A New Synthesis of *N*-Alkyl Pyrazolidine-3,5-diones and Tetrahydropyridazine-3,6-diones

Bertrand Le Bourdonnec [a], Emmanuelle Meulon, Saïd Yous, Raymond Houssin and Jean-Pierre Hénichart*

Institut de Chimie Pharmaceutique Albert Lespagnol, Université de Lille 2, rue du Professeur Laguesse, BP 83, 59006 Lille, France

Received October 4, 1999

N-alkyl pyrazolidine-3,5-diones and tetrahydropyridazine-3,6-diones have been synthesized by a new method in a three-step sequence from dialkyl malonates or succinates respectively.

J. Heterocyclic Chem., **37**, 1209 (2000).

The pyrazolidine-3,5-dione ring constitutes an important structural motif of certain medicinal products exemplified by the potent phenylbutazone class of anti-inflammatory agents [1]. Although numerous pyrazolidine-3,5-diones containing aryl substituents on one or both nitrogens are described, little is known about the preparation of the corresponding *N*-monosubstituted compounds containing alkyl substituents [2]. The most common reaction conditions [3] involve the cyclisation of disubstituted malonates with hydrazines in ethanol in the presence of sodium alkoxide. This method cannot be generalized since few *N*-alkylhydrazines are commercially available. Therefore, we were interested in developing a reaction scheme enabling an efficient construction of the pyrazolidine-3,5-dione skeleton where various alkyl substituents could be introduced at one of the nitrogen atoms of the heterocycle. Specifically, we sought to investigate a new method for the preparation of *N*-alkyl pyrazolidine-3,5-diones starting from commercially available benzylhydrazine. Hence, we anticipated that we could perform the cyclocondensation with benzylhydrazine, subsequently substitute on the free nitrogen and then finally remove the benzyl group to afford the desired *N*-alkyl pyrazolidine-3,5-diones.

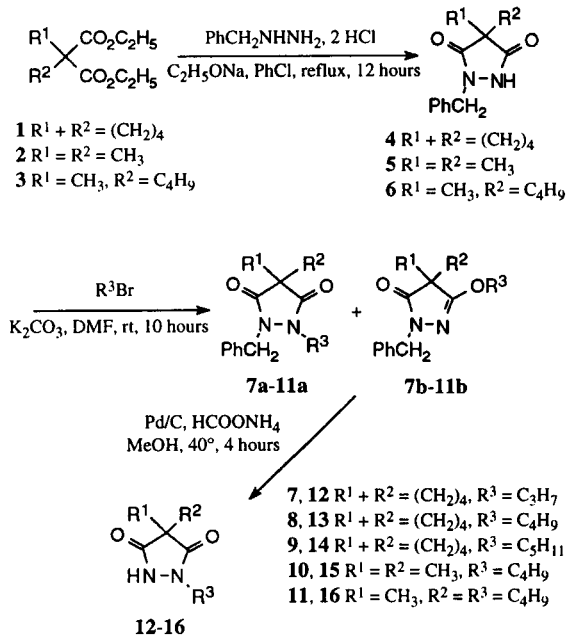
Results and Discussion.

The target compounds **12-16** were effectively synthesized in a two-step sequence (Scheme 1) from the key intermediates *N*-benzylpyrazolidine-3,5-diones **4-6**. These compounds have been obtained by condensation of various disubstituted malonates (**1** [4], **2**, and **3** [5]) with benzylhydrazine. When the cyclisation was performed in ethanol in the presence of sodium ethoxide (method of Conrad and Zart [3]), the *N*-benzyl derivatives **4-6** were obtained in about 20% yield. Furthermore, fusion of the esters with benzylhydrazine at 170 °C did not allow us to increase the yield of the condensation (significant degradation of benzylhydrazine was observed in this case). Changing the solvent from ethanol to chlorobenzene, however, enabled us to obtain the *N*-benzylpyrazolidine-3,5-diones **4-6** in moderate to good yields. Alkylation of **4-6** with the appropriate alkyl bromides (R^3Br) gave a mixture of two isomers **a** and **b**, corresponding to the *N*- and *O*-substituted alkyl derivatives of the tautomeric pyrazolidines, respectively. Non-selective alkylation of pyrazolidine-3,5-diones under basic conditions has been reported previously [2,6]. Furthermore, alkylation of 2-pyridone under Mitsunobu conditions has been reported to give mixture of *N*- and *O*-alkylation products [7].

