SYNTHESIS OF 7-CHLORO-5-(6,7,8,9-TETRAHYDRO--5*H*-BENZOCYCLOHEPTEN-2-YL)-2-METHYLAMINO-3*H*-1,4-BENZODIAZEPINE 4-OXIDE AND OF SOME RELATED COMPOUNDS*

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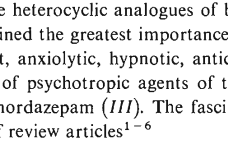
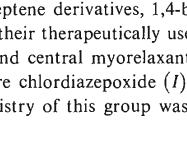
The base catalyzed condensation of 4-chloronitrobenzene with 2-(cyanomethyl)-6,7,8,9-tetrahydro--5*H*-benzocycloheptene afforded the 2,1-benzisoxazole derivative *VIa* which was reduced with iron in acetic acid to the 2-aminophenone *VIIa*. Its oxime *IXa* was treated with chloroacetyl chloride in acetic acid and gave the 4-substituted 6-chloro-2-chloromethylquinazoline 3-oxide (*Xa*). The treatment with methylamine in methanol led to the substitution reaction with a simultaneous ring enlargement and the title compound *IVa* was formed. A similar reaction with 1-methylpiperazine proceeded without rearrangement resulting in the quinazoline *XIa*. The object of further experiments was the preparation of the lactam *Va*, the norpethidine derivative *XV* and some new approaches to intermediates useful in the synthesis of 5-(2-chlorophenyl)-7-ethyl-1,3-dihydrothieno[2,3-*e*]-1,4-diazepin-2-ones.

Out of the heterocyclic analogues of benzocycloheptene derivatives, 1,4-benzodiazepines attained the greatest importance because of their therapeutically useful central depressant, anxiolytic, hypnotic, anticonvulsant and central myorelaxant activities; examples of psychotropic agents of this group are chlordiazepoxide (*I*), diazepam (*II*) and nordazepam (*III*). The fascinating chemistry of this group was treated in a series of review articles[1-6]



I

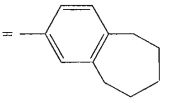


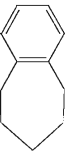
II, R = CH_3
III, R = H

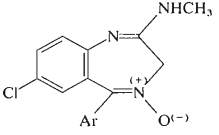
* Part XIV in the series Benzocycloheptenes and Heterocyclic Analogues as Potential Drugs; Part XIII: This Journal *40*, 1623 (1975).

The object of the first part of the present communication was an investigation of the influence of introducing a benzocycloheptene residue as aryl to position 5 of the 1,4-benzodiazepine skeleton on the activity. In the first line, it was necessary to prepare 5-(6,7,8,9-tetrahydro-5*H*-benzocycloheptene-2-yl) derivatives *IVa* and *Va*, *i.e.* analogues of chlordiazepoxide (*I*) and nordazepam (*III*). 6,7,8,9-Tetrahydro-5*H*-benzocycloheptene-2-acetonitrile[7], successfully used in one of the preceding communications of this series[8], was considered a suitable starting compound for our purpose. The starting step was a base catalyzed reaction of this nitrile with 4-chloronitrobenzene. It is known that some *para*-substituted nitrobenzene derivatives react with phenylacetonitrile and some of its derivatives in methanolic solutions of sodium or potassium hydroxides under the formation of 5-substituted 3-aryl-2,1-benzisoxazoles (ref.[9,10]). Especially well developed was the reaction of 4-chloronitrobenzene with phenylacetonitrile in methanolic sodium hydroxide[11] affording in an almost theoretical yield 5-chloro-3-phenyl-2,1-benzisoxazole which represent the basis of most of the recent manufacturing processes leading to psychotropic agents containing the 7-chloro-5-phenyl-1,4-benzodiazepine fragment. In our case, some 70% of a yellow product of the expected composition were obtained to which the structure of 5-chloro-3-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-yl)-2,1-benzisoxazole (*VIa*) could be assigned, confirmed in principle by the spectra recorded. Its infrared spectrum, however, shows in the region of out-of-plane vibrations of the aromatic C—H bonds a surprising band at 773 cm^{-1} which indicated a contamination of our product with an isomer with three adjacent hydrogen atoms in one aromatic nucleus. The used 6,7,8,9-tetrahydro-5*H*-benzocycloheptene-2-acetonitrile could be the only source of an impurity of this type; it was prepared from 6,7,8,9-tetrahydro-5*H*-benzocycloheptene by chloromethylation and by the following reaction with potassium cyanide[7]. The paper, according to which the intermediate of our work was prepared[7], supposed an unequivocal course of the chloromethylation reaction in position 2 of the tetrahydrobenzocycloheptene skeleton. More recent papers[12,13] dealing with this topic are more careful in the mentioned line: French authors[12] presented proof of the fact that under their experimental conditions, the product of chloromethylation of tetrahydrobenzocycloheptene contained in addition to 95% 2-chloromethyl derivative some 5% 1-chloromethyl compound; soviet authors[13] characterized their product of a similar reaction as consisting "mainly" of the 2-chloromethyl derivative. It is possible that the product prepared by us contained a higher percentage of the 1-chloromethyl compound than stated by the French authors[12]. We have thus to presume that our compound *VIa* is contaminated with a small amount of the isomer *VIb*. A similar presumption has to be considered for most of the further compounds prepared: they belong in principle to the "*a*" series but contain small amounts of isomers of the "*b*" series.

