POTENTIAL CHOLINERGIC AND ANTICHOLINERGIC COMPOUNDS: SYNTHESIS OF 2,8-SUBSTITUTED 2,8-DIAZASPIRO[4,5]DECANE--1,3-DIONES

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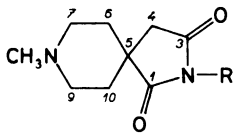
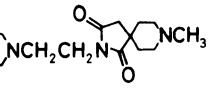
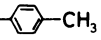
Heating the ammonium salt of (4-carboxy-1-methyl-4-piperidinyl)acetic acid (*XII*) gave 8-methyl--2,8-diazaspiro[4,5]decane-1,3-dione (*II*) which was N-alkylated with 2-bromoethanol and 4--bromobutanol to give the alcohols *III* and *V*. Compound *III* was transformed to the chloro compound *VI* which was reacted with the sodium salt of hexahydrobenzilic acid to give the ester *VII*. Compound *V* was transformed to the 4-toluenesulfonic ester *VIII* which reacted with 1-(2-pyrimidinyl)piperazine and gave *IX*. 2-(2-Propyl)-2,8-diazaspiro[4,5]decane-1,3-dione (*XVIII*) was similarly transformed via *XIX* to *XX* which reacted with the sodium salts of diphenylacetic, benzilic, hexahydrobenzilic, and (2-oxo-1-pyrrolidinyl)acetic acid to give the esters *XXI*—*XXIV*. The esters *VII* and *XXI*—*XXIV* were transformed to the methiodides. The compounds prepared were tested in the lines of activity of the analogous "RS-86" (*I*) but proved inactive.

2-Ethyl-8-methyl-2,8-diazaspiro[4,5]decane-1,3-dione (*I*) was described under the code number „RS-86" as an experimental orally active and centrally effective muscarinic cholinergic agonist with analgesic and sedative properties in animals, and with therapeutic potentiality in senile dementia and Alzheimer's disease[1-3]. In spite of the fact that it did not find practical utility in human pharmacotherapy, *I* deserves further interest and the present paper deals with the synthesis of analogues of *I*, variously substituted in positions 2 and 8. Some of the analogues prepared contain in their molecules acid ester residues and the quaternary ammonium group which are typical for structures of peripheral anticholinergic agents[4].

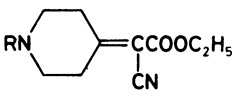
1-Methyl-4-piperidone was transformed via *X* (refs[2,3]), by the following addition of hydrogen cyanide (from potassium cyanide and hydrochloric acid) and by hydrolysis with hydrochloric acid accompanied by decarboxylation to the hydrochloride of the diacid *XII* (ref.[3]). The crude *XII*.HCl was dissolved in aqueous ammonia, the solution was evaporated under normal pressure to dryness and the residue was heated to 220—280°C giving 53% of the new and crystalline *II* which was characterized by spectra. Compound *II* was treated with sodium hydride in dimethylformamide and then with 2-bromoethanol at 75—80°C; *III* was obtained in the yield of 76% as the crystalline base (the hydrobromide was mentioned in ref.[5] without

specifying the preparative method) and also characterized by spectra. It was assumed that *III* could also be accessible by heating the 2-aminoethanol salt of *XII* to 200–210°C. In this way, a different compound was obtained in a low yield which was characterized by analysis and mass spectrum as having the composition $C_{26}H_{42}$.

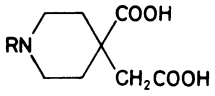


I, R = C_2H_5
II, R = H
III, R = CH_2CH_2OH
IV, R = 
V, R = $(CH_2)_4OH$
VI, R = CH_2CH_2Cl
VII, R = 
VIII, R = 
IX, R = 

$.N_6O_4$. This corresponds to its formulation as *IV* (IR and ^{1}H NMR spectra are not at variance with this formulation). It is clear that two 2-aminoethanol residues per one molecule of *XII* had to participate on the construction of the molecule of *IV*. Alkylation of *II* with 4-bromobutanol[6] in dimethylformamide after previous treatment of *II* with sodium hydride gave 51% of crystalline *V* which was transformed to the crystalline hydrogen fumarate. Treatment of *III* with thionyl chloride in chloroform afforded the crystalline hydrochloride of *VI*. The released base was also crystalline and its identity was corroborated by spectra.



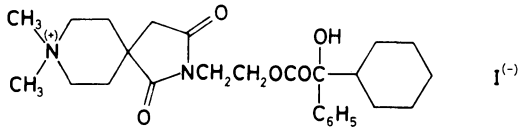
X, R = CH_3
XI, R = $CH_2C_6H_5$



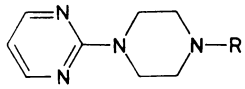
XII, R = CH_3
XIII, R = $CH_2C_6H_5$

Reaction of the sodium salt of hexahydrobenzilic acid[7] with *VI* in dimethylformamide at 130–140°C afforded the ester *VII* which was transformed to the crystalline

hydrogen fumarate and characterized by the mass spectrum. Its reaction with methyl iodide in acetone gave the quaternary salt *XIV*. The alcohol *V* was treated with 4-toluenesulfonyl chloride in a mixture of pyridine and dichloromethane and gave the crude oily *VIII* which was further processed without purification and characterization. It was reacted with 1-(2-pyrimidinyl)piperazine (*XV*) in boiling dioxane in the presence of sodium carbonate. The resulting mixture of the starting *XV* and of the product *IX* was separated by fractional crystallization of the fumarates. The less soluble hydrogen fumarate of *XV* crystallized first and the hygroscopic *IX* fumarate was obtained from the mother liquor in the yield of 39% as an oil. It was transformed to the crystalline dioxalate (crystallizing as a monohydrate) whose mass spectrum confirmed the composition of the base *IX*. The ^{1}H NMR spectrum of the oily base *IX* was also recorded and is consistent with the structure supposed. The starting *XV* was prepared via *XVI*. Reaction of 1-(ethoxycarbonyl)piperazine with 2-chloropyrimidine[8] was carried out according to the literature[9] and the product *XVI* melted by 10°C higher than reported[9]; it was, therefore, fully characterized and transformed to the hydrochloride which also melted differently than reported[9]. Hydrolysis of *XVI* with ethanolic potassium hydroxide gave 82% of *XV* (its preparation was described by reaction of 2-chloropyrimidine with piperazine[9]) which was transformed to crystalline salts: dihydrochloride (melting higher than reported[9]), oxalate, and fumarate.