When alkylation was carried out at room temperature in dimethylformamide and in the presence of potassium carbonate, equal amounts of isomers **a** and **b** were obtained. The ratios were determined from the ^1H nmr spectra of the reaction mixture. For the isomers **7b-11b**, the protons $O\text{-}CH_2\text{-}C_nH_{2n+1}$ are shifted more downfield (300 MHz, deuteriochloroform: t, 4.50-4.75 ppm) as compared to the isomers **7a-11a** ($N\text{-}CH_2\text{-}C_nH_{2n+1}$, t, 3.45-3.50 ppm). Different reaction conditions were tested in order to increase the proportion of the desired isomers **a**. Thus, we decided to study the effect of solvent, temperature, and the nature of the base on the regioselectivity of the alkylation of *N*-benzylpyrazolidine-3,5-diones **4-6**. However, in all the conditions investigated (dimethylformamide, sodium hydride, room temperature; acetone, potassium carbonate, room temperature; acetone, potassium carbonate, 0°), we obtained a 1:1 mixture of isomers **a** and **b**. Since the isomers **7a-11a** and **7b-11b** displayed similar Rf values on tlc, attempts to separate them by column chromatography were unsuccessful. Therefore, debenzylation was performed on the mixture of both isomers **a** and **b**. When this deprotection was carried out in methanol, in the presence of ammonium formate and a catalytic amount of palladium on carbon, only the isomers **a** underwent debenzylation. The remarkable resistance of isomers **b** to palladium-Catalysed Transfer Hydrogenation (CTH) seems to be a characteristic of the α-β unsaturated *N*-benzyl system; indeed, similar behaviour has been previously reported for pyridines (*i.e.* 1-benzylpyridine-2-one [8], 2-benzylaminopyridine [9]) and pyrimidines (*i.e.* 6-benzyladenine [8]). The target compounds **12-16** were easily separated from the reaction mixture due to their ability to form salts in aqueous sodium hydroxide. Furthermore, the iso-

lation of the *O*-alkylated isomers **7b-11b**, which could not be effected directly by resolving the mixture of the *N*- and *O*-alkylated compounds (**a** and **b**, respectively), became possible at the debenzylation step by extraction from the aqueous alkaline solution. In summary, the various *N*-alkyl pyrazolidine-3,5-diones **12-16** can be obtained in high purity with simple work up procedures from the *N*-benzyl precursors **4-6**.

