POTENTIAL NOOTROPIC AGENTS: SYNTHESIS OF SOME (2-OXO-1-PYRROLIDINYL)ACETAMIDES AND SOME RELATED COMPOUNDS

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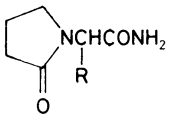
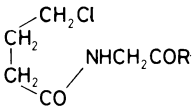
Ethyl (2-oxo-1-pyrrolidinyl)acetate was transformed by ester exchange to the 2-dimethylaminoethyl ester *VI* which was converted to the choline iodide ester *VII*. The mixed anhydride of (2-oxo-1-pyrrolidinyl)acetic acid and monoethyl carbonate was reacted with ethyl aminoacetate to give the ester *VIII* which was transformed on the one hand to the amide *IX*, and to the 2-dimethylaminoethyl ester *X* on the other. Reaction of the latter with methyl iodide afforded a further choline iodide ester *XI*. Reactions of (2-oxo-1-pyrrolidinyl)acetyl chloride with 4-chloroaniline and 3-aminopyridine gave the amides *XII* and *XIV*. The anilide *XIII* was obtained from 2-(2-oxo-1-pyrrolidinyl)butyric acid and 4-chloroaniline by means of dicyclohexylcarbodiimide. The benzo analogue (*XV*) of piracetam (*I*) was synthesized from oxindole via the ester *XVI*. The anilide *XII* (VÚFB-16 536) was found to potentiate significantly the anticonvulsant effect of diazepam in mice, to prolong the survival time of mice under conditions of nitrogen anoxia, and to prolong significantly the duration of the "gasping reflex" in mice.

A recent communication[1] described the synthesis of a series of (2-oxo-1-pyrrolidinyl)-acetic acid piperazides as potential nootropic agents and their pharmacological effects. The present communication represents a continuation of studies along the same line.

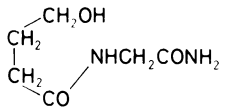
(2-Oxo-1-pyrrolidinyl)acetamide (*I*, piracetam, refs[2-4]) was the first compound of a series of nootropic 2-pyrrolidones. This compound has now been prepared by cyclization of *III* in ethanol at 50°C in the presence of sodium ethoxide which is one of the modifications of the procedure of the Yugoslav authors[5]. The starting *III* was prepared by a new two-step sequence consisting in reaction of ethyl 2-aminoacetate hydrochoride[6] with 4-chlorobutyryl chloride in benzene in the presence of aqueous sodium hydrogen carbonate and by the following ammonolysis of the obtained ester *IV* in methanol. The ester *IV* is a low-melting solid which was purified by distillation and characterized by the IR spectrum. The amide *III* was prepared earlier by different methods[5,7]. Compound *V* was prepared as an open model of *I* by heating glycinamide[8] with γ-butyrolactone to 120°C. It is a crystalline solid whose spectra were recorded.



I, R = H
II, R = C_2H_5

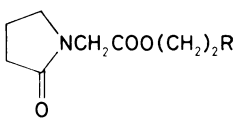


III, R = NH_2
IV, R = OC_2H_5

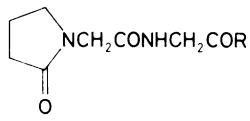


V

The memory deficits associated with aging seem to be related to the acetylcholine deficit in the brain (cf. ref.[9]). This led to the idea to combine the acetylcholine molecule with that of piracetam (*I*). Ethyl (2-oxo-1-pyrrolidinyl)acetate[10,11] was transformed by heating with 2-dimethylaminoethanol in boiling toluene in the presence of a catalytic amount of the corresponding sodium alkoxide to the 2-dimethylaminoethyl ester *VI*. The oily base was distilled in vacuo without decomposition, was characterized by spectra and transformed to crystalline salts, viz hydrochloride and hydrogen oxalate. Reaction of *VI* with methyl iodide in ethanol afforded the desired choline iodide ester *VII*. (2-Oxo-1-pyrrolidinyl)acetic acid[10,11] was reacted with ethyl chloroformate in chloroform in the presence of triethylamine and the mixed anhydride obtained was reacted "in situ" with ethyl aminoacetate giving 71% of *VIII* as an oily substance which could be distilled in vacuo without decomposition. On standing it slowly crystallized to give a homogeneous low-melting solid; ^{1}H NMR and IR spectra fully confirmed the identity. Treatment of *VIII* with ammonia in methanol without heating gave the amide *IX* which also was characterized by spectra. The ethyl ester *VIII* was subjected to transesterification with 2-dimethylaminoethanol in the presence of a catalytic amount of sodium methoxide. The resulting ester *X*



