH had been completed, the mixture wa stirred at 85°C for 3 hours. At this point, the suspension had turned to a solid mass, which was dissolved in H_2O (1000 mL). The aqueous layer was extracted with diethyl ether (3 x 500 mL) and was acidified with HCl (2N). The mixture was extracted with EtOAc and dried over $MgSO_4$. Evaporation gave an off-white solid which was recrystallized from ether/hexane (after cooling to -20°C) to give a white solid (27.5 g, 89%). ^1H NMR (DMSO-d_6, 400 MHz): δ 3.68 [s, 6H, (-CO_2Me)2], 5.79 (s, 1H, Ar-H), 7.12 (dd, J = 10.06 Hz, 2.61

Hz, 1H, Ar-H); IR (KBr, cm^{-1}): 3400-2700 (CO_2H), 1750 (CO), 1680 (CO); MS (m/e): 270 (M^+)-CH_3OH), 210 (M^+-CH_3OH, -CO), 151 (M^+ -CH_3OH-CO-CO_2CH_3); M.P. 121.5-123.0°C.

Anal. Calc'd: C, 53.34; H, 4.10
Found: C, 53.36; H, 3.93

The following compounds were prepared in substantially the same manner as that of Example 1 Step a):

(2-Carboxyphenyl)propanedioic Acid Dimethyl Ester

^1H NMR (DMSO-d_6, 400 MHz): δ 3.67 [s, 6H, -CH(C)$_2$C$\underline{H}_3$)$_2$], 5.72 [s, 1H, -C$\underline{H}$(CO_2CH_3)$_2$], 7.3 (d, J = 7.76 Hz, 1H, Ar-$\underline{H}$), 7.45 (dt, J = 7.66 Hz, 1.12 Hz, 1H, Ar-$\underline{H}$), 7.6 (dt, J = 7.66 Hz, 1.45 Hz, 1H, Ar-$\underline{H}$), 7.94 (dd, J = 7.8 Hz, 1.33 Hz, 1H, Ar-$\underline{H}$), 13.2 (s, 1H, -$CO_2\underline{H}$); IR (KBr, cm^{-1}): 3300-2700 (CO_2H), 1750 (CO), 1730 (CO), 1680 (CO); MS (m/e): 252 (M^+), 220 (M^+-CH_3OH), 188 (M^+-2xCH_3OH); M.P. 119-120°C.

Anal. Calc'd: C, 57.14; H, 4.80
Found: C, 57.05; H, 4.78

(2-Carboxy-6-chlorophenyl)propanedioic Acid Dimethyl Ester

^1H NMR (DMSO-d_6, 200 MHz): δ 3.69 [s, 6H, (-CO_2Me)$_2$], 5.78 [s, 1H, Ar-CH(CO_2Me)$_2$], 7.38 (d, J = 1.8 Hz, 1H, Ar-$\underline{H}$), 7.58 (dd, J = 7.8 Hz, 1.8 Hz, 1H, Ar-$\underline{H}$), 7.96 (d, J = 8.2 Hz, 1H, Ar-$\underline{H}$), 13.5 (br s, 1H, -$CO_2\underline{H}$); IR (KBr, cm^{-1}): 3200-2700 (CO_2H), 1760 (CO), 1740 (CO), 1690 (CO); MS (m/e): 286 (20 M^+), 254 (64, M^+-CH_3OH), 222 (60, M^+-2xCH_3OH)

Anal. Calc'd: C, 50.28; H, 3.87
Found: C, 50.40; H, 3.87

2-[(4-Bromo-2-fluorophenyl)methyl-6-fluoro-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolinecarboxylic Acid Methyl Ester

A mixture of (2-carboxy-6-fluorophenyl)propanedioic acid dimethyl ester (6.0 g, 22.22 mmol) and $SOCl_2$ (50 mL) was refluxed for 1 hour. The volatiles were removed in vacuo and the acid chloride was ddissolved in THF (20 mL). In a second flask were placed 4-bromo-2-fluorobenzylamine (4.98 g, 24.44 mmol), triethylamine (15.48 mL, 111.1 mmol) and THF (150 mL). The contents of the first flask were added to the second flask and the mixture was stirred for 20 minutes. The formed suspension was poured into H_2O (1500 mL), stirred for 10 minutes and acidified with HCl (2N). The mixture was extracted with EtOAc and the organic layer was dried over $MgSO_4$. Evaporation gave a yellowish solid which was recrystallized from acetone/ether/hexane (after cooling -20°C) to give a white solid (7.85 g, 83%). ^1H NMR (DMSO-d_6, 400 MHz): δ 3.98 (s, 3H, -$CO_2C\underline{H}_3$), 5.27 (s, 2H, -$NC\underline{H}_2$-), 7.08 (t, J = 7.95 Hz, 2H, Ar-H), 7.2 (m, 1H, Ar-H), 7.34 (m, 2H, Ar-H, -OH), 7.54 (m, 1H, Ar-H), 8.1-8.26 (m, 2H, Ar-H); IR (KBr, cm^{-1}): 1680 (CO), 1660 (CO), 1610 (CO); MS (m/e): 423 (M^+), 391 (M^+-CH_3OH); M.P.157-158°C.

Anal. Calc'd: C, 50.97; H, 2.85; N, 3.30
Found: C, 50.86; H, 2.86; N, 3.33

The following compounds were prepared in substantially the same manner as that of Example 1 Step b):

2-[(4-Bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinoline-carboxylic Acid Methyl Ester

^1H NMR (DMSO-d_6, 400 MHz): δ [3.67, 3.99 (s, 3H, -$CO_2C\underline{H}_3$, tautomeric], [5.06 (q, J = 15.4 Hz), 5.29 (s) 2H, N-$C\underline{H}_2$-, tautomeric], 5.03 (s, 1H, -$C\underline{H}CO_2CH_3$, tautomeric), 7.07-8.44 (m, 7H, Ar-H, tautomeric); IR (KBr, cm^{-1}): 1675 (CO), 1610 (CO), 1490 795 (m); MS (m/e): 405 (M^+), 373 (M^+-MeOH); M.P. 149-150°C.

