# POTENTIAL ANTICONVULSANTS: 3-CHLOROBENZOPHENONE DERIVATIVES

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Received December 7, 1988
Accepted January 9, 1989

Reactions of 2-(2-iodoacetamido)-5-chlorobenzophenone with 2-amino-2-phenylethanol, 2-amino-1-phenylethanol, 3-amino-2-phenylpropanol, D(+)-norpseudoephedrine, and 2-aminopropane-2-carbontrile gave the 2-substituted N-(2-benzoyl-4-chlorophenyl)acetamides *X*—*XIV*. 2,3′-Dichlorobenzhydrol (*XVI*) and 2,3′-dichlorobenzhydryl chloride (*XIX*) were transformed to the ethers *XVII* and *XVIII* and to the amines *XXI*—*XXIV*. Compound *XVI* was oxidized to the ketone *XXV* which was transformed via the oxime *XXVI* to compound *XXVII*. The basic products were converted to salts which were pharmacologically tested. Compounds *X*, *XVII*, *XXIII*, and *XXVII* showed anticonvulsant effects and some other neurotropic activities.

5-Aryl-7-chloro-1,3-dihydro-1,4-benzodiazepin-2-ones (*I*) (refs[1-3]) and 6-aryl-8-chloro-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepines (*II*) (refs[4,5]) are very active psychotropic agents with central depressant, anticonvulsant, anxiolytic, hypnotic, and myorelaxant activities. It was found that some of their open-ring analogues, i.e. derivatives of 2-amino-5-chlorobenzophenone and of 5-chloro-2-(triazolyl)benzophenone retain the ability of interacting with the "benzodiazepine receptors" in the brain and exhibit some of the mentioned activities. The first type of such compounds are the N-substituted N-(glycyl)aminobenzophenones[6] which are metabolically cleaved to N-(glycyl)aminobenzophenones with the free primary amino group which are then cyclized to the active 1,3-dihydro-1,4-benzodiazepin-2-ones. The first experimental drug of this series was lorzafone (*III*) (45-088-S, LY-123508) (refs[7-10]) showing a pharmacological profile similar to that of diazepam. It was followed by dinazafone (*IV*) (refs[11,12]) which exhibits anticonvulsant, anxiolytic, and myorelaxant effects. A further member of the series is ciprazafone (*V*) whose anticonvulsant properties were described[13]. The Soviet investigators[14] found similar compounds in the series of 2-(N-(glycyl)amino)-5-bromobenzophenones (*VI*). In the triazole series, compound "TB" (*VII*) was found to be a pro-drug of the potent hypnotic tria-

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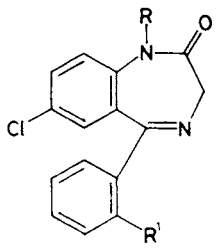
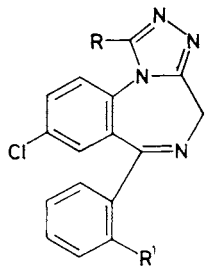
zolam[15,16]. Even more interest was devoted to rilmazafone (*VIII*) (450191-S) whose hypnotic potency is dependent of its metabolic conversion to the active 8-chloro-6--(2-chlorophenyl)-N,N-dimethyl-4*H*-1,2,4-triazolo[1,5-*a*]-1,4-benzodiazepine-2-carboxamide[17]. But anticonvulsant, sedative, and anxiolytic activities were claimed for variously N-substituted 2-(N-(glycyl)amino)-5-chlorobenzophenones (*IX*) (refs[18-21]) whose N-dealkylation hardly can be explained by the action of intestinal aminopeptidases (cf. also compounds *IV* and *V*); in these cases the involvement of unspecific hepatic oxidases is more likely.



*I*, R = H, $CH_3$; R' = H, F, Cl



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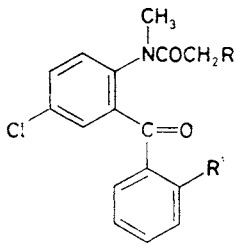
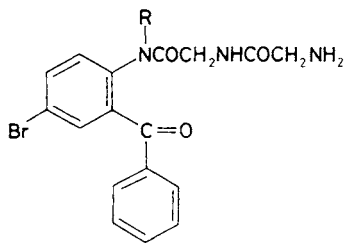