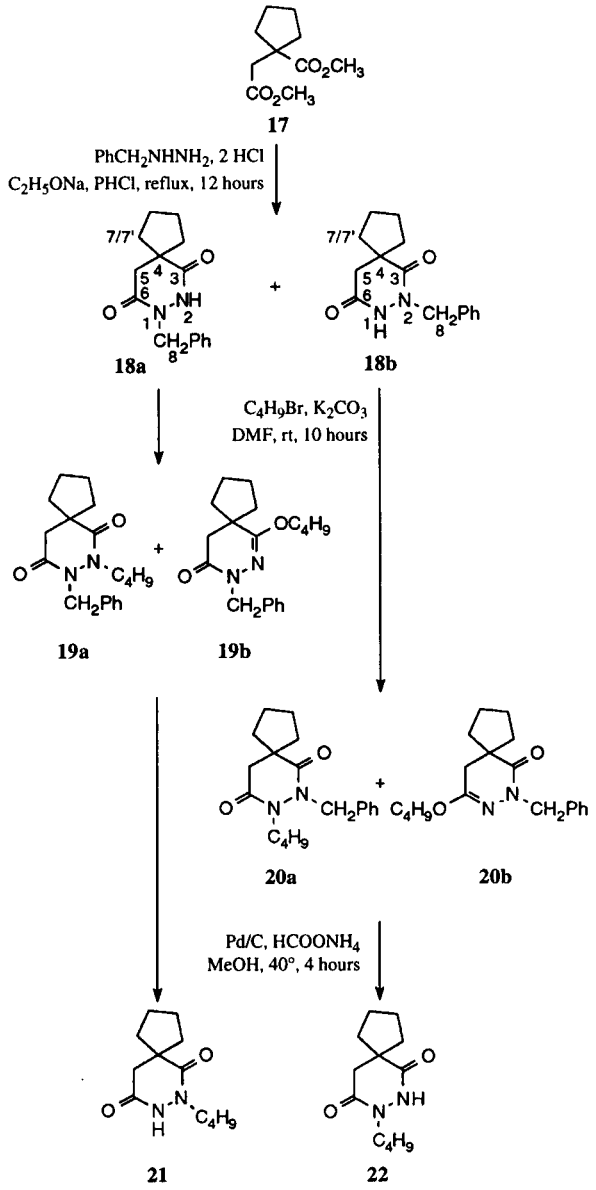
Scheme 1



In order to extend the scope of this method, we decided to use the same approach for the preparation of *N*-alkyl tetrahydropyridazine-3,6-diones. The syntheses of compound **21** and of its regioisomer **22**, six-membered ring analogs of compound **13**, are exemplified in Scheme 2.

Condensation of the diester **17** [10] with benzylhydrazine in the presence of sodium ethoxide resulted in the formation of the two regioisomers **18a** and **18b**. These isomers which were separated by fractional crystallization (diethyl ether) were isolated as pure compounds with the yields of 37% and 10% respectively. Study of the 2D nmr HSQC and HMBC spectra allowed us to unequivocally establish their structure. The structure elucidation was based on the HMBC correlation between H_8 and C_6 for isomer **18a** and H_8 and C_3 for isomer **18b**. Alkylation of the major isomer **18a** with butyl bromide in dimethylformamide, in the presence of potassium carbonate, resulted in the formation of both isomers **19a** and **19b** (present in equal amounts as deduced from the ^1H nmr analysis of the reaction mixture). *N*-Butyltetrahydropyridazine-3,6-dione

Scheme 2



21 was finally obtained from the mixture of isomers by debenzylation in methanol in the presence of ammonium formate and a catalytic amount of palladium on carbon. As noted previously, only the *N*-alkylated isomer **19a** underwent debenzylation. The same procedure has been applied to obtain the compound **22**, regioisomer of **21**, from the *N*-benzyl precursor **18b**.

In conclusion, we have developed a new and general method for the preparation of various *N*-alkyl pyrazolidine-3,5-diones and *N*-alkyl tetrahydropyridazine-3,6-diones. Application of this method is still under investigation. The target compounds **12-16** and **21**, **22** are being used as key intermediates for the preparation of various molecules of potential pharmacological interest.

EXPERIMENTAL

Melting points are uncorrected. Ir spectra were recorded on potassium bromide pellets. ^{1}H nmr were recorded at 80 or 300 MHz in deuteriochloroform or dimethylsulfoxide-d_6. Chemical shifts were recorded in ppm (δ) and coupling constants in Hertz, relative to tetramethylsilane as internal standard. Thin-layer chromatography was performed on silicagel $60F_{254}$ plates from E. Merck reagents and visualized by uv irradiation and/or iodine. Starting materials were purchased from Aldrich and used as received.

General Procedure for the Cyclocondensation of Benzylhydrazine with Dialkyl Malonates or Succinates.

Benzylhydrazine dihydrochloride (0.020 mole) was added to sodium ethoxide (0.0845 g Na, 0.020 mole, in 50 ml ethanol). After stirring at room temperature for 1 hour, the solvent was evaporated. To a suspension of the resulting solid in dry chlorobenzene (100 ml) was added the diester (0.024 mole) and the mixture was heated at reflux for 12 hours. After cooling, the solvent was removed under reduced pressure. Water (100 ml) was added and the solution was washed with diethyl ether, acidified with 6*M* aqueous hydrochloric acid and extracted with ethyl acetate. The combined organic extracts were washed with water, dried over magnesium sulfate, and the solvent was removed to afford the compounds **4-6**, **18a**, **18b**, which were further purified by recrystallization.