Anal. Calc'd: C, 53.22; H, 3.23; N, 3.45
Found: C, 52.91; H, 3.20; N, 3.27

Ester

^{1}H NMR (DMSO-d_6, 200 MHz): δ [3.23 (s), 3.44 (s), tautomeric, 3H, -NC<u>H</u>$_3$], [3.71 (s), 4.03 (s), tautomeric, 3H, -$CO_2C\underline{H}_3$], 7.3-8.4 (tautomeric, Ar-<u>H</u>, -OH, 4H); IR (KBr, cm^{-1}): 3440 (OH), 1680 (CO), 1600 (CO); MS (m/e): 267 (M^+), 235 (M^+-OMe); M.P. 166-167°C.

Anal. Calc'd: C, 53.85; H, 3.77; N, 5.23
Found: C, 53.66; H, 3.63; N, 5.14

1,2,3,4-Tetrahydro-2-methyl-1,3-dioxo-4-isoquinolinecarboxylic Acid Methyl Ester

^{1}H NMR (DMSO-d_6, 200 MHz): δ [3.24 (s), 3.46 (s), tautomeric, 3H, -NC<u>H</u>$_3$], [3.7 (s), 4.03 (s), tautomeric, 3H, -CO_2CH_3], 7.4-8.45 (tautomeric, 4H, Ar-H); IR (KBr, cm^{-1}): 3400 (OH), 1670 (CO), 1600 (CO); MS (m/e): 233 (M^+), 118 (M^+-CO_2Me, -CONCH$_3$); M.P. 130-131°C.

Anal. Calc'd: C, 61.80; H, 4.75; N, 6.01
Found: C, 61.62; H, 4.89; N, 5.92

Step c)
2-[(4-Bromo-2-fluorophenyl)methyl]-4-cyanomethyl-6-fluoro-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolinecarboxylic Acid Methyl Ester

To a cold (0°C) suspension of 2-[(4-bromo-2-fluorophenyl)methyl]-6-fluoro-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolinecarboxylic acid methyl ester (11.0 g, 25.94 mmol), K_2CO_3 (3.58 g, 25.94 mmol), DMF (50 mL) and acetone (50 mL) was added freshly distilled $BrCH_2CN$ (3.61 mL, 51.88 mmol) and the mixture was stirred for 10 hours at 0°C and kept in the refrigerator for 4 days. The mixture was then poured into H_2O, acidified with HCl (2N), and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography hexane/EtOAc (5/1) gave a light yellow solid (11.45 g, 95.4%). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.63 (s, 3H, -$CO_2C\underline{H}_3$), 3.73 (d, J = 16.8 Hz, 1H, -<u>H</u>CHCN), 3.9 (d, J = 16.8 Hz, 1H, -HC<u>H</u>CN), 5.14 (dd, J = 15.2 Hz, 2H, -NC<u>H</u>$_2$-), 7.16 (t, J = 8.1 Hz, 1H, Ar-<u>H</u>), 7.36 (dd, J = 8.1 Hz, 1.8 Hz, 1H, Ar-<u>H</u>), 7.57 (m, 2H, Ar-<u>H</u>), 7.64 (dd, J = 9.3 Hz, 2.4 Hz, 1H, Ar-<u>H</u>), 8.3 (dd, J = 8.7 Hz, 5.7 Hz, 1H, Ar-<u>H</u>); IR (KBr, cm^{-1}):

128°C.

Anal. Calc'd: C, 51.86; H, 2.83; N, 6.05
Found: C, 51.73; H, 3.00; N, 5.96

The following compounds were prepared in substantially the same manner as that of Example 2, Step c).

2-[(4-Bromo-2-fluorophenyl)methyl]-4-cyanomethyl-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolinecarboxylic Acid Methyl Ester

^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.61 (s, 3H, -CO_2CH_3), 3.72 (d, J = 17.0 Hz, 1H, -HCHCN), 3.88 (d, J = 17.0 Hz, 1H, -HCHCN), 5.14 (dd, J = 15.2 Hz, 2H, -NCH_2-), 7.17 (t, J = 8.3 Hz, 1H, Ar-H), 7.39 (dd, J = 8.3 Hz, 1.87 Hz, 1H, Ar-H), 7.55 (dd, J = 9.7 Hz, 2.1 Hz, 1H, Ar-H), 7.68 (m, 2H, Ar-H), 7.86 (dt, J = 7.7 Hz, 1.45 Hz, 1H, Ar-H), 8.21 (dd, J = 7.64 Hz, 1.25 Hz, 1H, Ar-H); IR (KBr, cm^{-1}): 2240 (CN), 1760 (CO), 1720 (CO), 1680 (CO); MS (m/e): 444 (M^+), 404 (M^+-CH_2CN); M.P. 108-110°C. (95% yield).

Anal. Calc'd: C, 53.94; H, 3.15; N, 6.29
Found: C, 53.94; H, 3.38; N, 5.93

4-Cyanomethyl-2-methyl-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolinecarboxylic Acid Methyl Ester

^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.31 (s, 3H, -NCH_3), 3.65 (s, 3H, -CO_2CH_3), 3.67 (d, J = 17.0 Hz, 1H, -HCHCN), 3.76 (d, J = 17.0 Hz, 1H, -HCHCN), 7.58 (dd, J = 7.9 Hz, 1.04 Hz, 1H, Ar-H), 7.69 (dt, J = 7.9 Hz, 1.04 Hz, 1H, Ar-H), 7.84 (dt, J = 7.26 Hz, 1.45 Hz, 1H, Ar-H), 8.2 (dd, J = 7.3 Hz, 1.45 Hz, 1H, Ar-H); IR (KBr, cm^{-1}): 2250 (CN), 1760 (CO), 1730 (CO), 1670 (CO); MS (m/e): 272 (M^+), 213 (M^+-CO_2CH_3); M.P. 120-122°C. (94.3%yield).

