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2,2'-Dipyrrolidine as a Precursor to Novel Diazatricyclic Systems

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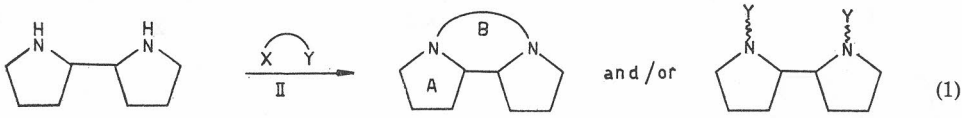
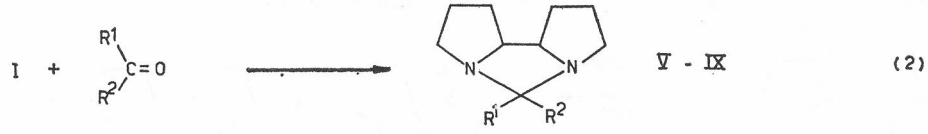
Reaction of newly available 2,2'-dipyrrolidine with a variety of biselectrophiles gave selectively either novel diazatricyclic systems having bridgehead nitrogen atoms or the *N,N'*-disubstituted--2,2'-dipyrrolidines in good to excellent yields.

The recent availability of 2,2'-dipyrrolidine (*I*) via a radical dehydrodimerization[1,2,3] led us to explore its synthetic potential, especially for heterocyclic chemistry. Reactions involving the strongly nucleophilic secondary nitrogen atoms of (*I*) and suitable biselectrophiles (*II*) give rise to the first representatives of diazatricyclic compounds (*III*), having a B ring of 5, 6 or 7 units. Alternatively, variation of the reaction conditions or use of a biselectrophile, in which X and Y are of significantly different reactivity, yields selectively the *N,N'*-disubstituted-2,2'-dipyrrolidines (*IV*) (Eq. 1).



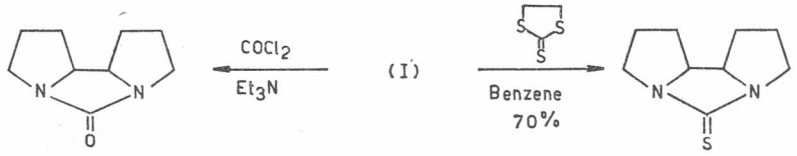
I III IV (1)

Compounds of type (*III*) having a five-membered B ring result from the reaction of (*I*) with 1,1-biselectrophiles. Condensation of (*I*) with aldehydes and ketones readily affords the corresponding aminals (*V*—*IX*) in high yields (Eq. 2).



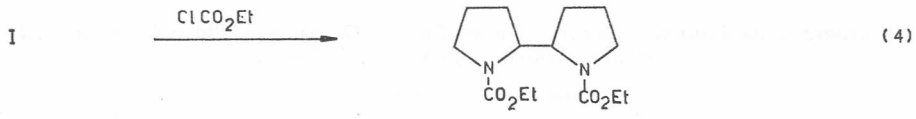
(2)

Other five-membered B rings are formed as the tricyclic urea (*X*) and thiourea (*XI*) by reaction of (*I*) with phosgene and ethylene trithiocarbamate respectively, and thus illustrate simple differential functionalisation (Eq. 3).



X XI

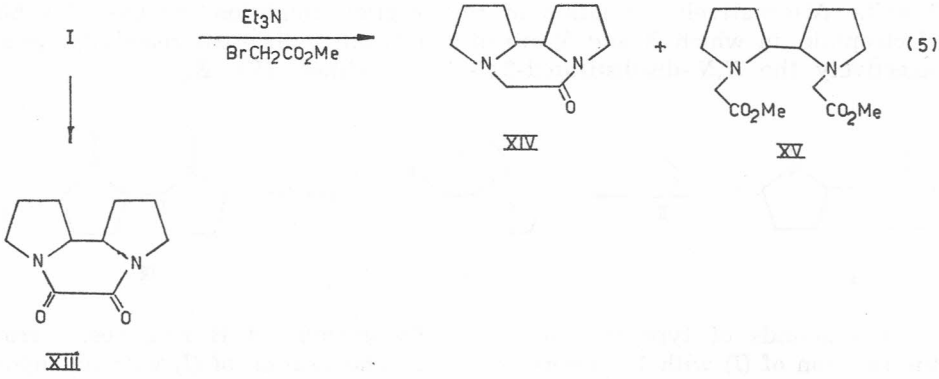
The ease of five-membered ring formation is reflected not only in the high yields obtained but also in the fact that no diacylation occurred. Ethyl chloroformate, however, produces the expected diurethane (*XII*) (Eq. 4).