2-Benzyl-2,3-diazaspiro[4.4]nonane-1,4-dione (**4**).

Yield 63%; mp 95° (cyclohexane); Rf 0.54 (ethyl acetate); ir ν 3100, 1715, 1640 cm^{-1}; ^{1}H nmr (80 MHz, dimethylsulfoxide-d_6) δ 1.70-2.10 (m, 8H), 4.70 (s, 2H), 7.10 (m, 5H).

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 67.59; H, 6.68; N, 11.26. Found: C, 67.95; H, 6.63; N, 11.58.

1-Benzyl-4,4-dimethylpyrazolidine-3,5-dione (**5**).

Yield 61%; mp 153.9° (95% alcohol); Rf 0.42 (ethyl acetate); ir ν 3090, 1740, 1655 cm^{-1}; ^{1}H nmr (300 MHz, deuteriochloroform) δ 1.28 (s, 6H), 4.71 (s, 2H), 7.30 (m, 5H).

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 60.03; H, 6.46; N, 12.83. Found: C, 60.15; H, 6.32; N, 12.91.

1-Benzyl-4-butyl-4-methylpyrazolidine-3,5-dione (**6**).

Yield 35%; mp 134.6-136.8° (acetonitrile); Rf 0.58 (ethyl acetate); ir ν 3100, 1740, 1640 cm^{-1}; ^{1}H nmr (300 MHz, deuteriochloroform) δ 0.85 (t, J = 7.2 Hz), 1.05-1.18 (m, 2H), 1.20-1.30 (m, 2H), 1.30 (s, 3H), 1.62-1.70 (m, 2H), 4.70 (s, 2H), 7.30 (m, 5H).

Anal. Calcd. for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.36; H, 7.67; N, 10.77.

8-Benzyl-7,8-diazaspiro[4.5]decane-6,9-dione (**18a**).

Separated from the mixture **18a** + **18b** by fractional crystallization in diethyl ether; yield 37%; mp 130.6° (acetonitrile); Rf 0.35 (hexane/ethyl acetate = 4:6); ir ν 3180-3100, 1640 cm^{-1}; ^{1}H nmr (300 MHz, deuteriochloroform) δ 1.44 (m, 2H), 1.69 (m, 4H), 1.94 (m, 2H), 2.60 (s, 2H), 4.78 (s, 2H), 7.33 (m, 5H), 9.50 (s, 1H, exchangeable with deuterium oxide); ^{13}C nmr (300 MHz, deuteriochloroform) δ 24.8, 33.7, 40.4, 45.5, 48.8, 127.9, 134.0, 164.7, 174.3.

Anal. Calcd. for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.82; H, 6.94; N, 10.95.

7-Benzyl-7,8-diazaspirol[4.5]decane-6,9-dione (**18b**).

Separated from the mixture **18a** + **18b** by fractional crystallization in diethyl ether; yield 10%; mp 135.5° (ethyl acetate); Rf 0.45 (hexane/ethyl acetate = 4:6); ir ν 3200-3140, 1680, 1625 cm^{-1}; ^{1}H nmr (300 MHz, deuteriochloroform) δ 1.53 (m, 2H), 1.67 (m, 2H), 1.77 (m, 2H), 2.17 (m, 2H), 2.39 (s, 2H), 4.70 (s, 2H), 7.40 (m, 2H), 7.56 (m, 3H); ^{13}C nmr (300 MHz, deuteriochloroform) δ 24.7, 33.9, 40.4, 45.6, 47.1, 126.9, 127.0, 128.0, 128.4, 130.0, 130.2, 134.2, 139.0, 141.1, 168.5, 173.6.

Anal. Calcd. for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.85; H, 6.89; N, 10.87.

General Procedure for the Alkylation of Compounds **4-6**, **18a**, **18b**, and Subsequent Debenzylation.