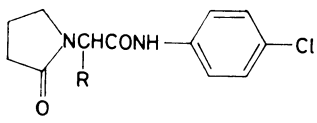
VI, R = $N(CH_3)_2$
VII, R = $\overset{(+)}{N}(CH_3)_3I^{(-)}$



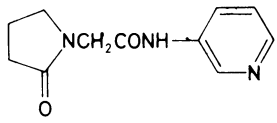
VIII, R = OC_2H_5
IX, R = NH_2
X, R = $OCH_2CH_2N(CH_3)_2$
XI, R = $OCH_2CH_2\overset{(+)}{N}(CH_3)_3I^{(-)}$

was oily and distilled with partial decomposition. It was isolated and characterized in the form of the crystalline hydrogen oxalate. The mass spectrum confirmed the expected elemental composition of the base and the structure was confirmed by the ^{1}H NMR and IR spectra. Reaction of the oily base *X* with methyl iodide in ethanol gave the methiodide *XI*, a further choline iodide ester encompassing the piracetam moiety.

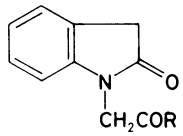
Reactions of the crude (2-oxo-1-pyrrolidinyl)acetyl chloride[12,13] with 4-chloroaniline and with 3-aminopyridine in benzene at 50–80°C gave the amides *XII* and *XIV*. In connection with etiracetam (*II*, ref.[14]), another experimental nootropic agent, the reaction of 2-(2-oxo-1-pyrrolidinyl)butyric acid[1] with 4-chloroaniline in the presence of dicyclohexylcarbodiimide in boiling chloroform was carried out and afforded the amide *XIII*. These amides are crystalline solids which were characterized by ^{1}H NMR and IR spectra. (2-Oxo-1-indolinyl)acetamide (*XV*) was synthesized as a benzo analogue of piracetam: Treatment of oxindole with sodium hydride in benzene, followed by ethyl chloroacetate gave the ester *XVI* (its synthesis by a different method was described[15]) which was subjected to ammonolysis in methanol giving *XV*.



XII, R = H
XIII, R = C_2H_5



XIV



XV, R = NH_2
XVI, R = OC_2H_5

The following compounds were pharmacologically tested: *V*, *VI* hydrochloride, *VI* hydrogen oxalate, *VII*, *IX*–*XIV*. Acute toxicity in mice, LD_{50} in mg/kg: *VI* hydrogen oxalate, about 600 i.v.; *VII*, about 7·5 i.v.; *IX*, 200 i.v., above 2 500 orally; *X*, about 900 i.v.; *XI*, 100 i.v.; *XII*, 25 i.v., 1 000 orally.

Anticonvulsant effect in the test of electroshock in mice: *V* in the oral dose of 10 mg/kg showed only mild protection from the lethal effect of the electroshock; *IX*, the oral dose of 200 mg/kg is devoid of the anticonvulsant effect; *XII*, 200 mg/kg p.o., mild anticonvulsant effect. Potentiation of the anticonvulsant effect of diazepam (ED_{50} 2·5 mg/kg p.o.): Diazepam + 200 mg/kg of *IX* p.o., ED_{50} 0·82 mg/kg; diazepam + 200 mg/kg of *XII* p.o., ED_{50} 0·05 mg/kg.

Influence on the spontaneous locomotor activity of mice in the photo-cell method of Dews: Doses of 100–150 mg/kg of *VI* s.c. and 10 mg/kg of *IX* p.o. significantly inhibit the activity; *XII* in the oral dose of 10 mg/kg in the intervals of 1 and 3 h after the administration was inactive. Compound *IX* in the oral dose of 300 mg/kg significantly prolonged the duration of the thiopental sleeping time in mice. Compounds *VI* (hydrogen oxalate), *X*, and *XI* in s.c. doses of 100 mg/kg did not influence

the body temperature of mice. Compound *X* (dose of 100 mg/kg s.c. administered daily in four days) potentiated mildly the hypothermia elicited by L-DOPA (50 mg/kg) + benserazide (25 mg/kg) but did not influence the hypothermia induced by apomorphine (1·25 mg/kg s.c.). Hydrogen oxalate of *VI* in doses of 100–150 mg/kg s.c. had significant anticataleptic effect in the test of perphenazine catalepsy in rats; piracetam (*I*) in the same doses had comparative effect. Compound *X* showed also a mild anticataleptic effect. This indicates for *VI* and *X* (together with the other findings) some influence on the dopaminergic system. Compound *VII* showed some myorelaxant effect on the rat gastrocnemius, ED = 15 mg/kg i.v.