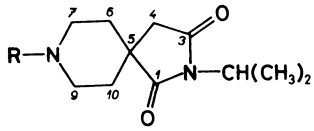
XIV



XV, R = H
XVI, R = $COOC_2H_5$

The second part of the work was started from 1-benzyl-4-piperidone which was transformed by known procedure[3] to *XI*. Its hydrochloride melted constantly by 20°C lower than reported[3] and was, therefore, fully characterized. The new crystalline base *XI* was also prepared and its ^{1}H NMR spectrum confirmed the identity of the product. Compound *XI* was further transformed to the hydrochloride of the diacid *XIII* (ref.[3]) which was further used without purification. Thermal reaction of its 2-propylamine salt at 200°C gave 83% of *XVII* which was crystalline and was cha-

racterized by spectra. The debenzylation of *XVII* to *XVIII* was carried out by catalytic hydrogenolysis at normal pressure using palladium on charcoal as catalyst in analogy to the method described in ref.[3]. Compound *XVIII* was obtained in crystalline state (the patent[3] mentioned only the boiling point) and its spectra were recorded. Alkylation of *XVIII* with 2-bromoethanol in boiling chloroform in the presence of sodium carbonate gave 96% *XIX* which was prepared as the crystalline base (spectra recorded) and as the hydrochloride. Treatment of *XIX* with thionyl chloride in benzene afforded the crystalline hydrochloride of *XX* from which the crystalline base was released and its spectra were recorded. Compound *XX* was reacted with the sodium salts of diphenylacetic[10], benzilic, and hexahydrobenzilic acid[7] in boiling 2-propanol and the esters *XXI*–*XXIII* were obtained as crystalline bases (spectra recorded) and hydrochlorides. The ester *XXII* was prepared also by transesterification of methyl benzilate[11] with *XIX* in boiling toluene in the presence of a catalytic amount of sodium methoxide.

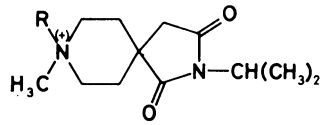


XVII, R = $CH_2C_6H_5$
XVIII, R = H
XIX, R = CH_2CH_2OH
XX, R = CH_2CH_2Cl
XXI, R = $CH_2CH_2OCOCH(C_6H_5)_2$
XXII, R = $CH_2CH_2OCOC(C_6H_5)_2$ (OH)
XXIII, R = $CH_2CH_2OCOC(C_6H_5)$ (OH)
XXIV, R = $CH_2CH_2OCOCH_2N$ (O)

Similar reaction of the sodium salt of (2-oxo-1-pyrrolidinyl)acetic acid[12] with *XX* in boiling 2-propanol gave the ester *XXIV* which was similarly characterized like *XXI*–*XXIII*. Reactions of the amino esters *XXI*–*XXIV* with methyl iodide in acetone afforded the quaternary salts *XXV*–*XXVIII*.

Compounds *VII*, *IX*, *XIV*, *XX*–*XXVIII* were pharmacologically tested in the form of salts (cf. Experimental) and compared with *I* (oral administration). While the effects described[1] for *I* could be confirmed (analgesic activity in the Haffner test in mice, PD_{50} 3·7 mg/kg; analgesic effect in the peritoneal test in mice, PD_{50} 2·0 mg/kg; sedative effect in the test of Dews in mice, ED_{50} 1·1 mg/kg (in 1 h); ataxic

activity in mice, ED_{50} 1·47 mg/kg; anticonvulsant effect against the electroshock in mice, PD_{50} 4·4 mg/kg; mydriasis in mice after 10 mg/kg; significant prolongation of survival of mice in nitrogen atmosphere after 2·5 mg/kg (1 h after the administra-



XXV, R = $CH_2CH_2OCOCH(C_6H_5)_2$

XXVI, R = $CH_2CH_2OCOC(C_6H_5)_2$ (OH)

XXVII, R = $CH_2CH_2OCOC(OH)(C_6H_5)$ (cyclohexyl)

XXVIII, R = $CH_2CH_2OCOCH_2N$ (pyrrolidone)

tion); significant prolongation of the gasping reflex in mice after 100 mg/kg), the compounds described here were ineffective in these lines. The only exception was compound *XX* which significantly prolonged the survival time of mice in the test of nitrogen anoxia (200 mg/kg 1 h after the administration). In high doses (100 mg/kg and more) it induced the appearance of the parkinsonic syndrome which lasted for more than 1 month. Similar doses (100–200 mg/kg) brought about ataxia in mice which persisted for 1 week after the administration. The long-lasting effects of this compound may be explained by its character of a substituted alkyl halide, i.e. alkylating agent. By alkylating some binding sites in the brain, the effect of the compound becomes practically irreversible. All the compounds tested did not show any appreciable affinity to muscarinic receptors in the rat brain which was assessed by inhibition of binding of 0·5 nM [^{3}H]quinuclidinyl benzilate in vitro.

EXPERIMENTAL

The melting points of analytical samples were determined in the Kofler block and they were not corrected; the samples were dried in vacuo of about 60 Pa at room temperature or at a suitably elevated temperature. IR spectra (in NUJOL, ν in cm^{-1}) were recorded with a Perkin–Elmer 298 spectrophotometer, NMR spectra (in $CDCl_3$ unless stated otherwise, δ in ppm, J in Hz) on a CW-NMR spectrometer TESLA BS 487C (^{1}H at 80 MHz) or on a FT-NMR spectrometer TESLA BS 567A (^{1}H NMR at 100 MHz, ^{13}C at 25·14 MHz), and the mass spectra (m/z, fragments and/or %) with Varian MAT 44S (GC-MS) spectrometer. The homogeneity of the substances and composition of the mixtures were checked by thin-layer chromatography (TLC) on silica gel (Silufol). The extracts were dried with $MgSO_4$ or K_2CO_3 and evaporated under reduced pressure on a rotary evaporator.