Potassium carbonate (0.060 mole) was added portionwise to a solution of compounds **4-6**, **18a**, **18b** (0.020 mole) in dimethylformamide (15 ml). After stirring for 1 hour, the desired alkyl bromide was added to the reaction mixture, which was allowed to stir for 10 hours at room temperature. Water (80 ml) was added and the resulting suspension was extracted with ethyl acetate. The combined organic extracts were washed with water, dried over magnesium sulfate, and the solvent was removed to afford the mixture of isomers (**7a,b-11a,b**; **19a,b**; **20a,b**) which were used in the next step without further purification. To a solution of isomers (**7a,b-11a,b**; **19a,b**; **20a,b**) in methanol (50 ml) was added successively palladium on carbon (0.20 mole) and ammonium formate (0.10 mole). The mixture was heated at 40° for 4 hours, cooled, and filtered through celite. The solvent was evaporated and 1*M* aqueous sodium hydroxide (50 ml) was added. The mixture was washed with diethyl ether. The combined organic extracts were washed with water, dried over magnesium sulfate, and the solvent was removed to afford the isomers **7b-11b**; **19b**; **20b**. The basic solution was acidified with 6*M* aqueous hydrochloric acid, and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with water, dried over magnesium sulfate, and the solvent was removed to afford compounds **12-16**, **21**, **22**.

2-Propyl-2,3-diazaspirol[4.4]nonane-1,4-dione (**12**).

Yield 44% from **4**; Rf 0.32 (ethyl acetate); ir ν 3100, 1740, 1660 cm^{-1}; ^{1}H nmr (300 MHz, deuteriochloroform) δ 0.93 (t, J = 7.5 Hz, 3H), 1.67 (m, 2H), 1.91 (m, 2H), 2.03 (m, 6H), 3.56 (t, J = 7.5 Hz, 2H).

Anal. Calcd. for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.21; N, 14.27. Found: C, 61.37; H, 8.12; N, 14.36.

2-Butyl-2,3-diazaspirol[4.4]nonane-1,4-dione (**13**).

Yield 45% from **4**; Rf 0.51 (ethyl acetate); ir ν 3100, 1720, 1650 cm^{-1}; ^{1}H nmr (300 MHz, deuteriochloroform) δ 0.90 (t, J = 7.2 Hz, 3H), 1.00-1.80 (m, 4H), 2.00 (m, 8H), 3.55 (t, J = 6.7 Hz, 2H).

Anal. Calcd. for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.62; N, 13.32. Found: C, 62.97; H, 8.53; N, 13.44.

2-Pentyl-2,3-diazaspirol[4.4]nonane-1,4-dione (**14**).

Yield 40% from **4**; Rf 0.63 (ethyl acetate); ir ν 3100, 1735, 1660 cm^{-1}; ^{1}H nmr (300 MHz, deuteriochloroform) δ 0.93 (t, J = 7.1 Hz, 3H), 1.30 (m, 4H), 1.62 (m, 2H), 1.88 (m, 2H), 1.97 (m, 6H), 3.58 (t, J = 6.9 Hz, 2H), 10.13 (s, 1H, exchangeable with deuterium oxide).

Anal. Calcd. for $C_{12}H_{20}N_2O_2$: C, 64.25; H, 8.98; N, 12.48. Found: C, 64.11; H, 9.06; N, 12.32.

1-Butyl-4,4-dimethylpyrazolidine-3,5-dione (**15**).

Yield 42% from **5**; Rf 0.36 (hexane/ethyl acetate = 6:4); ir ν 3140, 1740, 1660 cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform) δ 0.97 (t, J = 7.3 Hz, 3H), 1.36 (m, 8H), 1.68 (m, 2H), 3.65 (t, J = 7.3 Hz, 2H).

Anal. Calcd. for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.20. Found: C, 58.75; H, 8.66; N, 15.31.

1,4-Dibutyl-4-methylpyrazolidine-3,5-dione (**16**).

Yield 42% from **6**; Rf 0.26 (hexane/ethyl acetate = 6.4); ir ν 3100, 1740, 1670 cm^{-1}; ^1H nmr (80 MHz, deuteriochloroform) δ 0.80 (t, J = 7.2 Hz, 3H), 0.83 (t, J = 7.4 Hz, 3H), 1.10-1.31 (m, 8H), 1.20 (m, 3H), 1.50-1.70 (m, 2H), 3.60 (t, J = 7.2 Hz, 2H).