Anal. Calc'd: C, 61.76; H, 4.44; N, 10.29
Found: C, 61.72; H, 4.57; N, 10.07

carboxylic Acid Methyl Ester

^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.3 (s, 3H, -NC<u>H</u>$_3$), 3.67 (s, 3H, -CO$_2$C<u>H</u>$_3$), 3.74 (d, J = 17.0 Hz, 1H, -<u>H</u>CHCN), 3.87 (d, J = 17.0 Hz, 1H, -HC<u>H</u>CN), 7.7 (m, 2H, Ar-<u>H</u>), 8.2 (d, J = 9.1 Hz, 1H, Ar-<u>H</u>); IR (KBr, cm^{-1}): 2250 (CN), 1770 (CO), 1720 (CO), 1675 (CO); MS (m/e): 306 (M^+), 247 (M^+-CO$_2$CH$_3$); M.P. 130-132°C. (93.8% yield).

Anal. Calc'd: C, 54.83; H, 3.62; N, 9.13
Found: C, 54.74; H, 3.74; N, 8.89

Step d)
4-(2-Amino-2-oxoethyl)-2-[(4-bromo-2-fluorophenyl)methyl]-6-fluoro-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolinecarboxylic Acid Methyl Ester.

Dry HCl gas was passed through a cold (0°C) suspension of 2-[(4-bromo-2-fluorophenyl)methyl]-4-cyanomethyl-6-fluoro-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolinecarboxylic acid methyl ester (7.7 g, 16.63 mmol) in dimethyl ether (300 mL) and anhydrous MeOH (2.02 mL, 49.89 mmol). The suspension during the introduction of the HCl gas turned into a solution. The mixture was kept at room temperature for 4.5 days and then hexane (500 mL) was added.–Most of the volatiles were removed in vacuo to the point that a white solid started to precipitate, and the mixture was cooled to 0°C for 5 hours. The precipitated solid was filtered, washed with hexane and dried to yield a white solid (7.56 g, 95%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.49 (d, J = 16.65 Hz, 1H, -C<u>H</u>$_2$CONH$_2$), 3.56 (s, 3H, -CO$_2$C<u>H</u>$_3$), 3.59 (d, J = 16.65 Hz, 1H, -C<u>H</u>$_2$CONH$_2$), 5.08 (dd, J = 15.48 Hz, 2H, -NC<u>H</u>$_2$), 6.94 (s, 1H, -CONH$_2$),7.21 (t, J = 8.22 Hz, 1H, Ar-<u>H</u>), 7.30 (dd, J = 8.27 Hz, 1.64 Hz, 1H, Ar-<u>H</u>), 7.38-7.46 (m, 2H, Ar-<u>H</u>), 7.51 (s, 1H, -CONH$_2$), 7.54 (dd, J = 9.81 Hz, 1.83 Hz, 1H, Ar-<u>H</u>), 8.20 (dd, J = 8.74 Hz, 5.84 Hz, 1H, Ar-<u>H</u>); IR (KBr, cm^{-1}): 3440 (NH), 3350 (NH), 1740 (CO), 1710 (CO), 1670 (CO), 1660 (CO); MS (m/e): 481 $(M+H)^+$; M.P. 202-204°C.

Anal. Calc'd: C, 49.92; H, 3.14; N, 5.82
Found: C, 49.79; H, 3.36; N, 5.51

The following compounds were obtained in substantially the same manner as that of Example 1, Step d):

dioxo-4-isoquinolinecarboxylic Acid Methyl Ester

^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.53 (s, 3H, -CO_2CH_3), 3.51 (q, J = 16.6 Hz, 2H, -CH_2CONH_2), 5.1 (q, J = 15.4 Hz, 2H, -NCH_2-), 6.88 (s, 1H, -$CONH_2$), 7.23 (t, J = 8.0 Hz, 1H, Ar-H), 7.3 (dd, J = 8.3 Hz, 1.84 Hz, 1H, Ar-H), 7.46 (d, J = 7.98Hz, 1H, Ar-H), 7.52 (s, 1H, -$CONH_2$), 7.54-7.60 (m, 2H, Ar-H), 7.75 (dt, J = 7.76 Hz, 1.39 Hz, 1H, Ar-H), 8.1 (dd, J = 7.87 Hz, 1.22 Hz, 1H, Ar-H); IR (KBr, cm^{-1}): 3450 (NH), 17340 (CO), 1720 (CO), 1670 (CO); MS (m/e): 462 (M^+); M.P. 180-182°C. (95% yield).

Anal. Calc'd: C, 51.84; H, 3.46; N, 6.05
Found: C, 51.72; H, 3.65; N, 5.91

4-(2-Amino-2-oxoethyl)-6-chloro-1,2,3,4-tetrahydro-2-methyl-1,3-dioxo-4-isoquinoline-carboxylic Acid Methyl Ester

^{1}H NMR (DMSO-d_6, 200 MHz): δ 3.26 (s, 3H, -NCH_3), 3.51 (q, J = 17.5 Hz, 2H, -CH_2CONH_2), 3.59 (s, 3H, -CO_2CH_3), 6.85 (s, 1H, -$CONH_2$), 7.5 (s, 1H, -$CONH_2$), 7.53 (d, J = 2.0 Hz, 1H, Ar-H), 7.62 (dd, J = 8.6 Hz, 2.0 Hz, 1H, Ar-H), 8.16 (d, J = 8.0 Hz, 1H, Ar-H); IR (KBr, cm^{-1}): 3420 (NH), 1760 (CO), 1710 (CO), 1660 (CO); MS (m/e): 325 $(M+H)^+$; M.P. 220-222°C. (93.1% yield).