XII

Six-membered B rings are equally easily obtained, as exemplified by the reactions of *I* with dimethyl oxalate and methyl chloroacetate to give in high yields the oxalamide (*XII*) (90%)[4] and the piperazinone (*XIV*) (93%), respectively; the latter together with a disubstitution product (*XV*) (12% yield).

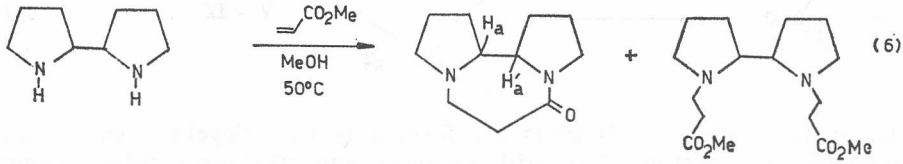
In contrast, addition of (*I*) to an excess of methyl bromoacetate at room temperature leads exclusively to (*XV*) in 82% yield (Eq. 5).



XIV XV

XIII

The seven-membered B ring formation producing the diazepinone (*XVI*) in 93% yield arises from the reaction of (*II*) with methyl acrylate. A small quantity of diadduct (*XVII*) (10%) accompanies the cyclisation (Eq. 6).



XVI a, b, 93% XVII 6%

The product distribution can be completely reversed when (*I*) is added slowly to a cold solution of excess methyl acrylate in methanol. Under these conditions (*XVII*) becomes the sole product in 82% yield.

The two stereoisomers of (*XVI*) are chromatographically separable, and for the more polar isomer (*XVIA*) (B. p. 155—160 °C/0.8 mm, air-bath) double resonance experiments at 200 MHz show that the coupling constant $J_{Ha,Ha'} = 2.5$ Hz. However, these values do not allow the decision whether this corresponds to the threo or the erytho form.

These reactions demonstrate the ease with which a variety of novel functionalized tricyclic systems may be synthetized from 2,2'-dipyrrolidine with the possibility of further chemical elaboration. In addition, these results offer guidelines for the selection of biselectrophiles and the choice of reaction conditions leading to the highly selective synthesis of either the tricyclic derivatives or the double substitution products.

EXPERIMENTAL

2,2'-Dipyrrolidine (I)

Twenty-fold excess of pyrrolidine (60 g) and ditertbutylperoxyde (60 g, 41 mmol) are introduced into a glass ampoule (~ 100 ml). The tube is degassed in three freeze-thaw cycles, sealed under vacuum and heated at 160 °C for 8 hours. Excess pyrrolidine is rotoevaporated to give 6.5 g of the crude residue. Main fraction is collected at ~ 55 °C 0.2 mm, 3.86 g (67%). Crystalline product, mixture *meso* and d, 1. M. p. 30—49 °C. IR ($CHCl_3$): $\nu = 2980$, 1640, 1280, 1080 cm^{-1}; ^{1}H-NMR ($CDCl_3$): $\delta = 1.22$—2.02 (m, 8H), 1.87 (s, NH), 2.76—3.06 (m, 6H).

General Procedures for the Condensation of 2,2'-Dipyrrolidine I with Aldehydes and Ketones

Method A. A solution of (*I*) (7.00 g, 50 mmol) and the aldehyde or ketone (60 mmol) in benzene is stirred at room temperature under nitrogen for 1 hour and then the water resulting from the reaction is removed by azeotropic distillation using a Dean-Stark trap. The reaction mixture is cooled to room temperature, the solvent evaporated under reduced pressure and the product purified by distillation.

Method B. A solution of (*I*) (1.40 g, 10 mmol) and the aldehyde or ketone (12 mmol) in benzene is stirred at room temperature for 30 min. under nitrogen. Anhydrous sodium sulphate is added and the reaction mixture is allowed to stand overnight. The mixture is filtered and the drying agent washed with benzene. The combined filtrates are evaporated under reduced pressure and the product is distilled.

1,3-Diazatricyclo (6,3,0,$0^{3,7}$) undecane (V)

A solution of (*I*) (2.80 g, 20 mmol) in 37% aqueous formaldehyde (10 ml, 125 mmol) is stirred for 15 min. at room temperature and then cooled in an ice-bath, while sufficient solid sodium hydroxide is added to cause the product to separate. The aqueous phase is separated and then extracted with three portions of ether. The combined organic phases are dried (Na_2SO_4) and evaporated under reduced pressure. Distillation of the residual oil affords (*V*) as a colourless oil, 2.89 g (95%). B. p. 65—70 °C/0.05 mm; IR($CHCl_3$): $\nu = 2960$, 1100 cm^{-1}; ^{1}H-NMR ($CDCl_3$): $\delta = 1.30$—2.20 (m, 16H), 2.45—3.60 (m, 12H), 3.70 (s, N—CH_2—, *dl* isomer), 4.00 (d, $J = 10$ Hz, N—CH_2—N, *meso* isomer), 4.55 (d, J = 10 Hz, N—CH_2—N, *meso* isomer).