8-Methyl-2,8-diazaspiro[4,5]decane-1,3-dione (*II*)

The crude *XII*.HCl[3] (164 g) was dissolved in 300 ml NH_4OH, the volatile components of the solution were distilled off at normal pressure, the residue was heated in vacuo at 230–280°C for 5 h, after cooling the solidified melt was treated with 100 ml hot water, 280 ml 50% K_2CO_3 and 2 ml 50% NaOH (pH 12), and the mixture was extracted with chloroform. Processing of the extract gave 60 g of crude product which was crystallized from 2-propanol; 38·3 g (53%) of *II*, m.p. 197–198°C (2-propanol–hexane). Mass spectrum: 182 (M^+, $C_9H_{14}N_2O_2$, 20), 167 (10), 153 (8), 139 (5), 110 (5), 96 (6), 70 (100), 57 (15). IR spectrum: 1 715, 1 755. 1 776 (CONCO of succinimide); 2 620, 2 690, 2 718 (intermolecular C=O···H—N); 3 140 (NH). ^{1}H NMR spectrum (100 MHz): 2·30 s, 3 H (NCH_3); 2·60 s, 2 H (CH_2CO). For $C_9H_{14}N_2O_2$ (182·2) calculated: 59·32% C, 7·74% H, 15·37% N; found: 59·03% C, 7·87% H, 15·47% N.

2-(2-Hydroxyethyl)-8-methyl-2,8-diazaspiro[4,5]decane-1,3-dione (*III*)

A solution of 18·2 g *II* in 100 ml dimethylformamide was treated with 3·2 g 85% NaH in mineral oil and the mixture was stirred for 1·5 h at 50°C. Over 80 min there was added a solution of 12·5 g 2-bromoethanol in 60 ml dimethylformamide and the mixture was stirred for 4 h at 75 to 80°C. After standing for 64 h at room temperature the mixture was filtered with 1 g active carbon and the filtrate was evaporated in vacuo. The residue was extracted with 250 + 100 + 100 ml chloroform, the solid salts were filtered off, the filtrate was evaporated in vacuo to a volume of 200 ml and was filtered through a layer of neutral Al_2O_3 (activity II). The filtrate was evaporated in vacuo and the residue crystallized after trituration with 20 ml hexane and 5 ml 2-propanol; 17·2 g (76%) of *III*, m.p. 94–97°C (2-propanol–hexane). IR spectrum: 1 040 (CH_2OH); 1 680, 1 758 (CONCO of succinimide); 2 740, 2 789 (CH_2–N, CH_3–N); 3 415 (OH). ^{1}H NMR spectrum (100 MHz): 2·30 s, 3 H (NCH_3); 2·58 s, 2 H (CH_2CO); 3·73 s, 4 H (NCH_2. .CH_2O). For $C_{11}H_{18}N_2O_3$ (226·3) calculated: 58·38% C, 8·02% H, 12·38% N; found: 58·54% C, 8·30% H, 12·17% N.

1,4-Bis(2-(8-methyl-1,3-dioxo-2,8-diazaspiro[4,5]decane-2-yl)ethyl)piperazine (*IV*)

A mixture of 90 g crude *XII*.HCl[3], 50 g 2-aminoethanol and 50 ml water was heated for removing the volatile components. The residue was evaporated in vacuo and the bath temperature was maintained for 5 h at 200–210°C. After cooling the melt was distributed between chloroform and a solution of 112 g K_2CO_3 in 100 ml water, the organic layer was evaporated, the residue was dissolved in 60 ml benzene and the solution was chromatographed on 240 g neutral Al_2O_3 (activity II). The first fractions (3·2 g), eluted with benzene, were oily, and the following fractions crystallized; 2·3 g, m.p. 151–154°C (benzene–hexane). It was characterized as *IV*. Mass spectrum: 502 (M^+, $C_{26}H_{42}N_6O_4$, 5), 432 ($C_{22}H_{34}N_5O_4$, 19), 307 ($C_{16}H_{27}N_4O_2$, 100), 71. IR spectrum: 1 700, 1 769 (CONCO of succinimide); 2 680, 2 740, 2 780, 2 810 (CH_2–N and CH_3–N). ^{1}H NMR spectrum (100 MHz): 3·58 t, 4 H (2 × $CONCH_2$); 1·50–3·00 m, 38 H (remaining CH_2 groups and 2 × NCH_3). For $C_{26}H_{42}N_6O_4$ (502·7) calculated: 62·12% C, 8·42% H, 16·72% N; found: 62·16% C, 8·47% H, 16·43% N.

2-(4-Hydroxybutyl)-8-methyl-2,8-diazaspiro[4,5]decane-1,3-dione (*V*)

A stirred solution of 10·0 g *II* in 70 ml dimethylformamide was treated with 1·81 g 80% NaH suspension in oil under nitrogen, the mixture was stirred for 10 min at 65°C, treated with 1·3 g Na_2CO_3 and then over 75 min with a solution of 8·4 g 4-bromobutanol[6] in 35 ml dimethyl-

formamide. The mixture was stirred for 5 h at 75–80°C and allowed to stand for 48 h at room temperature. Dimethylformamide was evaporated in vacuo and the residue was chromatographed on a column of 320 g silica gel. Chloroform eluted 7·1 g (51%) of homogeneous *V* which crystallized from hexane, m.p. 82–84°C (hexane). ^{1}H NMR spectrum (80 MHz): 2·22 s, 3 H (NCH_3); 2·45 s, 2 H (CH_2CON); 3·26 bs, 1 H (OH); 3·48 m, 4 H ($CONCH_2$ and CH_2O). For $C_{13}H_{22}N_2O_3$ (254·3) calculated: 61·39% C, 8·72% H, 11·02% N; found: 61·14% C, 8·42% H, 11·01% N.