In the test of passive avoidance in rats *VI* (hydrochloride) in s.c. doses of 40 mg/kg prolonged significantly the duration of the avoidance response which may be interpreted as a positive influence on the retention. In the test of nitrogen anoxia in mice, *XII* in the oral dose of 200 mg/kg in the interval of 1 h after the administration significantly prolonged the survival time; *IX* in the same dose was inactive. Influence on the duration of the "gasping reflex" in mice (acute brain ischemia induced by decapitation): *XII* prolonged the duration of the reflex significantly in the oral dose of 100 mg/kg (to 128% of the control (100%)) and in the oral dose of 300 mg/kg (to 169%); the effect of *IX* was not significant (the dose of 100 mg/kg p.o. prolonged to 113%).

In the line of biochemical pharmacology, no brain receptor affinities were found: 1,4-benzodiazepine receptors (influence on binding of 1 nM [^{3}H]flunitrazepam in the brain cortex) (*IX*, *XII*); muscarine receptors (influence on binding of 0·5 nM [^{3}H]-quinuclidinyl benzilate in the brain) (*IX*, *XII*, *XIV*); dopamine receptors (influence on binding of 0·5 nM [^{3}H]spiperone in the rat brain striatum) (*XII*); glutamate receptors in the membranes in the rat brain (inhibition of binding of 10 nM [^{3}H]-glutamate) (*XIV*).

In conclusion: Only compounds *IX* (VÚFB-16537) and *XII* (VÚFB-15536) showed interesting properties. Both of them potentiate significantly the anticonvulsant effect of diazepam (*XII* is very active) and *XII* prolonged greatly the survival time of mice in the test of nitrogen anoxia and significantly prolonged the duration of the "gasping reflex" in mice.

EXPERIMENTAL

The melting points of analytical samples were determined in the Kofler block and they are not corrected; the samples were dried in vacuo of about 60 Pa at room temperature or at a suitably elevated temperature. IR spectra (mostly in NUJOL, ν in cm^{-1}) were recorded with Unicam SP 200G or Perkin–Elmer 298 spectrophotometers, ^{1}H NMR spectra (in CD_3SOCD_3 unless stated otherwise, δ in ppm, J in Hz) on a CW-NMR spectrometer TESLA BS 487C (80 MHz) or on a FT-NMR spectrometer TESLA BS 567A (100 MHz), and the mass spectrum (m/z, fragments and %) on MCH 1320 and Varian MAT 44S (GC-MS) spectrometers. The homogeneity

of the substances and composition of the mixtures were checked by thin-layer chromatography (TLC) on silica gel (Silufol).

Ethyl 2-(4-Chlorobutyramido)acetate (*IV*)

A solution of 20·7 g 4-chlorobutyryl chloride in 120 ml benzene was slowly added at 10°C under vigorous stirring to a solution of 20·0 g ethyl 2-aminoacetate hydrochloride[6] and 30 g $NaHCO_3$ in 60 ml water. The mixture was stirred for 3 h at room temperature, the organic layer was washed with 10% $NaHCO_3$, 0·2M-tartaric acid, and water. After drying with $MgSO_4$ the solution was evaporated in vacuo and the residue was distilled; 24·1 g (81%) of *IV*, b.p. 131°C/40 Pa. The distillate slowly crystallized; m.p. 35·5–38·5°C (light petroleum). IR spectrum of the distillate (film): 1 030, 1 200, 1 743 (RCOOR'); 1 540, 1 655 (NHCO); 3 305 (NH). For $C_8H_{14}ClNO_3$ (207·7) calculated: 46·27% C, 6·79% H, 17·08% Cl, 6·74% N; found: 46·57% C, 6·79% H, 16·99% Cl, 6·57% N.