2-Methyl-1,3-diazatricyclo (6,3,0,$0^{3,7}$) undecane (VI)

Compound (*VI*) is obtained as a colourless oil from acetaldehyde and (*I*) (90% by method A, ~ 100% by method B); B. p. 70—75 °C/0.05 mm; IR ($CHCl_3$): $\nu = 2980$, 1390 cm^{-1}; ^{1}H-NMR ($CDCl_3$): $\delta = 1.15$ (d, $J = 5$ Hz, CH_3, one isomer), 1.30 (d, $J = 6$

Hz, CH_3 second isomer), 1.40—2.10 (m, 16H), 2.40—3.30 (m, 12H), 3.40—3.90 (m, N—C*H*(CH_3)—N, both isomers).

Anal. $C_{10}H_{18}N_2$ (166.26) calc'd.: C 72.24; H 10.91; N 16.85%
found: C 72.20; H 10.90; N 16.97%

Acetone yields *2,2-dimethyl-1,3-diazatricyclo (6,3,0,$0^{3,7}$) undecane (VII)* as a colourless oil (92% by method B); B. p. 60—65 °C/0.07 mm; ^{1}H-NMR ($CDCl_3$): $\delta = 1.25$ (s, 6H, CH_3), 1.33—2.20 (m, 8H), 2.30—3.40 (m, 4H);

Anal. $C_{11}H_{20}N_2$ (180.29) calc'd.: C 73.28; H 11.18; N 15.54%
found: C 73.32; H 11.24; N 15.41%

Cyclopentanone gives the spirotricyclic compound (*VIII*) as a colourless oil (91% by method A, 86% by method B); B. p. 65—70 °C/0.07 mm; IR ($CHCl_3$): ν = 2980, 1320, 1080 cm^{-1}; ^{1}H-NMR ($CDCl_3$): $\delta = 1.60$—2.20 (m, 16H), 2.80—3.40 (m, 6H).

Anal. $C_{13}H_{22}N_2$ (206.33) calc'd.: C 75.67; H 10.75; N 13.58%
found: C 75.66; H 10.80; N 13.60%

Cyclohexanone affords the spirotricyclic compound (*IX*) as a colourless oil (81% by method A, 80% by method B); B. p. 65—70 °C/0.05 mm Hg; IR ($CHCl_3$): 2990, 1450, 1090 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.00—2.10 (m, 18H), 2.60—3.00 (m, 4H), 3.10—3.30 (m, 1H), 3.50—3.60 (m, 1H).

Anal. $C_{14}H_{24}N_2$ (220.35) calc'd.: C 76.31; H 10.98; N 12.72%
found: C 76.30; H 11.04; N 12.88%

1,3-Diazatricyclo (6,3,0,$0^{3,7}$) undecane-2-one (X)

Phosgene (6 g, 60 mmol) is bubbled into an ice-cooled solution of (*I*) (7.00 g, 50 mmol) and triethylamine (15 ml) in toluene (100 ml). The reaction mixture is stirred for an additional hour at 0 °C and then poured over ice (100 g). The organic phase is separated and extracted successively with saturated aqueous sodium bicarbonate and brine. The organic phase is then dried (Na_2SO_4) and evaporated under reduced pressure. Distillation of the residual oil yields (*X*) as a colourless oil, 6.06 g (73%); B. p. 95—98 °C/0.1 mm; IR ($CHCl_3$): ν = 2950, 1690 cm^{-1}; ^{1}H-NMR ($CDCl_3$): $\delta = 1.40$—2.00 (m, 8H), 3.10—3.80 (m, 6H).

Anal. $C_9H_{14}N_2O$ (166.22) calc'd.: C 65.03; H 8.49; N 16.85; O 9.63%
found: C 65.00; H 8.61; N 16.80; O 9.70%

1,3-Diazatricyclo (6,3,0,$0^{3,7}$) undecane-2-thione (XI)

A solution of (*I*) (7.00 g, 50 mmol) and ethylene trithiocarbonate (6.80 g, 50 mmol) in benzene (100 ml) is refluxed under nitrogen for 16 hours. The solvent is removed and the residue is distilled under vacuum to give (*XI*) as a yellow oil, 6.28 g (69%), which crystallizes on standing; B. p. 160—155 °C/0.5 mm; IR ($CHCl_3$): ν = = 2980, 1400, 1270 cm^{-1}; ^{1}H-NMR ($CDCl_3$): $\delta = 1.40$—1.64 (m, 2H), 1.77—2.22 (m, 4H), 3.18—3.41 (2H), 3.70—4.24 (m, 4H).