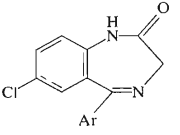
In formulae *IV* – *XIII*

a, Ar = 

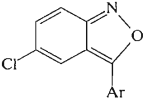
b, Ar = 



IV

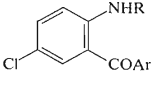


V

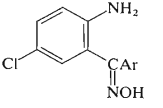


VI

The corresponding 2-aminobenzophenones[14] are the key intermediates in the synthesis of 5-aryl-1,4-benzodiazepines. They are accessible from 3-aryl-2,1-benzisoxazoles on the one hand by reduction with a combination of metals with acids[15,16], on the other by catalytic hydrogenation on palladium[17]. The reduction of compound *VIa* was carried out with iron and acetic acid and gave the amino ketone *VIIa*. This product was transformed to the oxime *IXa* (probably a mixture of the *syn*- and *anti*-isomer).



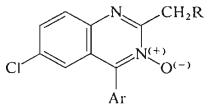
VII, R = H
VIII, R = $COCH_2Cl$



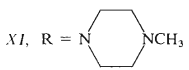
IX

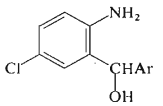
In further steps, an analogy to the classical Sternbach's chlordiazepoxide (*I*) synthesis[18,19] was used. Treatment of the crude oxime *IXa* with chloroacetyl chloride in acetic acid resulted in an aromatic N-oxide (ν(NO) 1290 cm^{-1}), corresponding by composition and spectra to the expected structure of 6-chloro-2-(chloromethyl)-4-(6, 7, 8, 9-tetrahydro-5*H*-benzocyclohepten-2-yl)quinazoline 3-oxide (*Xa*). The following reaction with a methanolic solution of methylamine effected the substitution and simultaneously the ring enlargement leading to the title compound *IVa*. Its IR spectrum shows bands at 1593 and 1628 cm^{-1} corresponding approximately to Sternbach's data[19] for the rearranged products and differing from positions of bands described for substitution products without rearrangement. A product of

the last mentioned type is evidently our next compound obtained by reaction of compound *Xa* with 1-methylpiperazine in methanol; structure *XIa* was assigned to this product. It is in complete agreement with literature reports[19,20] according to which reactions of this type with secondary amines (piperazine, 1-methylpiperazine) proceed without rearrangement; the bands at 1 550 and 1 600 cm^{-1} in the IR spectrum of our product are also in agreement with the assigned structure *XIa*.



X, R = Cl



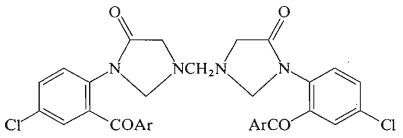


XII

Analogy of a further Sternbach's method[21], consisting in a reaction of the corresponding 2-aminobenzophenone with ethyl aminoacetate in boiling pyridine, was used in an attempt to prepare the lactam *Va*. When our compound *VIIa* was used, the described reaction gave a crystalline product which did not correspond analytically to the composition expected for *Va* and whose ^{1}H-NMR spectrum was more complicated than expected for *Va*. The problem was solved by the mass spectrum which showed that the substance consists of two components with empirical formulae $C_{20}H_{19}ClN_2O$ and $C_{18}H_{18}ClNO$. Whereas the first formula corresponds to the desired lactam *Va*, the second one represents the composition of the starting amino ketone *VIIa*; the spectrum simultaneously excluded the possibility that the mentioned components could be fragments of a molecule corresponding to the sum of the formulae given. On the other hand, the analysis is in full agreement with this sum. Because the compound behaves like a homogeneous substance, we had to conclude that we are dealing here with a molecular complex of the lactam *Va* and the starting amino ketone *VIIa*. The ^{1}H-NMR spectrum is in full accord with this structure assignment. Reduction of this complex with lithium aluminium hydride in a mixture of tetrahydrofuran and ether gave a substance $C_{18}H_{20}ClNO$ which proved identical with the product of a similar reduction of the ketone *VIIa*, *i.e.* we are dealing here with the benzhydrol derivative *XIIa* which was confirmed by the spectra recorded.

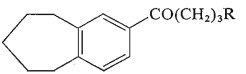
An additional attempt at preparing the lactam *Va* by an alternative route was undertaken using a reaction of the corresponding halogenoacetamidobenzophenone with hexamethylenetetramine (for analogy, *cf.*[22]). The amino ketone *VIIa* was transformed

by treatment with chloroacetyl chloride in chloroform to the chloroacetamido ketone *VIIIa* and this was subjected to treatment with hexamethylenetetramine in boiling ethanol. A crystalline product was obtained, the molecule of which lacks – according to the IR and ^{1}H-NMR spectra – the presence of the expected NH group and instead of one carbonyl function, it contains two different ones, one of which corresponding to a diaryl ketone and the second one to a N-substituted lactam with a five-membered ring. The structure elucidation was helped by an investigation of the Yugoslavian authors[23] who described that the transformation of *o*-(chloroacetamido)benzophenones to 5-aryl-1,3-dihydro-1,4-benzodiazepin-2-ones proceeds smoothly only with N-methylated compounds. With compounds containing the fragment NHCO, the reaction sequence shows the tendency to stop at the stage of one of the two intermediates containing a 4-imidazolidone residue in their molecules. For our case, *i.e.* with the absence of NH, only the structure *XIIIa* with a doubled molecule and three diaminomethane fragments in the chain $NCH_2NCH_2NCH_2N$ has to be considered. This structure is fully supported by the ^{1}H-NMR and IR spectra.