Anal. Calc'd: C, 51.78; H, 4.03; N, 8.63
Found: C, 51.76; H, 4.20; N, 8.32

4-(2-Amino-2-oxoethyl)-1,2,3,4-tetrahydro-2-methyl-1,3-dioxo-4-isoquinoline-carboxylic Acid Methyl Ester

^{1}H NMR (DMSO-d_6, 200 MHz): δ 3.27 (s, 3H, -NCH_3), 3.49 (s, 2H, -CH_2CO_2H), 3.56 (s, 3H, -CO_2CH_3), 6.78 (s, 1H, -$CONH_2$), 7.4-7.6 (m, 3H, Ar-H, -$CONH_2$), 7.69 (dt, J = 7.6 Hz, 2Hz, 1H, Ar-H), 8.16 (d, J = 8.2 Hz, 1H, Ar-H); IR (KBr, cm^{-1}): 3420 (NH), 1760 (CO), 1660 (CO); MS (m/e): 291 $(M+H)^+$; M.P. 229-231°C. (91.9% yield).

Anal. Calc'd: C, 57.93; H, 4.86; N, 9.65
Found: C, 57.59; H, 4.93; N, 9.49

2-[(4-Bromo-2-fluorophenyl)methyl]-6-fluorospiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone

To a solution of 4-(2-amino-2-oxoethyl)-2-[(4-bromo-2-fluorophenyl)methyl]-6-fluoro-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolinecarboxylic acid methyl ester (6.0 g, 12.47 mmol) in DMF (50 mL) was added portionwise NaH (80% dispersion in oil, 374.2 mg, 12.47 mmol) over a 10 minute period. After stirring for 30 minutes, the mixture was poured into H_2O, acidified with HCl (2N) and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexane/EtOAc 3/1) on acid washed silica gel (5% H_3PO_4 in MeOH), yielded a white solid (4.3 g, 86%). ^1H NMR (DMSO-d_6, 400 MHz): δ 3.44 (s, 2H, CONH-), 5.05 (s, 2H, -CN$\underline{H_2}$-), 7.14 (t, J = 8.42 Hz, 1H, Ar-$\underline{H}$), 7.32 (dd, J = 7.58 Hz, 1.26 Hz, 1H, Ar-$\underline{H}$), 7.48 (dt, J = 8.64 Hz, 2.1 Hz, 1H, Ar-$\underline{H}$), 7.53 (dd, 9.89 Hz, 1.89 Hz, 1H, Ar-$\underline{H}$), 7.75 (dd, 9.69 Hz, 2.32 Hz, 1H, Ar-$\underline{H}$), 8.22 (dd, J = 8.84 Hz, 5.89 Hz, 1H, Ar-$\underline{H}$), 12.0 (s, 1H, -CON$\underline{H}$CO-); IR (KBr, cm^{-1}): 3400 (NH), 3260 (NH), 1735 (CO), 1680 (CO); MS (m/e): 449 $(M+H)^+$; M.P. 230-232°C.

Anal. Calc'd: C, 50.80; H, 2.47; N, 6.24
Found: C, 50.87; H, 2.53; N, 6.08

The following compounds were prepared in substantially the same manner as that of example 1 step e):

2-[(4-Bromo-2-fluorophenyl)methyl]spiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone

^1H NMR (DMSO-d_6, 400 MHz): δ 3.47 (J = 18.24 Hz, 2H, -C$\underline{H_2}$CONH-), 5.06 (s, 2H, -NC$\underline{H_2}$-), 7.14 (t, J = 8.2 Hz, 1H, Ar-$\underline{H}$), 7.33 (dd, J = 8.28 Hz, 1.71 Hz, 1H, Ar-$\underline{H}$), 7.55 (dd, J = 9.9 Hz, 1.8 Hz, 1H, Ar-$\underline{H}$), 7.62 (t, J = 7.6 Hz, 1H, Ar-$\underline{H}$), 7.68 (d, J = 7.78 Hz, 1H, Ar-$\underline{H}$), 7.78 (dt, J = 8.85 Hz, 1.12 Hz, 1H, Ar-$\underline{H}$), 8.15 (dd, J = 7.86 Hz, 1.3 Hz, 1H, Ar-$\underline{H}$), 12.01 (s, 1H, -CON$\underline{H}$CO-); IR (KBr, cm^{-1}): 3450 (NH), 3250 (NH), 1730 (CO), 1680 (CO); MS (m/e): 430 (M^+), 387 (M^+-CONH); M.P. 112-114°C.

Anal. Calc'd: C, 52.92; H, 2.80; N, 6.50
Found: C, 52.61; H, 2.70; N, 6.46

6-Chloro-2-methylspiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone

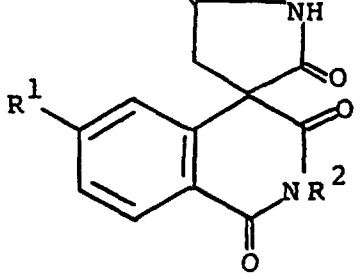
^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.22 (s, 3H, -NC<u>H</u>$_3$), 3.38 (s, 2H, C<u>H</u>$_2$CONH-), 7.66 (dd, J = 8.55 Hz, 2.02 Hz, 1H, Ar-<u>H</u>), 7.92 (d, J = 1.97 Hz, 1H, Ar-<u>H</u>), 8.13 (d, J = 8.52 Hz, 1H, Ar-<u>H</u>), 11.99 (s, 1H, -CON<u>H</u>CO-); IR (KBr, cm^{-1}): 3350 (NH), 1750 (CO), 1730 (CO), 1660 (CO); MS (m/e): 293 $(M+H)^+$; M.P. 213-214°C.