Hydrogen fumarate, m.p. 148–150°C (95% ethanol). For $C_{17}H_{26}N_2O_7$ (370·4) calculated: 55·12% C, 7·08% H, 7·56% N; found: 54·88% C, 7·14% H, 7·41% N.

2-(2-Chloroethyl)-8-methyl-2,8-diazaspiro[4,5]decane-1,3-dione (*VI*)

A solution of 3·5 g *III* in 20 ml chloroform was stirred and treated at 40°C over 20 min with a solution of 3·6 g $SOCl_2$ in 10 ml chloroform. The mixture was refluxed for 2 h, the volatile components were completely evaporated in vacuo, the crystalline residue was triturated with ether, filtered, and dried; 4·10 g (97%) of *VI*.HCl, m.p. 220–222·5°C (2-propanol). IR spectrum: 1 690, 1 769 (CONCO of succinimide); 2 420, 2 480, 2 555, 2 590 (NH^+). ^{1}HN MR spectrum (100 MHz, CD_3SOCD_3): 2·72 s, 2 H (CH_2CO); 2·74 s, 3 H (NCH_3); 3·78 s, 4 H (NCH_2CH_2Cl). For $C_{11}H_{18}Cl_2N_2O_2$ (281·2) calculated: 46·98% C, 6·45% H, 25·22% Cl, 9·96% N; found: 47·01% C, 6·46% H, 24·97% Cl, 9·92% N.

The base was released from the hydrochloride by 30% K_2CO_3 and was isolated by extraction with chloroform. After evaporation of the solvent it crystallized from a mixture of hexane and benzene, m.p. 65·5–67°C. IR spectrum: 1 704, 1 790 (CONCO of succinimide); 2 785 (N–CH_3). ^{1}H NMR spectrum (100 MHz): 2·33 s, 3 H (NCH_3); 2·60 s, 2 H (CH_2CO); 3·80 m, 4 H (NCH_2. .CH_2Cl). ^{13}C NMR spectrum: 33·46 t (C-6 and C-10); 39·81 t (C-4); 39·81 t and 40·04 t (NCH_2. .CH_2Cl); 42 58 s (C-5); 46·31 q (NCH_3); 51·61 t (C-7 and C-9); 171·31 s (C-3); 181·81 s (C-1). For $C_{11}H_{17}ClN_2O_2$ (244·7) calculated: 73·98% C, 7·00% H, 14·49% Cl, 11·45% N; found: 53·78% C, 7·00% H, 14·39% Cl, 11·28% N.

2-(8-Methyl-1,3-dioxo-2,8-diazaspiro[4,5]decane-2-yl)ethyl Hexahydrobenzilate (*VII*)

Hexahydrobenzilic acid[7] (2·34 g) was added to a solution of sodium ethoxide (from 10 ml ethanol and 0·23 g Na) and the solution obtained was evaporated in vacuo to dryness. The residue was treated with 10 ml dimethylformamide, 1·2 g Na_2CO_3 and 2·81 g *VI*, and the mixture was stirred for 3 h at 130–140°C. After cooling it was diluted with 50 ml toluene, the precipitated solid was filtered off, and the filtrate was evaporated in vacuo. The residue was dissolved in 100 ml toluene, the solution was washed with water and 10% Na_2CO_3, dried, and evaporated in vacuo giving 3·64 g (83%) of crude oily *VII*.

Hydrogen fumarate, m.p. 152–156°C (acetone–ether). Mass spectrum: 442 (M^+, $C_{25}H_{34}N_2O_5$, 10), 427 (2), 359 (22), 227 (44), 210 (38), 189 (36), 71 (100). For $C_{29}H_{38}N_2O_9$ (558·6) calculated: 62·35% C, 6·85% H, 5·02% N; found: 62·13% C, 6·77% H, 5·04% N.

Methiodide (XIV), m.p. 217–219°C (ethanol–ether). It was prepared by refluxing a solution of 5·0 g crude *VII* and 9·5 g methyl iodide in 20 ml acetone and by standing overnight at room temperature; 5·5 g (92%). For $C_{26}H_{37}IN_2O_5$ (584·5) calculated: 53·42% C, 6·38% H, 21·71% I, 4·79% N; found: 53·33% C, 6·46% H, 21·83% I, 4·59% N.

1-(Ethoxycarbonyl)-4-(2-pyrimidinyl)piperazine (*XVI*)

1-(Ethoxycarbonyl)piperazine (6·33 g) was reacted with 4·60 g 2-chloropyrimidine[8] in 25 ml

boiling ethanol in the presence of 8·0 g $NaHCO_3$ according to ref.[9] and gave 6·9 g (73%) of *XVI*, m.p. 77—79°C (hexane). IR spectrum: 777, 797 (3 adjacent Ar–H); 1 243, 1 690 (NCOOR), 1 490, 1 550, 1 590, 3 013 (Ar). ^{1}H NMR spectrum (100 MHz): 1·30 t, 3 H (CH_3, J = 7·0); 3·58 m and 3·80 m, 4 and 4 H (4 × CH_2N of piperazine); 4·19 q, 2 H (OCH_2, J = 7·0); 6·52 t, 1 H (H-4 of pyrimidinyl, J = 5·0); 8·35 d, 2 H (H-3 and H-5 of pyrimidinyl, J = 5·0). For $C_{11}H_{16}N_4O_2$ (246·3) calculated: 55·91% C, 6·83% H, 23·71% N; found: 55·75% C, 6·88% H, 23·55% N. Ref.[9], m.p. 67·5—69°C.

Hydrochloride, m.p. 154—158°C (ethanol–ether). For $C_{11}H_{17}ClN_4O_2$ (272·7) calculated: 48·44% C, 6·28% H, 13·00% Cl, 20·54% N; found: 48·42% C, 6·29% H, 13·03% Cl, 20·64% N. Ref.[9], m.p. 177—178°C.