N,N'-Diethoxycarbonyl-2,2'-dipyrrolidine (XII)

A solution of ethyl chloroformate (5.50 g, 51 mmol) in toluene (25 ml) is added dropwise to a stirred ice-cooled solution of (*I*) (3.50 g, 25 mmol) and triethylamine (7 ml) in toluene (100 ml). The reaction mixture is stirred for an additional hour and then filtered. The salts are washed with toluene and the combined filtrates are evaporated under reduced pressure. Distillation of the residual oil affords (*XII*) as a collourless oil, 5.40 g (76%); B. p. 140—141 °C/0.05 mm; IR ($CHCl_3$): ν = 2980, 1685 cm^{-1}; ^{1}H-NMR ($CDCl_3$): $\delta = 1.26$ (t, 6H, $J = 7$ Hz, CH_3), 1.50—2.43 (m, 8H), 3.07—3.71 (m, 6H), 4.02 (2q, 4H, $J = 7$ Hz, O—CH_2—).

Anal. $C_{14}H_{24}N_2O_4$ (284.35) calc'd.: C 59.13; H 8.51; N 9.85; O 22.51%
found: C 59.08; H 8.61; N 9.91; O 22.63%

1,4-Diazatricyclo (7,3,0,$0^{4,8}$) dodecane-2,3-dione (XIII)

A solution of (*I*) (2.80 g, 20 mmol) and dimethyl oxalate (2.36 g, 20 mmol) in toluene (50 ml) is refluxed under nitrogen for 13 hours. The solvent is then evapo-

rated under reduced pressure and the residue treated with ether to give pale yellow crystals. Recrystallization from CH_2Cl_2/ether gives colourless prisms, 3.49 g (90%); M. p. 232—236 °C; sublimes at 160 °C/0.03 mm; IR ($CHCl_3$): ν = 3000, 1690 cm^{-1}; H-NMR (200 MHz, $CDCl_3$): δ = 1.59—2.31 (m, 8H), 3.44—3.76 (m, 6H).

Anal. $C_{10}H_{14}N_2O_2$ (194.23) calc'd.: C 61.83; H 7.26; N 14.43; O 16.48%
found: C 61.97; H 7.39; N 14.62; O 16.60%

1,3-Diazatricyclo (7,3,0,$0^{4,8}$)dodecane-2-one (XIV)

A solution of ethyl chloroacetate (5.63 g, 50 mmol) in benzene (20 ml) is added dropwise to a refluxing solution of (*I*) (7.00 g, 50 mmol) and triethylamine (7.5 ml) in benzene (50 ml) under nitrogen. The reaction mixture is refluxed for 3 additional hours and, after cooling to room temperature, an equal volume of dry ether is added. The solution is filtered and the salts are washed with ether. The combined filtrates are evaporated under reduced pressure and the residue is distilled giving (*XIV*) as a colourless oil 8.38 g (93%); B. p. 115—120 °C/0.05 mm; IR ($CHCl_3$): ν = 2990, 1640 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 1.00—2.30 (m, 8H), 2.50—3.80 (m, 8H).

Anal. $C_{10}H_{16}N_2O$ (180.25) calc'd.: C 66.63; H 8.95; N 15.55; O 8.88%
found: C 66.75; H 9.00; N 15.50; O 9.06%

Dimethyl 2,2'-dipyrrolidine-N-N'-diacetate (XV)

A solution of (*I*) (1.40 g, 10 mmol) and triethylamine (14 ml) in benzene (50 ml) is added to a stirred solution of methyl bromoacetate (9.18 g, 60 mmol) in benzene (50 ml) over a period of 1 hour. The reaction mixture is stirred overnight and then filtered. The salts are washed with benzene and then the combined filtrates are evaporated. Distillation of the residual red oil affords (*XV*) as a colourless oil, 2.33 g (82%); B. p. 110—115 °C/0.03 mm; IR ($CHCl_3$): ν = 2960, 1730 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 1.45—1.90 (m, 8H), 2.15—4.15 (m, 6H), 3.65 (s, 6H, OCH_3), 3.25 and 3.75 (AB quartet, 4H, —NCH_2CO—).