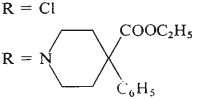


XIII

Janssen's report[24] stating that 1-(3-benzoylpropyl)-4-(ethoxycarbonyl)-4-phenylpiperidine was found to possess mixed morphine-like and chlorpromazine-like properties induced us to prepare the tetrahydrobenzocycloheptene analogue *XV*. A Friedel–Crafts reaction of 6,7,8,9-tetrahydro-5*H*-benzocycloheptene[25] with 4-chlorobutyryl chloride gave the chloro ketone *XIV* (a weak band in the IR spectrum at 750 cm^{-1} indicates again a slight contamination with a position isomer), transformed by a substitution reaction with 4-(ethoxycarbonyl)-4-phenylpiperidine[26] in dimethylformamide and in the presence of potassium carbonate to the desired amino ketone *XV*.

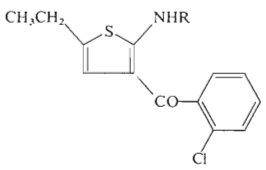


XIV, R = Cl

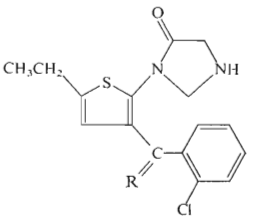


XV, R = N

The last part of this communication describes our experience with the synthesis of 5-(2-chlorophenyl)-7-ethyl-1-methyl-1,3-dihydrothieno[2,3-*e*]-1,4-diazepin-2-one, known as the anxiolytic and anticonvulsant agent "clothiazepam" (Y-6047) (ref.[27–29]), needed as a standard for comparison. The synthesis of this compound was described by Nakanishi and coworkers[30]. Following the work of these authors[30], we carried out the reaction of 2-chlorobenzoylacetonitrile with butyraldehyde and sulfur in dimethylformamide in the presence of triethylamine and obtained 2-amino--3-(2-chlorobenzoyl)-5-ethylthiophene (*XVI*) which is the key intermediate in the clothiazepam synthesis. The starting 2-chlorobenzoylacetonitrile was obtained by acylation of acetonitrile with ethyl 2-chlorobenzoate[31] in the presence of sodium hydride in tetrahydrofuran; the literature[32] reported its synthesis by a different method and our procedure was an analogy of a method, described for the preparation of 4-chlorobenzoylacetonitrile[33]. The amino ketone *XVI* was then transformed ac-



XVI, R = H
XVII, R = $COCH_2Cl$
XVIII, R = $COCH_2NH_2$



XIX, R = =O
XX, R = H, OH

cording to Nakanishi[30] to the N-(chloroacetyl) derivative *XVII* which was subjected to treatment with hexamethylenetetramine in boiling ethanol in order to get directly 5-(2-chlorophenyl)-7-ethyl-1,3-dihydrothieno[2,3-*e*]-1,4-diazepin-2-one in analogy to the report of the Yugoslavian authors[22]. Neither in this case were we able to prepare the desired product and it was again confirmed that the hexamethylenetetramine method[22] is not suitable to synthesis of compounds containing the fragment NHCO, *i.e.* free of the alkyl in position 1 of the skeleton. Our product was identified by analysis and the ^{1}H-NMR spectrum again as a 4-imidazolidone derivative but containing this time the NH group and only one diaminomethane fragment NCH_2NH, *i.e.* as compound *XIX*. It is a thiophene analogue of a compound described by the Yugoslavian authors[23] as a further intermediate of the reaction sequence leading from 5-chloro-2-(chloroacetamido)benzophenone to nordazepam (*III*). Reduction of this compound with sodium borohydride in ethanol, with avoiding the contact of the pro-

duct with acid, gave the secondary alcohol *XX* with the untouched 4-imidazolidone fragment. Hydrolysis of compound *XIX* with hydrochloric acid in aqueous ethanol gave the amino ketone *XVIII*, the characterization of which was completed by recording the spectra and preparation of a crystalline hydrochloride; the compound was prepared by two other methods by the Nakanishi team[30]. Two described steps[30] were then used to prepare the desired sample of clothiazepam.

Compounds *IV* (VÚFB-9444), *XI* (dihydrochloride hydrate VÚFB-9507) and *XV* (hydrochloride VÚFB-9999) were subjected to an orientation pharmacological evaluation (Dr A. Dlabač and Dr J. Metyš) pharmacological department of this institute; Dr J. Němec, affiliated unit of this institute at Rosice n/L). Compound *IV* proved nontoxic for mice until an oral dose of 4 g/kg and in a high dose of 1 g/kg, it was inactive as an anticonvulsant in mice towards pentetrazole convulsions. Compound *XI* has an acute toxicity in mice, LD_{50} = 820 mg/kg orally. It has a mild central depressant effect in the rota-rod test in mice (ED_{50} = 260 mg/kg orally) and a mild anticolvulsant effect. Towards pentetrazole convulsions in mice, the medium effective dose ED_{50} = 110 mg/kg orally (for diazepam, ED_{50} = 0·9 mg/kg); in the test of corneal electroshock, ED_{50} = 220 mg/kg orally. Compound *XV* has an acute toxicity in mice, LD_{50} = 2 g/kg orally. In the Haffner test in mice, it is analgetically inactive in an oral dose of 100 mg/kg; in the hot-plate test in mice, there is an indication of activity but the ED_{50} is higher than 100 mg/kg orally.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samplex were dried *in vacuo* of about 70 Pa over P_2O_5 at room temperature or at 100°C. The UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (in Nujol unless stated otherwise) with a Unicam SP 200G spectrophotometer, the ^{1}H-NMR spectra in $CDCl_3$ with a ZKR-60 (Zeiss, Jena) spectrometer (unless stated otherwise) and the mass spectrum with a MS 902 (AEI) spectrometer. The homogeneity of the compounds was checked on thin layers of silica gel.