2-(4-Chlorobutyramido)acetamide (*III*)

A solution of 27·4 g *IV* in 270 ml methanol was saturated at 20°C for 4 h with NH_3. The mixture was stirred for 2 h at room temperature and was evaporated in vacuo. The residue was dissolved in 500 ml boiling acetone, the solution was filtered with active carbon and the filtrate was treated with 100 ml hexane. Crystallization gave 19·5 g (83%) of *III*, m.p. 132·5°C (ethyl acetate). IR spectrum: 1 546, 1 658 (RCONHR'); 1 645 ($RCONH_2$); 3 188, 3 320, 3 380 (NH and NH_2). ^{1}H NMR spectrum (100 MHz): 1·98 m, 2 H (CH_2 in the middle of butyryl); 2·32 bt, 2 H (CH_2CO of butyryl); 3·65 m, 4 H (CH_2Cl and NCH_2CO); 7·02 bs and 7·30 bs, 1 and 1 H (NH_2); 8·10 bt, 1 H (CONH). Refs[5,7], m.p. 128–130°C.

(2-Oxo-1-pyrrolidinyl)acetamide (*I*)

A solution of sodium ethoxide (0·7 g Na and 35 ml ethanol) was added dropwise at 25°C to a stirred solution of 5·36 g *III* in 210 ml ethanol and the mixture was stirred at 50°C for 8 h. The solution was filtered with 1 g active carbon through a 1 cm layer of Al_2O_3, the filtrate was evaporated in vacuo, and the residue was crystallized from 35 ml 2-propanol; 2·04 g (45%) of *I*, m.p. 150–153°C. IR spectrum: 1 413, 1 492, 1 662 ($CONH_2$); 1 699 (CON in the ring); 3 175, 3 350 (NH_2). ^{1}H NMR spectrum (80 MHz): 1·60–2·40 m, 4 H ($COCH_2CH_2$ of pyrrolidone); 3·28 t, 2 H (CH_2N of pyrrolidone); 3·69 s, 2 H (NCH_2CO); 7·00 bs and 7·30 bs, 1 and 1 H ($CONH_2$). Ref.[2], m.p. 151·5–152·5°C.

2-(4-Hydroxybutyramido)acetamide (*V*)

A mixture of 4·3 g γ-butyrolactone and 3·7 g glycinamide[8] was heated for 3 h to 110°C and for further 3 h to 120°C. After cooling the solidified melt was crystallized from 30 ml 2-propanol giving 3·9 g (55%) of *V*, m.p. 110–112°C (2-propanol). IR spectrum: 1 034, 1 060 (CH_2OH); 1 545, 1 640 (RCONHR'); 1 655 ($RCONH_2$); 3 196, 3 310, 3 379 (NH, NH_2). ^{1}H NMR spectrum (80 MHz): 1·63 m, 2 H (CH_2 in the middle of hydroxybutyryl); 2·14 t, 2 H (CH_2CO of hydroxybutyryl); 3·40 m, after D_2O t, 2 H (CH_2O); 3·60 d, after D_2O s, 2 H (NCH_2CO, $J = 6·0$); 4·49 bt, 1 H (OH); 7·00 bs and 7·25 bs, 1 and 1 H ($CONH_2$); 7·99 bt, 1 H (CONH, $J = 6·0$). For $C_6H_{12}N_2O_3$ (160·2) calculated: 44·99% C, 7·55% H, 17·49% N; found: 44·76% C, 7·33% H, 17·43% N.

2-Dimethylaminoethyl (2-Oxo-1-pyrrolidinyl)acetate (*VI*)

A stirred mixture of 100 ml toluene, 36 g 2-dimethylaminoethanol, and 0·1 g Na was treated with 36 g ethyl (2-oxo-1-pyrrolidinyl)acetate[10,11] and the mixture was slowly distilled through a column. The distillate was continually substituted by pure toluene. After 24 h the reaction mixture was evaporated in vacuo and the residue was distilled giving 21·3 g (47%) of almost homogeneous *VI* (according to gas-liquid chromatography the content of *VI* was 97%), b.p. 122–126°C/40 Pa. IR spectrum: 1 185, 1 289, 1 740 (RCOOR'); 1 675 (CON in the cycle); 2 770 (N–CH_3); 3 460 (?). ^{1}H NMR spectrum ($CDCl_3$, 80 MHz): 1·90–2·60 m, 6 H (CH_2 adjacent to dimethylamino and $COCH_2CH_2$ of pyrrolidone); 2·20 s, 6 H ($N(CH_3)_2$); 3·41 t, 2 H (CH_2N of pyrrolidone, J = 6·5); 4·03 s, 2 H (NCH_2CO); 4·17 t, 2 H ($COOCH_2$, J = 6·0). For $C_{10}H_{18}N_2O_3$ (214·3) calculated: 56·05% C, 8·47% H, 13·08% N; found: 56·35% C, 8·55% H, 13·20% N.