*III*, R = $NHCOCH_2NH_2$; R' = Cl

*IV*, R = $NHCH_2C(CH_3)=CH_2$

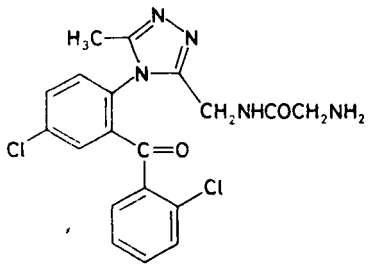
*V*, R = NH-cyclopropyl; R' = Cl



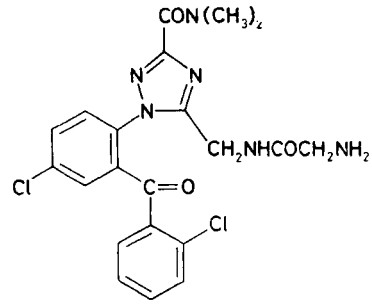
*VI*, R = H, $CH_3$

The first part of the present communication is a contribution to the topic just discussed. 2-(2-Iodoacetamido)-5-chlorobenzophenone[22] was reacted in acetone in the presence of potassium carbonate with D(−)-2-amino-2-phenylethanol[23] (obtained by reduction of ethyl D(−)-phenylglycinate with lithium aluminium hydride in analogy to ref.[24]), 2-amino-1-phenylethanol[25], 3-amino-2-phenylpropanol[26], and D(+)-norpseudoephedrine[27,28] and compounds *X*−*XIII* were obtained. The bases were crystalline, were characterized by spectra, and transformed to salts. 2-(2-Chloroacetamido)-5-chlorobenzophenone[29] did not react with 2-aminopropane-2-carbonitrile[30] in boiling benzene in the presence of triethylamine. It was, therefore, trans-

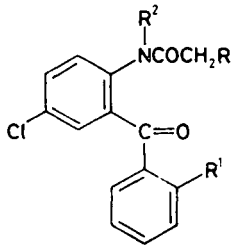
formed to the mentioned iodo compound by treatment with sodium iodide in boiling acetone and reacted "in situ" with 2-aminopropane-2-carbonitrile[30] in boiling acetone. The expected product *XIV* was obtained in a low yield. An attempt to react 2-(2-iodoacetamido)-5-chlorobenzophenone[22] with 1-aminocyclohexane-1-carboxamide[31] in pyridine at 60°C resulted in the formation of a yellow compound $C_{20}H_{14}$. .$ClIN_2O$ (analysis) which did not melt until 340°C. Its IR spectrum is in agreement with the assigned formula of the quaternary salt *XV* (the mass spectrum was not of use).




*VII*

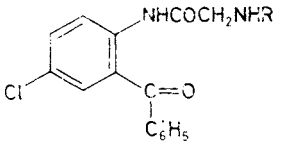


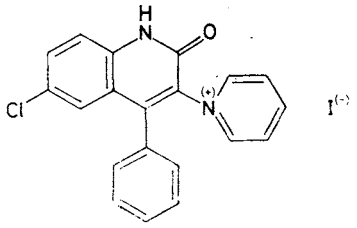

*VIII*



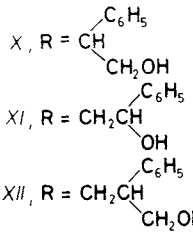

*IX*, R = $NR^3R^4$; $R^1$ = H, F, Cl; $R^2$ = H, $CH_3$

The second part of this communication is devoted to synthesis of compounds containing in their molecules the 2,3'-dichlorobenzhyryl or 2,3'-dichlorobenzhydrylidene fragment which appears in the molecules of lorazepam and triazolam (cf. ref.[3]), the most active anxiolytics and hypnotics of the 1,4-benzodiazepine series. 2,3'-Dichlorobenzhydrol (*XVI*) was prepared by reaction of 3-chlorophenylmagnesium bromide with 2-chlorobenzaldehyde in a mixture of ether and tetrahydrofuran (similar reaction in ether was described[32]). Its reaction with sodium hydride in toluene followed by 2-dimethylaminoethyl chloride resulted in the formation of *XVII*. The oily base was transformed to crystalline hydrogen oxalate whose mass and $^1$H NMR spectra were recorded.





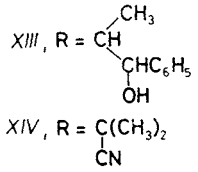
*XV*



*X*, R = CH(C6H5)CH2OH

*XI*, R = CH2CH(C6H5)OH

*XII*, R = CH2CH(C6H5)CH2OH

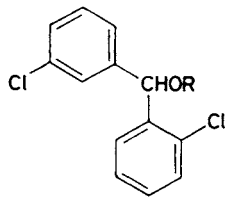


*XIII*, R = CH(CH3)CHC6H5OH

*XIV*, R = C(CH3)2CN

Treatment of *XVI* with thionyl chloride in toluene gave the chloride *XIX*. An attempt to prepare *XVIII* by reaction of 2-(4-methyl-1-piperazinyl)ethanol[33] with sodium hydride in dioxane followed by treatmnet with *XIX* in toluene gave *XX* as the main product. A similar formation of 1,1,2,2-tetraphenylethane by reaction of benzhydryl chloride with sodium 2-(1-piperidinyl)ethoxide in boiling xylene was observed many years ago[34]. A reaction of *XIX* with 2-(4-methyl-1-piperazinyl)-ethanol[33] at 150°C in the presence of potassium carbonate gave the desired *XVIII* (oily base and crystalline bis(hydrogen oxalate) confirmed by the mass spectrum).