5-Chloro-3-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-yl)-2,1-benzisoxazole (*VIa*)

A solution of 35·6 g 4-chloronitrobenzene and 44·0 g 6,7,8,9-tetrahydro-5*H*-benzocycloheptene-2-acetonitrile[7] in 100 ml benzene was added over 100 min to a stirred solution of 81 g powdered NaOH in 270 ml methanol at 25-30°C. The mixture was stirred for 2 h at 25°C and poured slowly into a mixture of a solution of 108 g NH_4Cl in 700 ml H_2O and 150 ml benzene. After shaking, the organic layer was separated and the aqueous one extracted with benzene. Benzene solutions were combined, dried with $CaCl_2$, filtered with charcoal and the filtrate evaporated under reduced pressure. The residue was crystallized from a mixture of benzene and benzine; 35·8 g (68%), m.p. 135—137°C. Analytical sample, m.p. 141—142°C (benzene–benzine). UV spectrum: λ_{max} 254 nm (log ε 4·16), 263 nm (4·22), 360 nm (4·25). IR spectrum: 773 (3 adjacent Ar—H, *cf. VIb*), 805, 820, 860, 890 (2 adjacent and solitary Ar—H), 1 060 (—O— in a ring), 1 502, 1 550 (Ar), 1 627 cm^{-1} (C=N). ^{1}H-NMR spectrum: δ 6·95—7·95 (m, 6 H, Ar—H), 2·60—3·05 (m, 4 H, CH_2ArCH_2), 1·80—2·05 (m, 6 H, remaining 3 CH_2). For $C_{18}H_{16}ClNO$ (297·8) calculated: 72·60% C, 5·41% H, 11·91% Cl, 4·70% N; found: 72·74% C, 5·63% H, 12·05% Cl, 5·02% N.

2'-Amino-5'-chlorophenyl 6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-2-yl Ketone (*VIIa*)

VIa (35 g) was added at 65°C to a mixture of 16·5 g Fe, 28 ml ethanol, 17 ml H_2O and 50 ml acetic acid and the mixture was refluxed for 2 h. After addition of 110 ml benzene, the hot mixture was filtered with suction and the solid washed with 220 ml boiling benzene. The cooled filtrate was washed with H_2O and 5% Na_2CO_3 solution, dried with $CaCl_2$, filtered and evaporated. The residue was crystallized from 200 ml heptane; 34·0 g (97%), m.p. 130–132°C. Analytical sample, m.p. 134–135°C (heptane). UV spectrum: λ_{max} 232·5 nm (log ε 4·41), 263 nm (3·89), 388 nm (3·83). IR spectrum: 720, 750, 780, 794 (3 adjacent Ar—H, *cf VIIb*), 815, 820, 879, 890 (2 adjacent and solitary Ar—H), 1250 (CO, NH_2), 1540, 1589 (Ar), 1622 (CO—H_2N), 3323, 3433 cm^{-1} (NH_2). ^{1}H-NMR spectrum: δ 6·60 (d, J = 9·0 Hz, 1 H, 3'-H), 7·00–7·50 (m, 5 H, remaining Ar—H), 5·92 (bs, disappears after D_2O, 2 H, NH_2), 2·85 (d, 4 H, CH_2ArCH_2), 1·75 (m, 6 H, remaining 3 CH_2). For $C_{18}H_{18}ClNO$ (299·8) calculated: 72·11% C, 6·05% H, 11·83% Cl, 4·67% N; found: 72·54% C, 6·18% H, 11·76% Cl, 4·63% N.

2'-Amino-5'-chlorophenyl 6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-2-yl Ketone Oxime (*IXa*)

A solution of 37·5 g *VIIa* and 14·8 g $NH_2OH.HCl$ in 150 ml ethanol was stirred and refluxed for 12 h and then evaporated under reduced pressure. The residue was stirred for 30 min with a solution of 12 g Na_2CO_3 in 90 ml H_2O, the solid was filtered, washed with H_2O, dried *in vacuo* and crystallized from a mixture of ethanol and hexane; 36 g (92%), m.p. 144–146°C. Analytical sample, m.p. 148–149°C (ethanol–hexane). UV spectrum: λ_{max} 245 nm (log ε 4·33), infl. 264·5 nm (4·16), infl. 313 nm (3·77). IR spectrum: 830, 893, 899 (2 adjacent and solitary Ar—H), 960 (C=NOH), 1493, 1562, 1594 (Ar), 1609 (Ar—NH_2), 1629 (C=N), 3340 (OH, NH_2), 3405 cm^{-1} (NH_2). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 11·50 (s, disappears after D_2O, 1 H, NOH), 6·50 to 7·35 (m, 6 H, Ar—H), 4·80 (s, disappears after D_2O, 2 H, NH_2), 2·40–3·00 (m, 4 H, CH_2ArCH_2), 1·65 (bs, 6 H, remaining 3 CH_2). For $C_{18}H_{19}ClN_2O$ (314·8) calculated: 68·68% C, 6·08% H, 11·26% Cl, 8·90% N; found: 68·88% C, 6·12% H, 11·28% Cl, 8·98% N.