Hydrochloride, m.p. 159–161·5°C (ethanol–ether). IR spectrum: 1 162, 1 180, 1 190, 1 750 (RCOOR'); 1 675 (CON in the ring); 2 445, 2 515, 2 570 (NH^+). ^{1}H NMR spectrum (D_2O, 80 MHz): 2·10 m, 2 H (CH_2 in position 4 of 2-pyrrolidone); 2·45 bt, 2 H (CH_2 in position 3 of 2-pyrrolidone); 2·90 s, 6 H ($N^+(CH_3)_2$); 3·50 m, 4 H (CH_2 in position 5 of 2-pyrrolidone and $COOCH_2$); 4·18 s, 2 H (NCH_2CO); 4·50 m, 2 H (CH_2N^+). For $C_{10}H_{19}ClN_2O_3$ (250·7) calculated: 47·90% C, 7·64% H, 14·14% Cl, 11·18% N; found: 48·00% C, 7·76% H, 14·28% Cl, 11·25% N.

Hydrogen oxalate, m.p. 118–120°C (ethanol). For $C_{12}H_{20}N_2O_7$ (304·3) calculated: 47·36% C, 6·62% H, 9·21% N; found: 47·36% C, 6·87% H, 8·97% N.

Methiodide VII was prepared by 48 h standing of a mixture of 9·64 g *VI*, 30 ml ethanol, and 6·4 g methyl iodide. There crystallized 14·3 g *VII*, m.p. 113·5–115·5°C. Further crystallization from a mixture of ethanol, acetone, and ether did not lead to raising of the melting point. IR spectrum: 1 200, 1 745 (RCOOR'); 1 665 (RCON in the ring). For $C_{11}H_{21}IN_2O_3$ (356·2) calculated: 37·09% C, 5·94% H, 35·63% I, 7·87% N; found: 36·80% C, 5·99% H, 35·93% I, 7·66% N.

Ethyl ((2-Oxo-1-pyrrolidinyl)acetamido)acetate (*VIII*)

A suspension of 21·6 g (2-oxo-1-pyrrolidinyl)acetic acid[10,11] in 150 ml chloroform was treated under stirring and cooling (10°C) with 17·7 g triethylamine, added dropwise. The mixture was cooled to −7°C and was treated under stirring over 45 min at −7–−5°C with a solution of 18·9 g ethyl chloroformate in 40 ml chloroform. The mixture was stirred for 45 min at −5°C and was treated over 1 h with a solution of ethyl aminoacetate, which was prepared from 23·1 g ethyl aminoacetate hydrochloride[6] and 17·7 g triethylamine in 150 ml chloroform. Stirring at −5°C was continued for 30 min and the mixture was allowed to stand overnight at room temperature. It was then washed with water, dried over $MgSO_4$, evaporated in vacuo, and the residue was distilled; 12·1 g (71%) of almost homogeneous *VIII*, b.p. 165–168°C/40 Pa. The distillate crystallized on standing, m.p. 56–58°C (cyclohexane–hexane). IR spectrum: 1 200, 1 742 (RCOOR'); 1 545, 1 656 (RCONHR'); 1 680 (CON in the ring); 3 265 (NH). ^{1}H NMR spectrum ($CDCl_3$, 80 MHz): 1·30 t, 3 H (CH_3, J = 7·0); 1·80–2·40 m, 4 H (2 × CH_2 in positions 3 and 4 of 2-pyrrolidone); 3·52 bt, 2 H (CH_2 in position 5 of 2-pyrrolidone); 3·97 d, 2 H (NCH_2·.COO); 4·00 s, 2 H (NCH_2CO); 4·20 q, 2 H ($COOCH_2$, J = 7·0); 7·15 bt, 1 H (NH). For $C_{10}H_{16}N_2O_4$ (228·3) calculated: 52·62% C, 7·07% H, 12·27% N; found: 52·43% C, 7·15% H, 12·31% N.