1-(2-Pyrimidinyl)piperazine (*XV*)

A mixture of 18·0 g *XVI* and solution of 44·2 g KOH in 90 ml ethanol was stirred and refluxed for 4 h. It was diluted with 100 ml water, ethanol was distilled off, the residue was diluted with 50 ml water and extracted with chloroform. Processing of the extract and distillation of the residue gave 10·6 g (82%) of oily *XV*, b.p. 85—86°C/80 Pa.

Dihydrochloride, m.p. 270°C with decomposition (ethanol–ether). For $C_8H_{14}Cl_2N_4$ (237·1) calculated: 40·52% C, 5·95% H, 23·63% N; found: 40·36% C, 5·95% H, 23·69% N. Ref.[9], m.p. 252·5—253°C.

Oxalate, m.p. 214°C (93% ethanol). For $C_{10}H_{14}N_4O_4$ (254·3) calculated: 47·23% C, 5·55% H, 22·04% N; found: 47·26% C, 5·53% H, 22·05% N.

Fumarate, m.p. 197—199°C (ethanol). For $C_{12}H_{16}N_4O_4$ (280·2) calculated: 51·42% C, 5·75% H, 19·99% N; found: 51·19% C, 5·50% H, 19·69% N.

1-(4-(8-Methyl-1,3-dioxo-2,8-diazaspiro[4,5]decane-2-yl)butyl)-
-4-(2-pyrimidinyl)piperazine (*IX*)

A stirred solution of 2·75 g *V* in a mixture of 3 ml pyridine and 3 ml dichloromethane was treated dropwise at 4—7°C with a solution of 2·3 g 4-toluenesulfonyl chloride in 15 ml dichloromethane and the mixture was stirred for 6 h at room temperature. After standing overnight it was diluted with 20 ml dichloromethane and decomposed at 10°C under stirring with 20 ml ice-cold water added dropwise. The organic layer was washed with water, dried and evaporated. The oily residue (3·85 g, 88%) was considered to be the crude *VIII*.

A mixture of 3·85 g crude *VIII*, 15 ml dioxane, 1·55 g *XV*, and 2·8 g Na_2CO_3 was stirred and refluxed for 6·5 h. After cooling the solid was filtered off and the filtrate was evaporated. The inhomogeneous residue was chromatographed on 150 g silica gel. There were obtained 1·9 g of a chloroform eluate which was enriched in the desired *IX*. It was neutralized with 0·55 g fumaric acid in 20 ml ethanol and the mixture of fumarates obtained was crystalized from 90% ethanol giving 0·8 g of *XV* fumarate, m.p. 197—199°C, which was found identical with the salt described above. Processing of the mother liquor gave 2·55 g of a different fumarate which was hygroscopic and, therefore, was transformed via the oily base *IX* (1·47 g, 39%) to the dioxalate monohydrate, m.p. 165—167°C (95% ethanol). Mass spectrum: 400 (M^+, $C_{21}H_{32}N_6O_2$), 330, 305, 293, 280, 235, 223, 177, 148, 122. For $C_{25}H_{36}N_6O_{10} + H_2O$ (598·6) calculated: 50·16% C, 6·40% H, 14·04% N; found: 50·25% C, 6·37% H, 13·89% N.

The released oily base (50% K_2CO_3 and extraction with chloroform) was used for recording the ^{1}H NMR spectrum (80 MHz): 2·24 s, 3 H (NCH_3); 2·50 s, 2 H (2 × H-4); 3·45 bt, 2 H

(CONCH$_2$, J = 6·7); 3·75 bt, 4 H (CH$_2$N^{4}CH$_2$ of piperazine, J = 5·2); 6·40 t, 1 H (H-4 of pyrimidinyl, J = 5·0); 8·23 d, 2 H (H-3 and H-5 of pyrimidinyl, J = 5·0).

Ethyl (1-Benzyl-4-piperidylidene)cyanoacetate (*XI*)

Reaction of 95 g 1-benzyl-4-piperidone with 70 g ethyl cyanoacetate in 250 ml distilling toluene in the presence of 2·5 g acetic acid according to ref.[3] gave 58·8 g (41%) of the crystalline *XI*.HCl which was repeatedly recrystallized from 2-propanol and melted constantly at 147·5—149°C. IR spectrum: 697, 753 (5 adjacent Ar–H); 1 241, 1 253, 1 289 (COOR); 1 499, 1 600 (Ar); 1 716, 1 726 (C=C—COOH); 2 222 (CN); 2 380, 2 460 (NH$^+$). For $C_{17}H_{21}ClN_2O_2$ (320·8) calculated: 63·64% C, 6·60% H, 11·05% Cl, 8·73% N; found: 63·61% C, 6·69% H, 11·08% Cl, 8·55% N. Ref.[3], m.p. 167°C.

The base was relased with aqueous NaHCO$_3$ and isolated by extraction with benzene. Processing of the extract gave the crystalline *XI*, m.p. 65—66°C (hexane). ^{1}H NMR spectrum (80 MHz): 1·28 t, 3 H (CH$_3$, J = 7·0); 2·40—3·20 m, 8 H (CH$_2$CH$_2$NCH$_2$CH$_2$ of piperidine); 3·50 s, 2 H (ArCH$_2$N); 4·20 q, 2 H (COOCH$_2$, J = 7·0); 7·22 s, 5 H (C$_6$H$_5$). For $C_{17}H_{20}N_2O_2$ (284·4) calculated: 71·80% C, 7·09% H, 9·85% N; found: 71·61% C, 7·32% H, 9·60% N.