Anal. Calcd. for $C_{12}H_{22}N_2O_2$: C, 63.68; H, 9.79; N, 12.37. Found: C, 63.80; H, 9.67; N, 12.49.

7-Butyl-7,8-diazaspiro[4.5]decane-6,9-dione (**21**).

Yield 41% from **18a**; Rf 0.38 (hexane/ethyl acetate = 4:6); ir ν 3160, 1685, 1635 cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform) δ 0.87 (t, J = 7.3 Hz, 3H), 1.22 (m, 2H), 1.42-1.80 (m, 8H), 2.10 (m, 2H), 2.48 (s, 2H), 3.64 (t, J = 7.3 Hz, 2H), 10.26 (s, 1H, exchangeable with deuterium oxide).

Anal. Calcd. for $C_{12}H_{20}N_2O_2$: C, 64.25; H, 8.98; N, 12.48. Found: C, 64.55; H, 9.07; N, 12.56.

8-Butyl-7,8-diazaspiro[4.5]decane-6,9-dione (**22**).

Yield 43% from **18b**; Rf 0.11 (heptane/ethyl acetate = 3:7); ir ν 3145, 1670, 1633 cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform) δ 0.95 (t, J = 7.2 Hz, 3H), 1.35 (m, 2H), 1.65 (m, 8H), 2.10 (m, 2H), 2.55 (s, 2H), 3.63 (t, J = 7.6 Hz, 2H), 9.70 (s, 1H, exchangeable with deuterium oxide).

Anal. Calcd. for $C_{12}H_{20}N_2O_2$: C, 64.25; H, 8.98; N, 12.48. Found: C, 64.39; H, 9.10; N, 12.66.

2-Benzyl-4-propyloxy-2,3-diazaspiro[4.4]non-3-en-1-one (**7b**).

Yield 43% from **4**; Rf 0.75 (hexane/ethyl acetate = 6:4); ir ν 1700, 1600 cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform) δ 1.02 (t, J = 7.4 Hz, 3H), 1.78 (m, 2H), 1.91 (m, 8H), 4.02 (t, J = 6.6 Hz, 2H), 4.72 (s, 2H), 7.40 (m, 5H).

Anal. Calcd. for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.04; H, 7.77; N, 9.66.

2-Benzyl-4-butyloxy-2,3-diazaspiro[4.4]non-3-en-1-one (**8b**).

Yield 45% from **4**; Rf 0.71 (hexane/ethyl acetate = 6:4); ir ν 1700, 1600 cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform) δ 0.92 (t, J = 7.4 Hz, 3H), 1.22-1.66 (m, 4H), 1.96 (m, 8H), 4.09 (t, J = 6.5 Hz, 2H), 4.78 (s, 2H), 7.29 (m, 5H).

Anal. Calcd. for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.32. Found: C, 72.10; H, 8.15; N, 9.42.

2-Benzyl-4-pentyloxy-2,3-diazaspiro[4.4]non-3-en-1-one (**9b**).

Yield 41% from **4**; Rf 0.79 (hexane/ethyl acetate = 6:4); ir ν 1700, 1600 cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform) δ 0.90 (t, J = 7.2 Hz, 3H), 1.30 (m, 4H), 1.65 (m, 2H), 1.95 (m, 8H), 4.10 (t, J = 6.7 Hz, 2H), 4.75 (s, 2H), 7.20 (m, 5H).

Anal. Calcd. for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.33; N, 8.91. Found: C, 72.67; H, 8.20; N, 9.04.

2-Benzyl-5-butyloxy-4,4-dimethylpyrazolidine-3-one (**10b**).

Yield 43% from **5**; Rf 0.52 (hexane/ethyl acetate = 6:4); ir ν 1700, 1600 cm^{-1}; ^1H nmr (80 MHz, deuteriochloroform) δ 0.90 (t, J = 7.3 Hz, 3H), 1.30 (m, 8H), 1.67 (m, 2H), 4.10 (t, J = 6.6 Hz, 2H), 4.75 (s, 2H), 7.30 (m, 5H).