((2-Oxo-1-pyrrolidinyl)acetamido)acetamide (*IX*)

A solution of 9·3 g *VIII* in 200 ml methanol was saturated for 25 min with NH_3. The mixture was heated for 1 h to 45°C and allowed to stand overnight at room temperature. Methanol was evaporated in vacuo and the residue was crystallized from 150 ml 2-propanol (filtration of the hot solution with active carbon through a 1 cm-layer of Al_2O_3); 6·5 g (79%) of *IX*, m.p. 144·5 to 146·5°C (2-propanol). IR spectrum: 1 570, 1 670 (RCONHR'); 1 655 (CON in the ring); 1 706 ($RCONH_2$); 3 190, 3 320, 3 360 (NH, NH_2). ^{1}H NMR spectrum (80 MHz): 1·70—2·40 m, 4 H (2 × CH_2 in positions 3 and 4 of 2-pyrrolidone); 3·30 bt, 2 H (CH_2 in position 5 of 2-pyrrolidone); 3·63 d, 2 H (NCH_2CON of the terminal aminoacetamide, J = 6·0); 2·85 s, 2 H (remaining NCH_2CON); 7·02 bs and 7·30 bs, 1 and 1 H ($CONH_2$); 8·10 bt, 1 H (NH). For C_8H_{13}. .N_3O_3 (199·2) calculated: 48·23% C, 6·58% H, 21·09% N; found: 48·08% C, 6·68% H, 20·98% N.

2-Dimethylaminoethyl ((2-Oxo-1-pyrrolidinyl)acetamido)acetate (*X*)

A mixture of 10·2 g *VIII*, 18·0 g 2-dimethylaminoethanol, and 0·1 g sodium methoxide was stirred for 6·5 h at 110—115°C. It was then diluted with 100 ml toluene which was slowly distilled off through a column. The residue was then diluted with 50 ml xylene which was also slowly distilled off affording 12·2 g (theoretical) of the crude oily *X*. It was dissolved in a mixture of 40 ml acetone and 5 ml ethanol and the solution was neutralized with a solution of 5·7 g oxalic acid dihydrate in 30 ml acetone. The separated semi-solid salt was isolated by decantation, dissolved in 10 ml dimethylformamide and the cooled solution was induced to crystallize by slow addition of 35 ml acetone. After 4 days standing the crystalline hydrogen oxalate of *X* was filtered; 10·5 g (64%), m.p. 119—122°C (2-propanol). Mass spectrum: 271 (M^+, $C_{12}H_{21}N_3O_4$, 0·3), 201 (1), 98 (C_5H_8NO, 10), 58 (100). IR spectrum: 1 180 (C–O); 1 550, 1 658 (RCONHR'); 1 689 (CON in the ring); 1 745 (RCOOR'); 2 500, 2 660, 2 720 (NH^+); 3 035, 3 275 (NH). ^{1}H NMR spectrum (D_2O, 80 MHz): 2·12 m, 2 H (CH_2 in position 4 of 2-pyrrolidone); 2·50 bt, 2 H (CH_2 in position 3 of 2-pyrrolidone); 2·95 s, 6 H ($N^+(CH_3)_2$); 3·50 m, 4 H (CH_2 in position 5 of 2-pyrrolidone and CH_2N^+); 4·10 s, 4 H ($NCH_2CONHCH_2COO$); 4·50 m, 2 H ($COOCH_2$). For $C_{14}H_{23}N_3O_8$ (361·3) calculated: 46·53% C, 6·42% H, 11·63% N; found: 46·34% C, 6·54% H, 12·02% N.

Methiodide (XI), m.p. 143—145·5°C (ethanol–acetone–ether). IR spectrum: 1 180, 1 759 (RCOOR'); 1 528, 1 670 (RCONHR' and CON in the ring); 3 245, 3 430 (NH). ^{1}H NMR spectrum (80 MHz): 2·05 m, 2 H (CH_2 in position 4 of 2-pyrrolidone); 2·25 bt, 2 H (CH_2 in position 3 of 2-pyrrolidone); 3·20 s, 9 H ($N^+(CH_3)_3$); 3·20—4·70 m, 10 H (remaining 5 × CH_2). For $C_{13}H_{24}IN_3O_4$ (413·3) calculated: 37·78% C, 5·85% H, 30·71% I, 10·17% N; found: 37·84% C, 5·99% H, 30·94% I, 10·16% N.