6-Chloro-2-(chloromethyl)-4-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-yl)quinazoline 3-Oxide (*Xa*)

A mixture of 26·0 g crude *IXa* and 50 ml acetic acid was cooled to 10°C and treated under stirring with 14 ml chloroacetyl chloride. The mixture was stirred for 40 min at 50–55°C, cooled, diluted with 80 ml ether and the precipitated solid was filtered off. The filtrate was evaporated under reduced pressure, the residue mixed with 250 ml ether, the product filtered, washed with ether and dried; 18·5 g (60%), m.p. 187–190°C. Analytical sample, m.p. 196–197°C (ethanol–ether). UV spectrum: λ_{max} 270 nm (log ε 4·50), infl. 340 nm (3·78). IR spectrum: 675 (C—Cl), 749, 759 (3 adjacent Ar—H, *cf. Xb*), 820, 879 (2 adjacent and solitary Ar—H), 1290 (N—O), 1481, 1555 (Ar), 1610 cm^{-1} (C=N). ^{1}H-NMR spectrum: δ 7·60–8·08 (2 d, 2 H, 5·7-H_2), 7·20–7·65 (m, 4 H, remaining Ar—H), 5·06 (s, 2 H, CH_2Cl), 2·20–3·10 (m, 4 H, CH_2ArCH_2), 1·50–2·10 (m, 6 H, remaining 3 CH_2). For $C_{20}H_{18}Cl_2N_2O$ (373·3) calculated: 64·36% C, 4·85% H, 18·99% Cl, 7·51% N; found: 64·48% C, 4·98% H, 18·92% Cl, 7·80% N.

7-Chloro-5-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-yl)-2-methylamino-3*H*-1,4-benzodiazepine 4-Oxide (*IVa*)

Xa (11·0 g) was added to a solution of 30 g methylamine in 100 ml methanol, the mixture was stirred for 15 h and then allowed to stand for 48 h. The precipitated solid was filtered, washed with ethanol and dried *in vacuo*; 10·0 g (87%), m.p. 210–212°C. Analytical sample, m.p. 212 to

213°C (ethanol). Analysis and spectra showed the substance to be a solvate with ethanol. UV spectrum: λ_{max} 260 nm (log ε 4·54), infl. 315 nm (3·93). IR spectrum: 820, 838, 860 (2 adjacent and solitary Ar—H), 1 165 (N—O), 1 570, 1 593 (Ar), 1 628 (C=N), 3 080 (NH), 1 000, 1 265, 3 260, 3 460 cm^{-1} (OH of ethanol). ^{1}H-NMR spectrum: δ 7·90 (1 H, NH), 6·90—7·50 (m, 6 H, Ar—H), c. 3·80 (m, 0·5 H, OH of ethanol), 3·65 (q, 1 H, 0·5 CH_2 of ethanol), c. 3·75 (m, 6 H, CH_2ArCH_2 and CH_2 in position 3), 3·80 (d, after D_2O s, 6 H, remaining 3 CH_2), 1·70 (m, 3 H, NCH_3), 1·18 (t, 1·5 H, 0·5 CH_3 of ethanol). For $C_{21}H_{22}ClN_3O + 0{\cdot}5\ C_2H_6O$ (390·9) calculated: 67·60% C, 6·45% H, 9·07% Cl, 10·73% N; found: 67·61% C, 6·39% H, 9·30% Cl, 10·32% N.

6-Chloro-4-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-yl)-
2-(4-methylpiperazinomethyl)quinazoline 3-Oxide (*XIa*)

A mixture of 10·0 g *Xa*, 10·0 g 1-methylpiperazine and 70 ml methanol was stirred for 20 h at 40—50°C and allowed to stand overnight in a refrigerator, the precipitated product was filtered, washed with a mixture of methanol and light petroleum, and dried *in vacuo*; 9·0 g (77%), m.p. 133—135°C. Analytical sample, m.p. 138—139°C (heptane–benzene). UV spectrum: λ_{max} 221·5 nm (log ε 4·67), 268 nm (4·43), 327 nm (3·83). IR spectrum: 700 (C—Cl), 751 (3 adjacent Ar—H, *cf. XIb*), 826, 865 (2 adjacent and solitary Ar—H), 1 285 (N—O), 1 550, 1 600 cm^{-1} (Ar, C=N). For $C_{25}H_{29}ClN_4O$ (437·0) calculated: 68·71% C, 6·69% H, 8·11% Cl, 12·83% N; found: 69·04% C, 6·79% H, 8·00% Cl, 12·98% N.

Dihydrochloride monohydrate, m.p. 198—200°C (aqueous ethanol–ether). For $C_{25}H_{31}Cl_3N_4O + H_2O$ (527·9) calculated: 56·92% C, 6·30% H, 20·10% Cl, 10·62% N; found: 57·00% C, 6·16% H, 19·94% Cl, 10·93% N.