Anal. Calc'd: C, 53.35; H, 3.10; N, 9.57
Found: C, 53.43; H, 3.09; N, 9.38

2-Methylspiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone

^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.24 (s, 3H, -N-C<u>H</u>$_3$), 3.43 (q, J = 18.38 Hz, 2H, -C<u>H</u>$_2$CONH-), 7.58-7.64 (m, 2H, Ar-<u>H</u>), 7.74 (dt, J = 7.64 Hz, 1.2 Hz, 1H, Ar-<u>H</u>), 8.15 (dd, J = 7.72 Hz, 0.94 Hz, 1H, Ar-<u>H</u>), 12.0 (2, 1H, -CON<u>H</u>CO-), IR (KBr, cm^{-1}): 3340 (NH), 1720 (CO), 1660(CO); MS (m/e): 258 (M^+); M.P. 224-225°C.

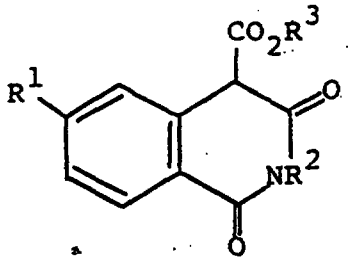
Anal. Calc'd: C, 60.47; H, 3.90; N, 10.85
Found: C, 60.27; H, 4.03; N, 10.82



(II)

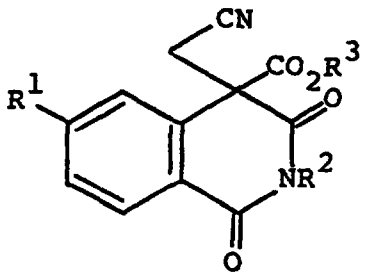
in which R^1 is hydrogen or halogen and R^2 is methyl or dihalogen- substituted benzyl, in which

(1) a compound having the formula III



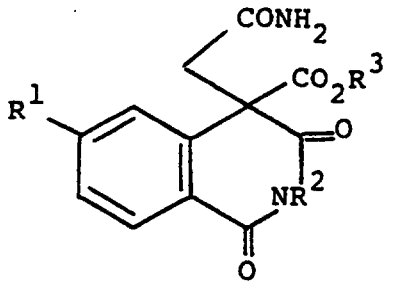
(III)

in which R^1 and R^2 are as defined above and $-CO_2R^3$ is an ester group, is cyanomethylated to prepare a compound having the formula IV



(IV)

prepare an amide having the formula V



(V)

in which R^1, R^2 and CO_2R^3 are as defined above; and

(3) the amide having the formula V is cyclized with a base to form the compound having formula II.

2. A process as claimed in claim 1 in which R^1 is halogen.

3. A process as claimed in claim 1 or 2, in which R^2 is dihalogen-substituted benzyl.

4. A process as claimed in claim 1, in which R^1 is fluorine and R^2 is (4-bromo-2-fluorophenyl) methyl.

5. A process as claimed in any one of claims 1 to 4, wherein R^3 is methyl.

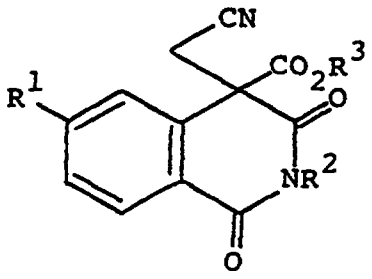
6. A process as claimed in any one of claims 1 to 5, wherein the compound having formula III is reacted with bromoacetonitrile in the presence of potassium carbonate.

hydrogen bromide under essentially anhydrous conditions.

8. A process as claimed in claim 7, wherein the hydration is carried out with hydrogen chloride gas and methanol.

9. A process as claimed in any one of claims 1 to 8, wherein the cyclization of the amide (V) is carried out in the presence of NaH in DMF.

10. A nitrile having the formula

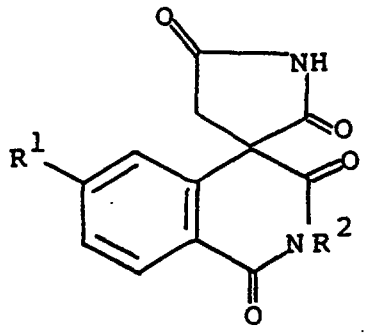


(IV)

wherein R^1, R^2 and $-CO_2R^3$ are as defined in claim 1.

11. A nitrile as claimed in claim 10, wherein R^1 and R^2 are as defined in claim 4.

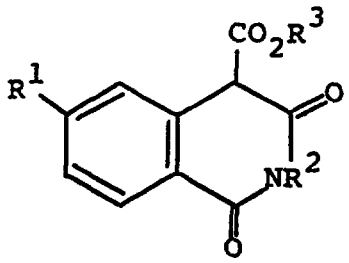
12. A nitrile as claimed in claim 10 or 11 wherein R^3 is methyl.



(II)

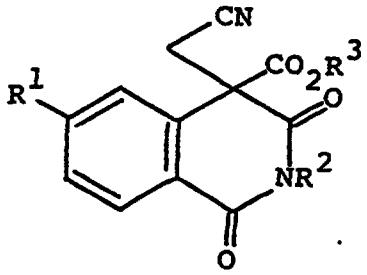
in which R^1 is hydrogen or halogen and R^2 is methyl or dihalogen- substituted benzyl, in which

(1) a compound having the formula III



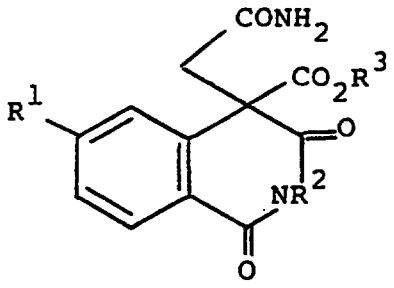
(III)

in which R^1 and R^2 are as defined above and $-CO_2R^3$ is an ester group, is cyanomethylated to prepare a compound having the formula IV



(IV)

prepare an amide having the formula V



(V)

in which R^1, R^2 and CO_2R^3 are as defined above; and

(3) the amide having the formula V is cyclized with a base to form the compound having formula II.