8-Benzyl-2-(2-propyl)-2,8-diazaspiro[4,5]decane-1,3-dione (*XVII*)

A solution of 162 g crude *XIII*.HCl (ref.[3]) in 200 ml water was treated with 140 g 2-propylamine and the mixture was distilled in a bath of 160°C. The remainder of the volatile components was removed by evaporation in vacuo and the residue was heated for 1 h to 200°C. After cooling the melt was diluted with 250 ml water, was made alkaline with 65 ml 50% NaOH, and the mixture was extracted with benzene. Processing of the extract gave 82 g (83%) of almost homogeneous *XVII*, m.p. 93—99°C. Analytical sample, m.p. 99—101°C (2-propanol). IR spectrum: 700, 740 (5 adjacent Ar–H); 1 490, 1 600, 3 020, 3 080 (Ar); 1 680, 1 761 (CONCO of succinimide) 2 770, 2 810 (CH$_2$–N). ^{1}H NMR spectrum (80 MHz): 1·40 m and 2·00 m, 2 and 2 H (2 × H-6 and 2 × H-10); 2·35 d, 6 H (2 × CH$_3$, J = 7·0); 2·10 m and 2·90 m, 2 and 2 H (2 × H-7 and 2 × H-9); 2·45 s, 2 H (2 × H-4); 3·50 s, 2 H (ArCH$_2$N); 4·35 m, 1 H (NCH of 2-propyl); 7·28 s, 5 H (C$_6$H$_5$). For $C_{18}H_{24}N_2O_2$ (300·4) calculated: 71·96% C, 8·05% H, 9·33% N; found: 71·68% C, 8·03% H, 9·26% N.

2-(2-Propyl)-2,8-diazaspiro[4,5]decane-1,3-dione (*XVIII*)

The hydrogenation of 23·0 g *XVII* in 200 ml methanol and 60 ml water was carried out in the presence of 2·0 g 5% Pd/C in analogy to the procedure described in ref.[3]. There were obtained 14·8 g (93%) of *XVIII*, m.p. 74—78°C. Analytical sample, m.p. 77—78°C (benzene–hexane). IR spectrum: 1 690, 1 796 (CONCO of succinimide); 2 760, 2 810 (CH$_2$–N); 3 245 (NH). ^{1}H NMR spectrum (80 MHz): 1·38 d, 6 H (2 × CH$_3$, J = 7·0); 1·60 bs, 1 H (NH); 1·50 and 1·85 m, 2 and 2 H (2 × H-6 and 2 × H-10); 2·52 s, 2 H (2 × H-4); 2·72 m and 3·12 m, 2 and 2 H (2 × H-7 and 2 × H-9); 4·35 m, 1 H (NCH of 2-propyl). For $C_{11}H_{18}N_2O_2$ (210·3) calculated: 62·83% C, 8·63% H, 13·32% N; found: 62·54% C, 8·59% H, 13·09% N. Ref.[3] characterized this compound as an oil.

8-(2-Hydroxyethyl)-2-(2-propyl)-2,8-diazaspiro[4,5]decane-1,3-dione (*XIX*)

A stirred suspension of 12·0 g *XVIII* and 12·1 g Na$_2$CO$_3$ in 50 ml chloroform was treated over 1 h at 60—65°C with a solution of 8·2 g 2-bromoethanol in 20 ml chloroform, and the mixture was refluxed for 7 h. Further 4·8 g Na$_2$CO$_3$ and 1·8 g 2-bromoethanol in 10 ml chloroform

were added and the refluxing was continued for 6 h. After cooling the solid was filtered off, the filtrate was treated with 3·0 g active carbon and the mixture was filtered through a layer of 30 g Al_2O_3 (activity II). Evaporation of the filtrate gave 13·9 g (96%) of crude *XIX*, m.p. 84 to 89°C. Analytical sample, m.p. 86–89°C (benzene–hexane). IR spectrum: 1 060 (CH_2OH); 1 689, 1 763 (CONCO of succinimide); 2 765, 2 820 (CH_2–N); 3 250 (OH). ^{1}H NMR spectrum (80 MHz): 1·35 d, 6 H (2 × CH_3, J = 7·0); 2·50 s, 2 H (2 × H-4); 3·60 bt, 2 H (CH_2O); 4·35 m, 1 H (NCH of 2-propyl). For $C_{13}H_{22}N_2O_3$ (254·3) calculated: 61·39% C, 8·72% H, 11·02% N. found: 61·14% C, 8·64% H, 11·30% N.

Hydrochloride, m.p. 198–202·5°C (ethanol). For $C_{13}H_{23}ClN_2O_3$ (290·8) calculated: 53·69% C, 7·97% H, 12·19% Cl, 9·64% N; found: 53·72% C, 7·88% H, 12·36% Cl, 9·46% N.

8-(2-Chloroethyl)-2-(2-propyl)-2,8-diazaspiro[4,5]decane-1,3-dione (*XX*)

A stirred solution of 2·54 g *XIX* in 10 ml benzene was treated at 30–40°C with a solution of 1·5 g $SOCl_2$ in 5 ml benzene, added dropwise. The mixture was refluxed for 1·5 h and the volatile components were completely evaporated in vacuo. The residue (2·9 g, 94%) was the crude crystalline *XX*.HCl, m.p. 190–195°C. Analytical sample, m.p. 199–201°C (2-propanol–ether). IR spectrum: 1 690, 1 771 (CONCO of succinimide); 2 400 (NH^+). ^{1}H NMR spectrum (80 MHz, CD_3SOCD_3): 1·38 d, 6 H (2 × CH_3, J = 6·5); 2·75 s, 2 H (2 × H-4); 3·50 bt, 2 H (CH_2N in chloroethylamino); 4·20 m, 3 H (CH_2Cl and NCH). For $C_{13}H_{22}Cl_2N_2O_2$ (309·2) calculated: 50·49% C, 7·17% H, 22·93% Cl, 9·06% N; found: 50·45% C, 7·13% H, 22·01% Cl, 9·03% N.