Anal. $C_{14}H_{24}N_2O_4$ (284.35) calc'd.: C 59.13; H 8.51; N 9.85%
found: C 59.08; H 8.61; N 9.91%

Reaction of Methyl Acrylate with 2,2'-dipyrrolidine

A solution of methyl acrylate (1.00 g, 12 mmol) in methanol (25 ml) is added dropwise to a refluxing solution of (*I*) (1.40 g, 10 mmol) in methanol (25 ml) under nitrogen. The reaction mixture is then refluxed overnight and the solvent removed under reduced pressure. The residual oil is chromatographed on neutral alumina (10% deactivated) using elution with toluene/ethyl acetate.

The first fraction (R_f = 0.75, toluene/ethyl acetate, 9 : 1) gave a colourless oil shown to be *dimethyl 2,2'-dipyrrolidine-N,N'-di(3-propionate) (XVII)* 0.17 g (6%); identical in all respects to that synthesized as described below.

The second fraction (R_f = 0.28, toluene/ethyl acetate, 9 : 1) affords one diastereomer of *1,5-diazatricyclo 8,3,0,$0^{5,9}$-tridecane-2-one (XVIa)* as a colourless oil, 1.24 g (64%); IR ($CHCl_3$): ν = 2980, 1640 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.44—2.08 (m, 7H), 2.16—2.32 (m, 1H), 2.50—2.66 (m, 1H), 2.69—2.91 (m, 5H), 2.98—3.10 (m, 1H), 3.28—3.43 (m, 1H), 3.69—3.84 (m, 1H), 4.33—4.45 (m, 1H).

The last fraction (R_f = 0.23, toluene/ethyl acetate, 9 : 1) gave the second diastereomeric product (*XVIb*) as a colourless oil, 0.56 g (29%); IR ($CHCl_3$): ν = 2980, 1640 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.40—2.04 (m, 8H), 2.04—2.24 (m, 1H), 2.24—2.42 (m, 2H), 2.55—2.85 (m, 2H), 3.00—3.19 (m, 2H), 3.19—3.36 (m, 1H), 3.50—3.69 (m, 1H), 3.76—3.90 (m, 1H).

A mixture of the diastereomers was distilled to give an analytically pure sample; B. p. 110—115 °C/0.03 mm.

Anal. $C_{11}H_{18}N_2O$ (194.27) calc'd.: C 68.00; H 9.34; N 14.42; O 8.24%
found: C 68.09; H 9.46; N 14.30; O 8.32%

Dimethyl 2,2'-dipyrrolidine-N,N'-*di(3-propionate) (XVII)*

A solution of (*I*) (1.40 g, 10 mmol) in methanol (25 ml) is added to an ice-cooled solution of methyl acrylate (5.16 g 60 mmol) in methanol (25 ml) over a period of 1 hour. The solution is stirred at 0 °C for 3 additional hours and then the solvent is removed under reduced pressure. Distillation of the residue affords (*XVII*) as a colourless oil, 2.36 g (82%); B. p. 120—125 °C/0.03 mm Hg; IR ($CHCl_3$): $\nu = 2960$, 1740 cm^{-1}; ^{1}H-NMR ($CDCl_3$): $\delta = 1.33$—1.67 (m, 8H), 2.30—2.67 (m, 10H), 2.83—3.30 (m, 4H), 3.55 (s, 6H, —OCH_3).

Anal. $C_{16}H_{28}N_2O_4$ (312.40). calc'd.: C 61.51; H 9.03; N 8.97; O 20.49%
found: C 61.00; H 9.40; N 9.12; O 20.40%

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4. It is possible to isolate one stereoisomer of (*XIII*) by recrystallisation from acetone (m. p. 235—236°C), although it is difficult to establish its configuration by simple spectroscopic means. The ^{13}C-NMR spectrum exhibits only five lines (20 MHz, $CDCl_3$) 23.4 (t); 30.0 (t), 30.0 (t), 45.1 (t), 61.6 (d) and 156.7 (s).

POVZETEK

2,2'-Dipirolidin kot izhodna spojina za nove diazatricikličnе sisteme

T. G. Bird, K. Moschner, M.-H. Robert, J. Collard-Motte, Z. Janousek, R. Merenyi in H. G. Viehe

Pri reakcijah 2,2'-dipirolidina, pripravljenega na nov način, z vrsto biselektrofilov, nastanejo selektivno novi diazatricikлični sistemi z mostnim dušikom ali pa *N,N'*-disubstituirani-2,2'-dipirolidini v dobrem ali zelo dobrem izkoristku.