Anal. Calcd. for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.15; H, 7.97; N, 10.36.

1-Benzyl-4-butyl-3-butyloxy-4-methylpyrazolidine-5-one (**11b**).

Yield 45% from **6**; Rf 0.78 (hexane/ethyl acetate = 6:4); ir ν 1710, 1610 cm^{-1}; ^1H nmr (80 MHz, deuteriochloroform) δ 0.79 (m, 6H), 0.84-1.00 (m, 8H), 1.25 (s, 3H), 1.59 (m, 2H), 4.12 (t, J = 6.7 Hz, 2H), 4.75 (s, 2H), 7.31 (m, 5H).

Anal. Calcd. for $C_{19}H_{28}N_2O_2$: C, 72.11; H, 8.92; N, 8.85. Found: C, 72.43; H, 9.06; N, 9.01.

8-Benzyl-6-butyloxy-7,8-diazaspiro[4.5]dec-6-en-9-one (**19b**).

Yield 43% from **18a**; Rf 0.53 (hexane/ethyl acetate = 6:4); ir ν 1660, 1620 cm^{-1}; ^1H nmr (80 MHz, deuteriochloroform) δ 0.91 (t, J = 7.3 Hz, 3H), 1.35 (m, 2H), 1.47-1.70 (m, 8H), 1.90 (m, 2H), 2.45 (s, 2H), 4.00 (t, J = 6.4 Hz, 2H), 4.80 (s, 2H), 7.30 (m, 5H).

Anal. Calcd. for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.33; N, 8.90. Found: C, 72.74; H, 8.20; N, 8.95.

7-Benzyl-9-butyloxy-7,8-diazaspiro[4.5]dec-8-en-6-one (**20b**).

Yield 46% from **18b**; Rf 0.43 (heptane/ethyl acetate = 8:2); ir ν 1668, 1645 cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform) δ 0.91 (t, J = 7.3 Hz, 3H), 1.36 (m, 2H), 1.63 (m, 8H), 2.07 (m, 2H), 2.40 (s, 2H), 4.01 (t, J = 6.5 Hz, 2H), 4.81 (s, 2H), 7.27 (m, 5H).

Anal. Calcd. for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.33; N, 8.90. Found: C, 72.31; H, 8.15; N, 9.04.

Acknowledgement.

We gratefully thank Dr. Solo Goldstein for helpful discussions and UCB Pharma Sector for its cooperation.

REFERENCES AND NOTES

[a] Present address: Department of Medicinal Chemistry, College of Pharmacy, University of Minnesota, 308 Harvard Street S.E., MN 55455, Minneapolis, Minnesota, USA.

[1] G. H. Hamor, Principles of Medicinal Chemistry, W. O. Foye, Lea and Febiger, eds, Philadelphia, London, chapter 23, 1989, p 503.

[2] M. J. Kornet, J. H. Thorstenson and W. C. Lubawy, *J. Pharm. Sci.*, **63**, 1090 (1974).

[3] M. Conrad and A. Zart, *Chem. Ber.*, **39**, 2282 (1906).

[4] G. B. Heisig and F. H. Stodoler, *Org. Synth.*, **23**, 16 (1943).

[5] Compound **3** was prepared by adding methyl iodide to a solution of the sodium salt of diethyl butylmalonate in tetrahydrofuran.

[6] M. I. Al-Ashmawi, K. M. Ghoneim and M. Khalifa, *Pharmazie*, **35**, 591 (1980).

[7] D. L. Comins and G. Jianhua, *Tetrahedron Lett.*, **35**, 2819 (1994).

[8] G. K. Jnaneshwara, A. Sudalai and V. H. Deshpande, *J. Chem. Res. (S)*, 160 (1998).

[9] B. M. Adger, C. O' Farrell, N. J. Lewis and M. B. Mitchell, *Synthesis*, 53 (1987).

[10] H. Le Moal, A. Foucaud, R. Carrié, D. Danion and C. Fayat, *Bull. Soc. Chim. Fr.*, **4**, 828 (1964).