The base *XX* was released by decomposition of 19·1g hydrochloride with 150 ml 10% $NaHCO_3$ and was extracted with benzene. Processing of the extract gave 16·8 g of *XX*, m.p. 61–65°C. Analytical sample, m.p. 65–66°C (cyclohexane). IR spectrum: 1 700, 1 762 (CONCO of succinimide); 2 770 (CH_2–N). ^{1}H NMR spectrum (100 MHz): 1·35 d, 6 H (2 × CH_3, J = 7·0); 2·50 s, 2 H (2 × H-4); 2·76 t, 2 H (NCH_2 in chloroethylamino, J = 7·0); 1·30–2·20 m and 2·80 m, 4 and 4 H (2 × H-6, 2 × H-7, 2 × H-9, and 2 × H-10); 3·60 t, 2 H (CH_2Cl, J = 7·0); 4·37 m, 1 H (CONCH). For $C_{13}H_{21}ClN_2O_2$ (272·8) calculated: 57·24% C, 7·76% H, 13·00% Cl, 10·27% N; found: 56·86% C, 7·73% H, 13·07% Cl, 10·12% N.

2-(2-(2-Propyl)-1,3-dioxo-2,8-diazaspiro[4,5]decane-8-yl)ethyl Diphenylacetate (*XXI*)

Diphenylacetic acid[10] (3·6 g) was added to a solution of sodium 2-propoxide (from 0·4 g Na and 20 ml 2-propanol) and the suspension obtained was treated dropwise with a solution of 4·6 g *XX* in 15 ml 2-propanol over 45 min. The mixture was stirred and refluxed for 8 h, evaporated in vacuo, and the residue was distributed between 150 ml benzene and 50 ml water. The organic layer was washed with 10% $NaHCO_3$, dried and evaporated; 6·4 g (85%) of crystalline *XXI*, m.p. 90–96°C. Analytical sample of the crystalline modification *A*, m.p. 97–99°C (cyclohexane–hexane). IR spectrum: 700, 713 (5 adjacent Ar–H); 1 055, 1 140, 1 229, 1 270 (C–O–C of ester); 1 495, 1 500, 1 585, 1 600, 3 020 (Ar); 1 700, 1 759 (CONCO of succinimide); 1 730 (RCOOR'); 2 740 (CH_2–N). ^{1}H NMR spectrum (100 MHz): 1·31 d, 6 H (2 × CH_3, J = 7·0); 2·42 s, 2 H (2 × H-4); 2·62 t, 2 H (NCH_2 outside of piperidine, J = 7·0); 2·00 m and 2·80 m, 4 and 4 H (2 × H-6, 2 × H-7, 2 × H-9, and 2 × H-10); 4·30 t, 2 H (CH_2O, J = 7·0); 4·40 m, 1 H (NCH), 5·04 s, 1 H (Ar_2CHCO); 7·28 s, 10 H (2 × C_6H_5). For $C_{27}H_{32}N_2O_4$ (448·6) calculated: 72·29% C, 7·19% H, 6·24% N; found: 72·00% C, 7·23% H, 6·21% N.

The base *XXI* crystallized from 2-propanol as the crystal modification *B*, m.p. 107·5–108°C. For $C_{27}H_{32}N_2O_4$ (448·6) calculated: 72·29% C, 7·19% H, 6·24% N, found: 72·00% C, 7·23% H, 6·21% N.

Hydrochloride, m.p. 189–191°C (2-propanol). For $C_{27}H_{33}ClN_2O_4$ (485·0) calculated: 66·86% C, 6·86% H, 7·31% Cl, 5·78% N; found: 66·83% C, 6·87% H, 7·59% Cl, 6·00% N.

Methiodide (XXV), m.p. 184–185°C (ethanol). IR spectrum: 1 231, 1 725 (RCOOR'); 1 690, 1 769 (CONCO of succinimide). For $C_{28}H_{35}IN_2O_4$ (590·5) calculated: 56·95% C, 5·97% H, 21·49% I, 4·75% N; found: 57·21% C, 6·05% H, 21·49% I, 4·71% N.

2-(2-(2-Propyl)-1,3-dioxo-2,8-diazaspiro[4,5]decane-8-yl)ethyl Benzilate (*XXII*)

A) Benzilic acid (4·22 g) was transformed to the sodium salt by sodium 2-propoxide (from 0·43 g Na and 20 ml 2-propanol) and this was reacted with 5·0 g *XX* in 35 ml 2-propanol similarly like in the preceding case. There were obtained 4·8 g (56%) of crystalline *XXII*, m.p. 110–112°C (2-propanol). IR spectrum: 704, 756 (5 adjacent Ar–H); 1 056, 1 228, 1 370 (C–O–C of ester); 1 156 (C–OH); 1 592, 1 600, 3 030, 3 055, 3 090 (Ar); 1 692, 1 770 (CONCO of succinimide); 1 712 (RCOOR'); 2 740, 2 800, 2 825 (CH_2–N); 3 500 (OH). ^{1}H NMR spectrum (100 MHz): 1·38 d, 6 H (2 × CH_3, J = 7·0); 2·00 m and 2·80 m, $\sum$ 8 H (2 × H-6, 2 × H-7, 2 × H-9, and 2 × H-10); 2·42 s, 2 H (2 × H-4); 2·62 t, 2 H (CH_2N outside of piperidine, J = 7·0); 4·28 bs, 1 H (OH); 4·39 t, 2 H (OCH_2, J = 7·0); 4·40 m, 1 H (CHN); 7·20–7·60 m, 10 H (2 × C_6H_5). For $C_{27}H_{32}N_2O_5$ (464·6) calculated: 69·80% C, 6·94% H, 6·03% N; found: 69·43% C, 6·99% H, 6·29% N.

Hydrochloride, m.p. 210–214°C with decomposition (ethanol). IR spectrum: 700, 751 (5 adjacent Ar–H); 1 216, 1 229, 1 735 (RCOOR'); 1 594, 1 600, 3 058 (Ar); 1 694, 1 770 (CONCO of succinimide); 2 540 (NH^+); 3 185, 3 248 (OH). For $C_{27}H_{33}ClN_2O_5$ (501·0) calculated: 64·72% C, 6·64% H, 7·08% Cl, 5·59% N; found: 64·40% C, 6·81% H, 7·38% Cl, 5·36% N.