2. A process as claimed in claim 1 in which R^1 is halogen.

3. A process as claimed in claim 1 or 2, in which R^2 is dihalogen-substituted benzyl.

4. A process as claimed in claim 1, in which R^1 is fluorine and R^2 is (4-bromo-2-fluorophenyl) methyl.

5. A process as claimed in any one of claims 1 to 4, wherein R^3 is methyl.

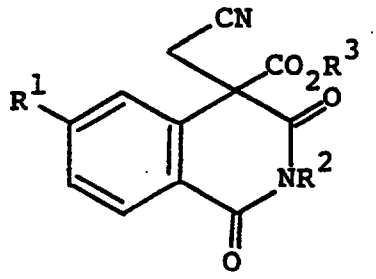
6. A process as claimed in any one of claims 1 to 5, wherein the compound having formula III is reacted with bromoacetonitrile in the presence of potassium carbonate.

hydrogen bromide under essentially anhydrous conditions.

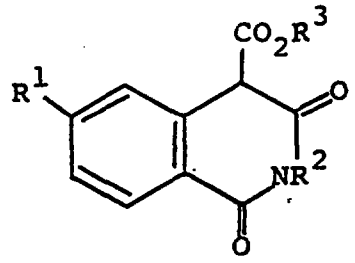
8. A process as claimed in claim 7, wherein the hydration is carried out with hydrogen chloride gas and methanol.

9. A process as claimed in any one of claims 1 to 8, wherein the cyclization of the amide (V) is carried out in the presence of NaH in DMF.

10. A process for the preparation of a nitrile having formula



(IV)



(III)

where R^1, R^2 and - CO_2R^3 are as defined above.

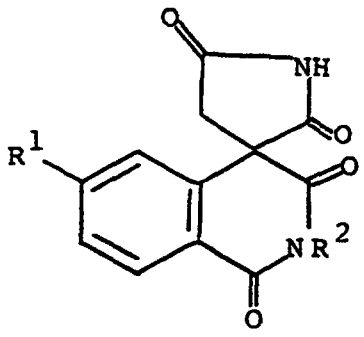
11. A process as claimed in claim 10, wherein R^1 and R^2 are as defined in claim 4.

12. A process as claimed in claim 10 or 11, wherein R^3 is methyl.

* C L M S *

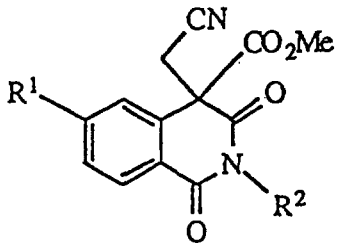
PROCESS AND INTERMEDIATE FOR THE PREPARATION OF ISOQUINOLINE DERIVATIVES

The invention presents a process for the preparation of spiro[isoquinoline-4(1H),3′-pyrrolidine]-1,2′,3,5′(2H)-tetrones which are useful as aldose reductase inhibitors and have the formula II



(II)

where R^1 is hydrogen or halogen and R^2 is methyl or dihalogen-substituted benzyl. The process comprises a three step method from 1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolinecarboxylic acid esters via the 4-(cyanomethyl) and 4-(2-amino-2-oxoethyl) derivatives thereof.



(IX)

wherein R^1 and R^2 are as defined above.

(IX) is useful as an intermediate for preparing spiro[isoquinoline]-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrones of formula (I) which have strong aldose reductase inhibiting activity and are expected useful as remedies for diabetic complications.

The following examples further illustrate this invention.

Example 1

2-[(4-Bromo-2-fluorophenyl)methyl]-6-fluorospiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone

Step a)

(2-Carboxy-5-fluorophenyl)propanedioic Acid Dimethyl Ester

To a rapidly stirred cold suspension (0°C) of 2-chloro-4-fluorobenzoic acid (20.0 g, 114.6 mmol), cuprous bromide (1.64 g, 11.46 mmol) and dimethyl malonate (250 g) was added NaH (80% in mineral oil, 8.25 g, 275.04 mmol) over a 30 minute period, while a stream of dry N_2 was passed over the mixture. After the addition of the NaH had been completed, the mixture wa stirred at 85°C for 3 hours. At this point, the suspension had turned to a solid mass, which was dissolved in H_2O (1000 mL). The aqueous layer was extracted with diethyl ether (3 x 500 mL) and was acidified with HCl (2N). The mixture was extracted with EtOAc and dried over $MgSO_4$. Evaporation gave an off-white solid which was recrystallized from ether/hexane (after cooling to -20°C) to give a white solid (27.5 g, 89%). ^1H NMR (DMSO-d_6, 400 MHz): δ 3.68 [s, 6H, (-CO_2Me)2], 5.79 (s, 1H, Ar-H), 7.12 (dd, J = 10.06 Hz, 2.61

This Sheet Has Been Replaced



Hz, 1H, Ar-H); IR (KBr, cm^{-1}): 3400-2700 (CO_2H), 1730 (CO), 1680 (CO); MS (m/e): 270 (M^+)-CH_3OH), 210 (M^+-CH_3OH, -CO), 151 (M^+ -CH_3OH-CO-CO_2CH_3); M.P. 121.5-123.0°C.