N-(4-Chlorophenyl)-(2-oxo-1-pyrrolidinyl)acetamide (*XII*)

A solution of 3·0 g crude (2-oxo-1-pyrrolidinyl)acetyl chloride[12,13] in 10 ml benzene was added dropwise over 3 min to a stirred solution of 5·1 g 4-chloroaniline in 10 ml benzene and the mixture was stirred for 1 h at 50°C. After cooling it was diluted with 50 ml benzene, the mixture was washed three times with 12 ml 1M-HCl and with water, it was dried with $MgSO_4$ and evaporated. The solid residue (4·6 g, 91%) was the crude *XII* which was purified by crystallization from ethanol; m.p. 222—222·5°C. IR spectrum: 800, 825, 840 (2 adjacent Ar–H); 1 490, 1 595 (Ar); 1 555, 1 670 (CONHAr); 1 700 (CON in the ring); 3 075, 3 130, 3 200, 3 270, 3 320 (NH). ^{1}H NMR spectrum (80 MHz): 1·95 m, 2 H (CH_2 in position 4 of 2-pyrrolidone); 2·13 t, 2 H (CH_2 in position 3 of 2-pyrrolidone, J = 7·0); 3·39 t, 2 H (CH_2 in position 5 of 2-pyrrolidone,

J = 7·0); 4·00 s, 2 H (NCH_2CO); 7·29 d, 2 H (H-3 and H-5 of 4-chlorophenyl, J = 8·5); 7·60 d, 2 H (H-2 and H-6 of 4-chlorophenyl, J = 8·5); 11·90 bs, 1 H (CONH). For $C_{12}H_{13}ClN_2O_2$ (252·7) calculated: 57·03% C, 5·18% H, 14·03% Cl, 11·09% N; found: 56·74% C, 5·35% H, 14·30% Cl, 11·14% N.

N-(3-Pyridyl)-(2-oxo-1-pyrrolidinyl)acetamide (*XIV*)

A solution of 11·5 g crude (2-oxo-1-pyrrolidinyl)acetyl chloride[12,13] in 30 ml benzene was added dropwise over 30 min to a stirred solution of 13·2 g 3-aminopyridine in 40 ml benzene at 60°C. The mixture was stirred for 30 min at this temperature and refluxed for 1·5 h. After cooling the precipitated solid was filtered off, washed with benzene and light petroleum, and the filtrate was evaporated in vacuo. The inhomogeneous residue was chromatographed on 400 g silica gel. The first chloroform eluates were discarded; further eluates gave 10·0 g (66%) of crystalline *XIV* which was purified by crystallization from a mixture of ethanol and cyclohexane, m.p. 180 to 180·5°C. IR spectrum: 710, 810, 915 (3 adjacent and solitary Ar–H); 1 480, 1 490, 1 553, 1 606, 3 000, 3 080, 3 100, 3 128, 3 188, 3 240, 3 262, 3 310 (NH); 1 662, 1 700 (CON in the ring). ^{1}H NMR spectrum ($CDCl_3$, 100 MHz): 2·15 m, 2 H (CH_2 in position 4 of 2-pyrrolidone); 2·48 t, 2 H (CH_2 in position 3 of 2-pyrrolidone); 3·62 t, 2 H (CH_2 in position 5 of 2-pyrrolidone); 4·14 s, 2 H (NCH_2CO); 7·22 dd, 1 H (H-5 of pyridyl, J = 8·0; 5·0); 8·09 m, 1 H (H-4 of pyridyl, J = 8·0); 8·32 dd, 1 H (H-6 of pyridyl, J = 5·0; 1·0); 8·63 d, 1 H (H-2 of pyridyl, J = 2·5); 9·80 bs, 1 H (CONH). For $C_{11}H_{13}N_3O_2$ (219·2) calculated: 60·26% C, 5·98% H, 19·17% N; found: 59·98% C, 6·07% H, 18·90% N.