7-Chloro-5-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-yl)-
1,3-dihydro-1,4-benzodiazepin-2-one (*Va*) Molecular Complex with *VIIa*

A mixture of 3·0 g *VIIa*, 2·1 g ethyl aminoacetate hydrochloride and 25 ml pyridine was slowly distilled through a column; 10 ml pyridine were distilled off over 4 h and were substituted by 10 ml pyridine. The mixture was then refluxed for 13 h and evaporated under reduced pressure. The residue was made alkaline with 20% NaOH and extracted with a mixture of ether and benzene. The extract was washed with H_2O, dried with K_2CO_3, filtered with charcoal and evaporated under reduced pressure. The residue was crystallized from 3 ml acetone; 1·80 g (28%) molecular complex of *Va* with *VIIa*. Analytical sample, m.p. 159—160°C (ethanol with several drops of benzene). The mass spectrum detected the components $C_{20}H_{19}ClN_2O$ and $C_{18}H_{18}ClNO$. ^{1}H-NMR spectrum: δ 9·93 (bs, 1 H, CONH of *Va*), 6·90—7·70 (m, 11 H, Ar—H), 6·65 (d, 1 H, 3-H of *VIIa*), 5·98 (s, 2 H, NH_2 of *VIIa*), 4·27 (s, 2 H, $COCH_2$ of *Va*), 2·60—3·10 (m, 8 H, 2 CH_2ArCH_2), 1·30—2·60 (m, 12 H, remaining 6 CH_2). For $C_{38}H_{37}Cl_2N_3O_2$ (638·6) calculated: 71·50% C, 5·84% H, 11·09% Cl, 6·57% N; found: 72·04% C, 6·15% H, 10·90% Cl, 6·50% N.

2′-Amino-5′-chlorophenyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptene-2-yl-methanol (*XIIa*)

A) A solution of 2·0 g *VIIa* in 20 ml tetrahydrofuran was added dropwise to a stirred suspension of 1·5 g lithium aluminium hydride in 15 ml ether and the mixture was refluxed for 2 h. After cooling, it was diluted with ether, decomposed with 6 ml 20% NaOH, the solid filtered off, the filtrate dried and evaporated; 2·0 g (100%) crude product. Most of the product dissolved in 40 ml boiling heptane. The insoluble fraction was filtered off and the filtrate allowed to crystallize by cooling, m.p. 100—101°C (heptane). IR spectrum (KBr): 690 (C—Cl), 737, 768 (C adjacent Ar—H, *cf. XIIb*), 826, 848, 872, 900 (2 adjacent and solitary Ar—H), 1 100 (CHOH), 1 488 (Ar),

1618 (Ar—NH_2), 3230 (OH), 3300, 3480 cm^{-1} (NH_2). ^{1}H-NMR spectrum: δ 6·40—7·20 (m, 6 H, Ar—H), 5·61 (s, 1 H, Ar—CH—Ar'), c 3·45 (bs, 3 H, NH_2 and OH), 2·75 (m, 4 H, CH_2ArCH_2), 1·72 (m, 6 H, remaining 3 CH_2). For $C_{18}H_{20}ClNO$ (301·7) calculated: 71·64% C, 6·69% H, 11·73% Cl, 4·64% N; found: 71·82% C, 6·77% H, 11·43% Cl, 4·64% N.

B) Molecular complex of *Va* with *VIIa* (1·0 g) was reduced with 2·0 g $LiAlH_4$ in 15 ml tetrahydrofuran and 50 ml ether similarly like under *A*. Crystallization of the crude product from a mixture of 1 ml benzene and 20 ml hexane gave 0·35 g product, m.p. 97°C which proved identical with *XIIa* (mixed melting point, TLC, analysis, spectra).

2'-(Chloroacetamido)-5'-chlorophenyl 6,7,8,9-Tetrahydro-5*H*-benzocycloheptene-2-yl Ketone (*VIIIa*)

A solution of 30 g *VIIa* in 100 ml chloroform was treated with a solution of 10 ml chloroacetyl chloride in 50 ml chloroform, the mixture was stirred for 1 h and evaporated under reduced pressure. The residue was crystallized from 330 ml ethanol; 33 g (88%) yellow needles, m.p. 100—102°C. Analytical sample, m.p. 102—103°C (ethanol). UV spectrum: λ_{max} 236 nm (log ε 4·36), 273 nm (4·19), infl. 327 nm (3·61). IR spectrum: 675 (C—Cl), 745, 760, 782, 790 (3 adjacent Ar—H, *cf. VIIIb*), 818, 850, 895 (2 adjacent and solitary Ar—H), 1520, 1575, 1600 (Ar, CONH), 1635 (ArCOAr'), 1690 (CONH), 3190 cm^{-1} (NH). ^{1}H-NMR spectrum: δ 11·41 (bs, 1 H, NH), 8·57 (m, J = 10·0 Hz, 1 H, 3-H in the benzocycloheptene residue), 7·20—7·70 (m, 5 H, remaining Ar—H), 4·12 (s, 2 H, CH_2Cl), 2·85 (m, 4 H, CH_2ArCH_2), 1·73 (m, 6 H, remaining 3 CH_2). For $C_{20}H_{19}Cl_2NO_2$ (376·3) calculated: 63·85% C, 5·09% H, 18·84% Cl, 3·72% N; found: 63·92% C, 5·23% H, 18·95% Cl, 3·73% N.