Methiodide (XXVI), m.p. 216–217°C (aqueous ethanol). IR spectrum: 700, 753 (5 adjacent Ar–H); 1 205, 1 229, 1 743 (RCOOR'); 1 690, 1 770 (CONCO of succinimide); 3 268 (OH). For $C_{28}H_{35}IN_2O_5$ (606·5) calculated: 55·45% C, 5·82% H, 20·02% I, 4·62% N; found: 55·36% C, 5·86% H, 20·72% I, 4·47% N.

B) A mixture of 3·8 g *XIX*, 3·9 g methyl benzilate[11], 100 ml toluene, and 0·05 g sodium methoxide was slowly distilled through a column. After removal of toluene, the residue was diluted with 50 ml xylene and the mixture was refluxed for 4 h. Xylene was evaporated in vacuo and the residue was dissolved in 20 ml benzene. The solution was washed with water, dried, filtered through a column of 60 g neutral Al_2O_3 (activity II), and evaporated in vacuo; 3·6 g (70%) of oily *XXII* which gave the hydrochloride melting at 210–214°C with decomposition, identical with the salt described under *A*).

2-(2-(2-Propyl)-1,3-dioxo-2,8-diazaspiro[4,5]decane-8-yl)ethyl Hexahydrobenzilate (*XXIII*)

Hexahydrobenzilic acid[7] (4·3 g) was transformed to the sodium salt by reaction with sodium 2-propoxide (from 0·42 g Na and 20 ml 2-propanol) and this was reacted with 5·0 g *XX* in 50 ml 2-propanol similarly like in the preceding cases. There were obtained 6·2 g (72%) of *XXIII*, m.p. 96–98°C (2-propanol–hexane). IR spectrum: 693, 732 (5 adjacent Ar–H); 1 114 (C–OH); 1 230, 1 700 (RCOOR'); 1 490, 1 598, 3 060 (Ar); 1 700, 1 769 (CONCO of succinimide); 2 738, 2 810 (CH_2–N); 3 535 (OH). ^{1}H NMR spectrum (100 MHz): 1·36 d, 6 H (2 × CH_3, J = 7·0); 2·44 s, 2 H (2 × H-4); 3·70 bs, 1 H (OH); 4·30 bt, 2 H ($COOCH_2$); 4·38 m, 1 H (CHN); 7·00–7·80 m, 5 H (C_6H_5). For $C_{27}H_{38}N_2O_5$ (470·6) calculated: 68·91% C, 8·14% H, 5·95% N; found: 68·78% C, 8·12% H, 6·19% N.

Hydrochloride, m.p. 209–210°C (2-propanol). For $C_{27}H_{39}ClN_2O_5$ (507·1) calculated: 63·95% C, 7·75% H, 6·99% Cl, 5·52% N; found: 63·90% C, 7·50% H, 7·15% Cl, 5·50% N.

Methiodide (XXVII), m.p. 220–221°C (ethanol). IR spectrum: 698, 730 (5 adjacent Ar–H); 1 240, 1 730, 1 750 (RCOOR'); 1 690, 1 770 (CONCO of succinimide); 3 440 (OH). For $C_{28}H_{41}IN_2O_5$ (612·5) calculated: 54·90% C, 6·75% H, 20·72% I, 4·57% N; found: 54·96% C, 6·78% H, 20·73% I, 4·45% N.

2-(2-(2-Propyl)-1,3-dioxo-2,8-diazaspiro[4,5]decane-8-yl)ethyl (2-Oxo-1-pyrrolidinyl)acetate (*XXIV*)

(2-Oxo-1-pyrrolidinyl)acetic acid[12] (1·72 g) was transformed to the sodium salt by reaction with sodium 2-propoxide (from 0·3 g Na and 12 ml 2-propanol) and this was reacted with 3·0 g *XX* in 40 ml 2-propanol similarly like in the preceding cases. There were obtained 4·2 g (theoretical) of crude *XXIV*, m.p. 128–132°C. Analytical sample, m.p. 134–135°C (benzene–light petroleum). IR spectrum: 1 685, 1 752, 1 761 (CON of pyrrolidone and CONCO of succinimide); 2 745, 2 810 (CH_2–N). ^{1}H NMR spectrum (100 MHz): 1·30–2·30 m and 2·90 m, $\sum$ 10 H (CH_2CH_2.NCH_2CH_2 and 2 × H-4 of 2-pyrrolidone); 1·37 d, 6 H (2 × CH_3, J = 7·0); 2·44 t, 2 H ($COCH_2$ of 2-pyrrolidone); 2·49 s, 2 H (2 × H-4); 2·65 t, 2 H (NCH_2 outside of piperidine, J = 7·0); 3·52 t, 2 H (NCH_2 of pyrrolidone, J = 6·5); 4·09 s, 2 H ($OCCH_2N$); 4·26 t, 2 H (CH_2O, J = = 7·0); 4·40 m, 1 H (CHN). For $C_{19}H_{29}N_3O_5$ (379·4) calculated: 60·14% C, 7·70% H, 11·07% N; found: 60·27% C, 7·70% H, 11·07% N.

Hydrochloride, m.p. 208–210°C (2-propanol–ether). For $C_{19}H_{30}ClN_3O_5$ (415·9) calculated: 54·86% C, 7·27% H, 8·53% Cl, 10·10% N; found: 54·61% C, 7·22% H, 8·56% Cl, 10·20% N.

Methiodide (XXVIII), m.p. 184–186°C (ethanol). IR spectrum: 1 164, 1 235 (RCOOR'); 1 685, 1 750 (CON of pyrrolidone and CONCO of succinimide). For $C_{20}H_{32}IN_3O_5$ (521·4) calculated: 46·07% C, 6·19% H, 24·34% I, 8·06% N; found: 46·05% C, 6·22% H, 24·50% I, 7·93% N.

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