Anal. Calc'd: C, 53.34; H, 4.10
Found: C, 53.36; H, 3.93

The following compounds were prepared in substantially the same manner as that of Example 1 Step a):

(2-Carboxyphenyl)propanedioic Acid Dimethyl Ester

^1H NMR (DMSO-d_6, 400 MHz): δ 3.67 [s, 6H, -CH(C)$_2$CH_3)$_2$], 5.72 [s, 1H, -CH(CO_2CH_3)$_2$], 7.3 (d, J = 7.76 Hz, 1H, Ar-H), 7.45 (dt, J = 7.66 Hz, 1.12 Hz, 1H, Ar-H), 7.6 (dt, J = 7.66 Hz, 1.45 Hz, 1H, Ar-H), 7.94 (dd, J = 7.8 Hz, 1.33 Hz, 1H, Ar-H), 13.2 (s, 1H, -CO_2H); IR (KBr, cm^{-1}): 3300-2700 (CO_2H), 1750 (CO), 1730 (CO), 1680 (CO); MS (m/e): 252 (M^+), 220 (M^+-CH_3OH), 188 (M^+-2xCH_3OH); M.P. 119-120°C.

Anal. Calc'd: C, 57.14; H, 4.80
Found: C, 57.05; H, 4.78

(2-Carboxy-5-chlorophenyl)propanedioic Acid Dimethyl Ester

^1H NMR (DMSO-d_6, 200 MHz): δ 3.69 [s, 6H, (-CO_2Me)$_2$], 5.78 [s, 1H, Ar-CH(CO_2Me)$_2$], 7.38 (d, J = 1.8 Hz, 1H, Ar-H), 7.58 (dd, J = 7.8 Hz, 1.8 Hz, 1H, Ar-H), 7.96 (d, J = 8.2 Hz, 1H, Ar-H), 13.5 (br s, 1H, -CO_2H); IR (KBr, cm^{-1}): 3200-2700 (CO_2H), 1760 (CO), 1740 (CO), 1690 (CO); MS (m/e): 286 (20 M^+), 254 (64, M^+-CH_3OH), 222 (60, M^+-2xCH_3OH)

Anal. Calc'd: C, 50.28; H, 3.87
Found: C, 50.40; H, 3.87

This Sheet Has Been Replaced



2-[(4-Bromo-2-fluorophenyl)methyl-6-fluoro-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolinecarboxylic Acid Methyl Ester

A mixture of (2-carboxy-5-fluorophenyl)propanedioic acid dimethyl ester (6.0 g, 22.22 mmol) and $SOCl_2$ (50 mL) was refluxed for 1 hour. The volatiles were removed in vacuo and the acid chloride was ddissolved in THF (20 mL). In a second flask were placed 4-bromo-2-fluorobenzylamine (4.98 g, 24.44 mmol), triethylamine (15.48 mL, 111.1 mmol) and THF (150 mL). The contents of the first flask were added to the second flask and the mixture was stirred for 20 minutes. The formed suspension was poured into H_2O (1500 mL), stirred for 10 minutes and acidified with HCl (2N). The mixture was extracted with EtOAc and the organic layer was dried over $MgSO_4$. Evaporation gave a yellowish solid which was recrystallized from acetone/ether/hexane (after cooling -20°C) to give a white solid (7.85 g, 83%). ^1H NMR (DMSO-d_6, 400 MHz): δ 3.98 (s, 3H, -CO_2CH_3), 5.27 (s, 2H, -NCH_2-), 7.08 (t, J = 7.95 Hz, 2H, Ar-H), 7.2 (m, 1H, Ar-H), 7.34 (m, 2H, Ar-H, -OH), 7.54 (m, 1H, Ar-H), 8.1-8.26 (m, 2H, Ar-H); IR (KBr, cm^{-1}): 1680 (CO), 1660 (CO), 1610 (CO); MS (m/e): 423 (M^+), 391 (M^+-CH_3OH); M.P.157-158°C.

Anal. Calc'd: C, 50.97; H, 2.85; N, 3.30
Found: C, 50.86; H, 2.86; N, 3.33

The following compounds were prepared in substantially the same manner as that of Example 1 Step b):

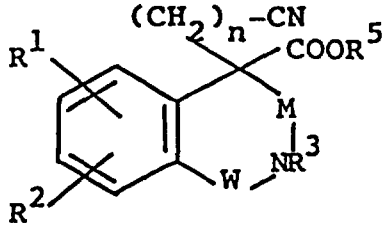
2-[(4-Bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinoline-carboxylic Acid Methyl Ester

^1H NMR (DMSO-d_6, 400 MHz): δ [3.67, 3.99 (s, 3H, -CO_2CH_3, tautomeric], [5.06 (q, J = 15.4 Hz), 5.29 (s) 2H, N-CH_2-, tautomeric], 5.03 (s, 1H, -$CHCO_2CH_3$, tautomeric), 7.07-8.44 (m, 7H, Ar-H, tautomeric); IR (KBr, cm^{-1}): 1675 (CO), 1610 (CO), 1490 795 (m); MS (m/e): 405 (M^+), 373 (M^+-MeOH); M.P. 149-150°C.

Anal. Calc'd: C, 53.22; H, 3.23; N, 3.45
Found: C, 52.91; H, 3.20; N, 3.27

preparation of spiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrones which are useful as aldose reductase inhibitors. The invention also relates to novel intermediates useful in the process.

EP 0 365 324A discloses a class of nitriles having the general formula I



I

in which R^1 and R^2 represent hydrogen or various substituents, R^3 represents hydrogen or various substituents, M and W are independently carbonyl, thiocarbonyl, sulfonyl, sulfoxo or C_1 or C_2 lower alkylene and n is 1 to 3. The nitriles are disclosed for the purpose of preparing thioamides by reaction with $HSP(=S)(OEt)_2/HCl$. The present invention includes a selected novel subgenus of compounds falling within the said class. The novel compounds have the advantage of being useful in an improved method of preparing spiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrones from 1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolinecarboxylic acid esters.