N-(4-Chlorophenyl)-2-(2-oxo-1-pyrrolidinyl)butyramide (*XIII*)

A solution of 5·13 g 2-(2-oxo-1-pyrrolidinyl)butyric acid[1] and 3·83 g 4-chloroaniline in 35 ml chloroform was treated with 6·2 g dicyclohexylcarbodiimide, the mixture was stirred for 1 h at room temperature and then refluxed for 3 h. After standing overnight the precipitated solid was filtered off, the filtrate was washed with dilute hydrochloric acid and water, dried, and evaporated. The crystalline residue (5·84 g, 69%) was the almost homogeneous *XIII* which was purified by crystallization from a mixture of 2-propanol and hexane, m.p. 118–122°C. IR spectrum: 783, 816, 839 (2 adjacent Ar–H); 1 490, 1 537, 1 594, 1 603, 3 052 (Ar); 1 660 (CON in the ring); 1 690 (RCONHAr); 3 110, 3 186, 3 255, 3 300 (NH). ^{1}H NMR spectrum ($CDCl_3$, 100 MHz): 0·93 t, 3 H (CH_3, J = 7·0); 1·80 m, 2 H (CH_2 of ethyl); 2·10 m, 2 H (CH_2 in position 4 of 2-pyrrolidone); 2·48 bt, 2 H (CH_2 in position 3 of 2-pyrrolidone); 3·52 m, 2 H (CH_2 in position 5 of 2-pyrrolidone); 4·65 t, 1 H (NCHCO, J = 8·0); 7·27 d, 2 H (H-3 and H-5 of 4-chlorophenyl, J = 8·5); 7·56 d, 2 H (H-2 and H-6 of 4-chlorophenyl, J = 8·5); 9·18 bs, 1 H (CONH). For $C_{14}H_{17}ClN_2O_2$ (280·8) calculated: 59·88% C, 6·10% H, 12·63% Cl, 9·98% N; found: 59·58% C, 6·11% H, 12·57% Cl, 9·83% N.

Ethyl (2-Oxo-1-indolinyl)acetate (*XVI*)

A solution of 10·0 g oxindole in 100 ml benzene was stirred and treated at 50°C with 2·0 g 80% NaH (suspension in oil). At 60–70°C the stirred mixture was treated over 1·5 h with a solution of 9·75 g ethyl chloroacetate in 10 ml benzene. After refluxing for 5 h the mixture was cooled, washed with 1M-NaOH and water, dried with $MgSO_4$, and evaporated in vacuo. The inhomogeneous residue (5·5 g) was chromatographed on 200 g neutral Al_2O_3 (activity II). Evaporation of the benzene eluates gave 2·8 g (17%) of crude *XVI* which was purified by crystallization from a mixture of cyclohexane and ethanol, m.p. 125–127·5°C. ^{1}H NMR spectrum ($CDCl_3$, 80 MHz):

1·25 t, 3 H (CH_3, J = 7·0); 3·55 bs, 2 H (2 × H-3 of oxindole); 4·20 q, 2 H ($COOCH_2$, J = 7·0); 4·45 s, 2 H (NCH_2CO); 6·60–7·40 m, 4 H (4 × ArH). Ref.[15], m.p. 128–129°C.

(2-Oxo-1-indolinyl)acetamide (*XV*)

A solution of 2·2 g *XVI* in 75 ml methanol was saturated for 3 h with NH_3 at 30–35°C. It was stirred for 2 h at room temperature, allowed to stand overnight, and methanol was evaporated. The residue was chromatographed on 120 g neutral Al_2O_3 (activity II). Elution with chloroform and with a mixture of chloroform and methanol (1 : 1) gave 1·35 g (71%) of crude crystalline *XV* which was purified by crystallization from methanol, m.p. 231·5–233·5°C. IR spectrum (KBr): 760 (4 adjacent Ar–H); 1 490, 1 616 (Ar); 1 683 ($RCONH_2$); 1 714 (CON in the ring); 3 110, 3 270 (NH_2). ^{1}H NMR spectrum (80 MHz, 50°C): 3·60 s, 2 H (2 × H-3 of oxindole); 4·28 s, 2 H (NCH_2CO); 6·80–7·40 m, 4 H (4 × ArH); 7·40 bs, 2 H ($CONH_2$). For $C_{10}H_{10}N_2O_2$ (190·2) calculated: 63·14% C, 5·30% H, 14·73% N; found: 63·34% C, 5·40% H, 15·50% N.

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