Bis[3-(4-chloro-2-[6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-yl-carbonyl])-4-oxoimidazolidin-1-yl]methane (*XIIIa*)

A mixture of 28·5 g *VIIIa*, 30 g hexamethylenetetramine and 500 ml ethanol was refluxed for 12 h and evaporated under reduced pressure. The residue was decomposed with 200 ml H_2O and extracted with benzene, the extract was dried with Na_2SO_4 and evaporated *in vacuo*. The residue solidified after boiling with 150 ml ether, the solid was filtered and crystallized from a mixture of benzene and hexane; 7·0 g (25%), m.p. 174—176°C. Analytical sample, m.p. 175—176°C (benzene–hexane). IR spectrum: 786 (3 adjacent Ar—H, *cf. XIIIb*), 831, 889 (2 adjacent and solitary Ar—H), 1100 (CO), 1250, 1291 (C—N), 1569, 1600 (Ar), 1673 (ArCOAr'), 1705 cm^{-1} (CO—N in a five-membered ring). ^{1}H-NMR spectrum (Tesla BS 487C, 80 MHz): δ 7·00—7·70 (m, 12 H, Ar—H), 4·51 (s, 4 H, 2 NCH_2N in the ring), 3·19 (s, 4 H, 2 $COCH_2N$), 3·16 (s, 2 H, NCH_2N between the rings), 2·80 (m, 8 H, 2 CH_2ArCH_2), 1·71 (m, 12 H, remaining 6 CH_2). For $C_{43}H_{42}Cl_2N_4O_4$ (749·7) calculated: 68·88% C, 5·65% H, 9·46% Cl, 7·47% N; found: 68·84% C, 5·67% H, 9·84% Cl, 7·40% N.

2-(4-Chlorobutyryl)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*XIV*)

A stirred solution of 20·5 g 6,7,8,9-tetrahydro-5*H*-benzocycloheptene[25] and 20·5 g 4-chlorobutyryl chloride in 140 ml benzene was treated over 25 min at 0—6°C with 20·5 g powdered $AlCl_3$. The mixture was stirred for 1·5 h at 6°C and for 1·5 h at room temperature, allowed to stand overnight, poured into a mixture of 140 g ice and 30 ml hydrochloric acid, and extracted with benzene. The extract was washed with 5% NaCl solution, with saturated $NaHCO_3$ solution, dried with Na_2SO_4 and distilled; 25·5 g (73%),) b.p. 205—208°C/0·5 kPa. The product crystallized

on standing and the analytical sample was obtained by crystallization from ethanol, m.p. 51 to 52°C. UV spectrum: λ_{max} 211 nm (log ε 4·35), 259 nm (4·18). IR spectrum: 750 (1-substituted benzocycloheptene?), 820, 860 (2 adjacent and solitary Ar—H), 1320 (CO), 1572, 1602 (Ar), 1674 (ArCO), 3000, 3040 cm^{-1} (CH_2, Ar—H). ^{1}H-NMR spectrum: δ 7·68 (mcd, J = 9·0; 2·0 Hz, 1 H, 3-H), 7·65 (mcs, J = 2·0 Hz, 1 H, 1-H), 7·13 (d, J = 9·0 Hz, 1 H, 4-H), 3·60 (t, J = 6·0 Hz, 2 H, CH_2Cl), 3·10 (t, J = 7·0 Hz, 2 H, $COCH_2$), 2·82 (m, 4 H, CH_2ArCH_2), 2·20 (m, 2 H, remaining butyryl CH_2), 1·72 (m, 6 H, remaining 3 CH_2 in positions 6, 7 and 8). For $C_{15}H_{19}ClO$ (250·8) calculated: 71·84% C, 7·64% H, 14·14% Cl; found: 71·63% C, 7·62% H, 14·29% Cl.

6,7,8,9-Tetrahydro-5*H*-benzocycloheptene-2-yl 3′-(4-Ethoxycarbonyl-4-phenylpiperidino)-propyl Ketone (*XV*)

A mixture of 11·0 g 4-(ethoxycarbonyl)-4-phenylpiperidine[26], 14·0 g *XIV*, 6·5 g K_2CO_3 and 25 ml dimethylformamide was stirred and heated to 100—110°C for 10 h. After cooling, it was diluted with 50 ml benzene, the inorganic salts filtered off and washed with benzene. The combined organic layers were evapored, the residue was dissolved in 70 ml benzene and 30 ml ether and the solution shaken with 100 ml ice-cold 1 : 9 diluted hydrochloric acid. The precipitated hydrochloride was filtered, washed with water and ether, and dried *in vacuo*; 11·0 g (41%), m.p. 131 to 132°C (ethanol–ether). IR spectrum: 698, 728, 822, 868 (5 and 2 adjacent and solitary Ar—H), 1230, 1278 (CO, COOR), 1500, 1610 (Ar), 1686 (ArCO), 1730 (RCOOR′), 2460, 2520, 2540 cm^{-1} (NH^+). For $C_{29}H_{38}ClNO_3$ (484·1) calculated: 71·95% C, 7·91% H, 7·33% Cl, 2·89% N; found: 71·66% C, 8·27% H, 7·30% Cl, 2·87% N.

2-Chlorobenzoylacetonitrile

A suspension of 12·0 g NaH in a boiling solution of 74 g ethyl 2-chlorobenzoate[31] in 240 ml tetrahydrofuran was treated over 10 min with a solution of 17·2 g acetonitrile in 50 ml tetrahydrofuran. The mixture was refluxed for 2 h, stirred for 30 min at room temperature, diluted with 700 ml ether and allowed to stand overnight in a refrigerator. The precipitated sodium enolate was filtered, washed with ether, dissolved in water, the solution acidified with hydrochloric acid and the product extracted with ether. The extract was dried (Na_2SO_4) and evaporated. The residue (66 g) was dissolved in benzene and filtered through a column of 650 g Al_2O_3 (activity II). The filtrate was evaporated under reduced pressure and the residue crystallized from a mixture of 55 ml benzene and 30 ml light petroleum; 26·4 g (37%), m.p. 58—60°C. Analytical sample m.p. 59—60°C (ethanol–light petroleum). The literature[32] reported for a product prepared differently the m.p. of 56—57°C.