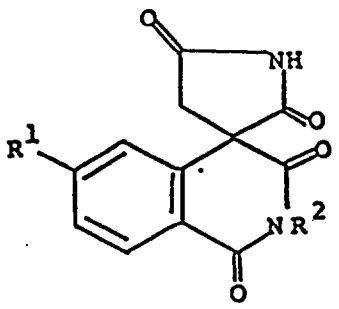
EP O 365 324A also discloses a method of preparing spiro [isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrones from 1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolinecarboxylic acid esters. The method

derivative of the starting compound. The third step comprises reacting the carboxylic acid with a coupling agent followed by ammonia to prepare the 4-(2-amino-2-oxoethyl) derivative of the starting compound. The fourth step comprises cyclization of this amide in the presence of a suitable base.

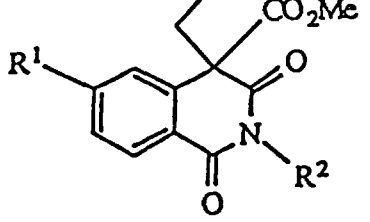
The prior art method employs three steps for the conversion of the starting compound into its 4-(2-amino-2-oxoethyl) derivative. The present invention provides a process in which this conversion is carried out in fewer steps, namely two steps. Each of these steps can be performed in very high yield. Thus the invention has the advantage that it can be carried out in higher yields than the prior art method.

EP-A-O 254 149 teaches that 2',3'-dihydrospiro [pyrroline-3,6'(5'H)-pyrrolo[1,2,3-de][1,4]benzoxazine]-2,5,5'-triones can be prepared from 6-cyanomethyl-2,3-dihydro-5-oxopyrrolo[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid lower alkyl esters either directly or via 6-carbamoylmethyl-2,3-dihydro-5-oxopyrrolo[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid lower alkyl esters.

The present invention provides a process for the preparation of a compound having the formula II



(II)



(IX)

wherein R^1 and R^2 are as defined above.

(IX) is useful as an intermediate for preparing spiro[isoquinoline]-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrones of formula (I) which have strong aldose reductase inhibiting activity and are expected useful as remedies for diabetic complications.

The following examples further illustrate this invention.

Example 1

2-[(4-Bromo-2-fluorophenyl)methyl]-6-fluorospiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone

Step a)

(2-Carboxy-5-fluorophenyl)propanedioic Acid Dimethyl Ester

To a rapidly stirred cold suspension (0°C) of 2-chloro-4-fluorobenzoic acid (20.0 g, 114.6 mmol), cuprous bromide (1.64 g, 11.46 mmol) and dimethyl malonate (250 g) was added NaH (80% in mineral oil, 8.25 g, 275.04 mmol) over a 30 minute period, while a stream of dry N_2 was passed over the mixture. After the addition of the NaH had been completed, the mixture wa stirred at 85°C for 3 hours. At this point, the suspension had turned to a solid mass, which was dissolved in H_2O (1000 mL). The aqueous layer was extracted with diethyl ether (3 x 500 mL) and was acidified with HCl (2N). The mixture was extracted with EtOAc and dried over $MgSO_4$. Evaporation gave an off-white solid which was recrystallized from ether/hexane (after cooling to -20°C) to give a white solid (27.5 g, 89%). ^1H NMR (DMSO-d_6, 400 MHz): δ 3.68 [s, 6H, (-CO_2Me)2], 5.79 (s, 1H, Ar-H), 7.12 (dd, J = 10.06 Hz, 2.61

M.P. 121.5-123.0°C.

Anal. Calc'd: C, 53.34; H, 4.10
Found: C, 53.36; H, 3.93

The following compounds were prepared in substantially the same manner as that of Example 1 Step a):

(2-Carboxyphenyl)propanedioic Acid Dimethyl Ester

^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.67 [s, 6H, -CH(C)$_2$C$\underline{H}_3$)$_2$], 5.72 [s, 1H, -C$\underline{H}$(CO$_2$CH$_3$)$_2$], 7.3 (d, J = 7.76 Hz, 1H, Ar-$\underline{H}$), 7.45 (dt, J = 7.66 Hz, 1.12 Hz, 1H, Ar-$\underline{H}$), 7.6 (dt, J = 7.66 Hz, 1.45 Hz, 1H, Ar-$\underline{H}$), 7.94 (dd, J = 7.8 Hz, 1.33 Hz, 1H, Ar-$\underline{H}$), 13.2 (s, 1H, -CO$_2\underline{H}$); IR (KBr, cm^{-1}): 3300-2700 (CO$_2$H), 1750 (CO), 1730 (CO), 1680 (CO); MS (m/e): 252 (M$^+$), 220 (M$^+$-CH$_3$OH), 188 (M$^+$-2xCH$_3$OH); M.P. 119-120°C.

Anal. Calc'd: C, 57.14; H, 4.80
Found: C, 57.05; H, 4.78

(2-Carboxy-5-chlorophenyl)propanedioic Acid Dimethyl Ester

^{1}H NMR (DMSO-d_6, 200 MHz): δ 3.69 [s, 6H, (-CO$_2$Me)$_2$], 5.78 [s, 1H, Ar-CH(CO$_2$Me)$_2$], 7.38 (d, J = 1.8 Hz, 1H, Ar-$\underline{H}$), 7.58 (dd, J = 7.8 Hz, 1.8 Hz, 1H, Ar-$\underline{H}$), 7.96 (d, J = 8.2 Hz, 1H, Ar-$\underline{H}$), 13.5 (br s, 1H, -CO$_2\underline{H}$); IR (KBr, cm^{-1}): 3200-2700 (CO$_2$H), 1760 (CO), 1740 (CO), 1690 (CO); MS (m/e): 286 (20 M$^+$), 254 (64, M$^+$-CH$_3$OH), 222 (60, M$^+$-2xCH$_3$OH)

Anal. Calc'd: C, 50.28; H, 3.87
Found: C, 50.40; H, 3.87