3-(2-Chlorobenzoyl)-5-ethyl-2-(5-oxoimidazolidin-1-yl)thiophene (*XIX*)

A mixture of 16·1 g 2-(chloroacetamido)-3-(2-chlorobenzoyl)-5-ethylthiophene (*XVII*) (ref.[30]), 12·8 g hexamethylenetetramine, 200 ml ethanol and 20 ml H_2O was refluxed for 2 h. After cooling, the precipitated product was filtered, washed with 70% ethanol and dried; 12·3 g (78%), m.p. 192—196°C. Analytical sample, m.p. 207—209°C (benzene-light petroleum). ^{1}H-NMR spectrum: δ 12·70 (bs, 1 H, NH), 7·35 (s, 4 H, Ar—H of *o*-phenylene), 6·29 (s, 1 H, thiophene 4-H), 4·00 (s, 2 H, NCH_2N), 3·82 (s, 2 H, $COCH_2N$), 2·60 (q, J = 7·0 Hz, 2 H, CH_2 of ethyl), 1·16 (t, J = 7·0 Hz, 3 H, CH_3). For $C_{16}H_{15}ClN_2O_2S$ (334·8) calculated: 57·39% C, 4·52% H, 10·59% Cl, 8·37% N, 9·58% S; found: 57·82% C, 4·58% H, 10·28% Cl, 8·07% N, 9·23% S.

5-Ethyl-2-(5-oxoimidazolidin-1-yl)-3-thienyl-2′-chlorophenylmethanol (*XX*)

A mixture of 1·5 g *XIX*, 0·55 g $NaBH_4$ and 20 ml ethanol was refluxed for 1·5 h and allowed to stand overnight at room temperature. Ethanol was evaporated *in vacuo*, the residue decomposed with H_2O and extracted with chloroform. The extract was washed with H_2O, dried (K_2CO_3) and evaporated. The residue crystallized from a mixture of 5 ml benzene and 8 ml light petroleum; 0·6 g (40%), m.p. 186—187°C with decomposition. Analytical sample, m.p. 184—187°C with decomposition (chloroform–light petroleum). UV spectrum: λ_{max} 282 nm (log ε 4·07). IR spectrum: 749, 824 (Ar—H), 1 130, 1 272 (CHOH), 1 530, 1 586 (Ar), 1 661 (CO—N), 3 225, 3335 cm^{-1} (NH, OH). ^{1}H-NMR spectrum (Tesla BS 487 C, 80 MHz, CD_3SOCD_3): δ 10·80 (bs, disappears after D_2O, 1 H, NH). 7·65 (m, 1 H, 6-H in chlorophenyl), 7·30 (m, 3 H, remaining Ar—H in chlorophenyl), 6·41 (bd, J = 4·0 Hz, disappears after D_2O, 1 H, OH), 6·18 (s, 1 H, 4-H of thiophene), 6·12 (bd, after D_2O s, 1 H, Ar—CH—O), 3·82 (bs, 2 H, NCH_2N), 3·62 (bs, 2 H, $COCH_2N$), 2·59 (q, J = 7·0 Hz, 2 H, CH_2 of ethyl), 1·11 (t, J = 7·0 Hz, 3H, CH_3). For $C_{16}H_{17}ClN_2O_2S$ (336·8) calculated: 57·05% C, 5·09% H, 10·53% Cl, 8·32% N, 9·52% S; found: 57·11% C, 5·12% H, 10·44% Cl, 8·22% N, 9·48% S.

2-(Aminoacetamido)-3-(2-chlorobenzoyl)-5-ethylthiophene (*XVIII*)

A mixture of 20·0 g *XIX*, 50 ml ethanol, 25 ml H_2O and 55 ml hydrochloric acid was refluxed for 5 min and cooled. The crystallized hydrochloride was filtered, washed with ethanol and dried *in vacuo*; 17·0 g (79%), m.p. 217—219°C with decomposition (ethanol). For $C_{15}H_{16}Cl_2N_2O_2S$ (359·3) calculated: 50·14% C, 4·49% H, 19·74% Cl, 7·80% N, 8·92% S; found: 50·31% C, 4·51% H, 20·02% Cl, 7·67% N, 9·11% S.

Treatment of the hydrochloride with NH_4OH gave the free base which was isolated by extraction with benzene, m.p. 149—151°C (ethanol). UV spectrum: λ_{max} 240 nm (log ε 4·24), 270 nm (4·06), 351 nm (3·95). IR spectrum: 745, 762, 790, 819, 842 (Ar—H), 1 516 (NHCO), 1 598 (Ar), 1 632 (ArCOAr′), 1 681 (CONH), 3 230, 3 360, 3 405 cm^{-1} (NH_2). ^{1}H-NMR spectrum (Tesla BS 487C, 80 MHz): δ 7·30 (m, 5 H, Ar—H of *o*-phenylene and NH), 6·30 (mcs, 1 H, of thiophene), 3·59 (s, 2 H, $COCH_2N$), 2·54 (mcq, J = 7·5 Hz, 2 H, CH_2 of ethyl), 1·70 (bs, 2 H, NH_2), 1·16 (t, J = 7·5 Hz, 3 H, CH_3). The literature[30] reported for a product prepared differently the m.p. of 148—149°C.

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