Reactions of *XIX* with excessive hexamethyleneimine, 1-methylpiperazine, 2-(1--piperazinyl)ethanol, and 3-(1-piperazinyl)propanol[35] in boiling dioxane or mixtures of dioxane and chloroform resulted in the formation of amines *XXI*–*XXIV* (oily bases giving crystalline salts which were characterized by spectra).



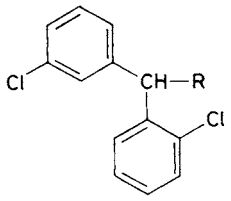
*XVI*, R = H

*XVII*, R = CH2CH2N(CH3)2

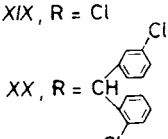
*XVIII*, R = CH2CH2N⟨⟩NCH3

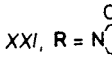
Oxidation of *XVI* with chromic acid in boiling acetic acid gave the ketone *XXV* (literature[36] described a different method) which was transformed to the oxime

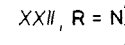
*XXVI*. Reaction of *XXVI* with sodium hydride in toluene followed by treatment with 2-dimethylaminoethyl chloride gave *XXVII* (oily base and crystalline hydrochloride, characterized by spectra).

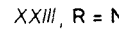


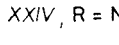
*XIX*, R = Cl

*XX*, R = 

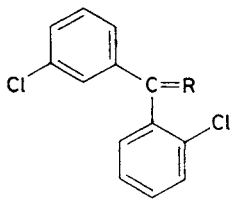
*XXI*, R = 

*XXII*, R = 

*XXIII*, R = 

*XXIV*, R = 

Most of the compounds prepared were pharmacologically tested for anticonvulsant and psychotropic activities or using the general screening programme. The compounds were administered orally (unless stated otherwise) in the form of salts, described in the Experimental; the doses given were calculated per bases. The activities are expressed in the usual $D_{50}$ doses or in effective doses ED (significant response or percent of positively responding animals given) in mg/kg.



*XXV*, R = =O

*XXVI*, R = =NOH

*XXVII*, R = =NOCH$_2$CH$_2$N(CH$_3$)$_2$

Acute toxicity in mice ($LD_{50}$ in mg/kg): *X*, >2 500; *XI*, >2 500; *XII*, 80 i.v.; *XIII*, >2 500; *XVII*, 193 (30 i.v.); *XVIII*, 388; *XXI*, 100 i.v.; *XXII*, 326 (40 i.v.); *XXIII*, 245 (30 i.v.) *XXIV*, 326 (30 i.v.); *XXVII*, 315. Doses (D in mg/kg) used in the screening: *X*, 300; *XI*, 300; *XII*, 15 i.v.; *XIII*, 300; *XVII*, 6 i.v.; *XXI*, 25 i.v.; *XXII*, 8 i.v.; *XXIII*, 6 i.v.; *XXIV*, 6 i.v.

Anticonvulsant effect against pentetrazole: *X*, ED for convulsions, 10–50; ED for the lethal effect, 300. Anticonvulsant effect against the maximum electroshock

in mice: *XVII*, the dose of 50 mg/kg protects 60% of animals from the convulsant effect and 100% from the lethal effect; *XXIII*, the dose of 50 mg/kg protects 30% from the convulsions and 100% from the lethal effect; *XXVII*, $PD_{50}$ = 37 mg/kg, doses above 40 mg/kg protect 100% of animals from the lethal effect.

Potentiation of the thiopental sleeping time in mice: *X*, the dose D prolonged to 200% of the control value (100%).

Inhibition of the spontaneous motility in mice (test of Ther): *X*, the dose D inhibits significantly.

Analgesic (antinociceptive) action (ED in mg/kg given) in the test of inhibition of the writhing syndrome in mice using stimulation with intraperitoneal 0·7% acetic acid (results in % of inhibition of pain): *X*, 300, 58%; *XI*, 300, 75%; *XII*, 75, 58%; *XIII*, 300, 50%; *XXI*, 125, mild effect.

Antitussive action in guinea-pigs (dose and reduction of the number of cough attacks elicited by the aerosol of citric acid solution in % of the control value (100%)): *XVII*, 30, 24%; *XXIII*, 30, 49%; *XXIV*, 30, 26%.

Antireserpine activity in the test of inhibition of reserpine-induced hypothermia in mice: *XIII*, the dose D had significant effect. Anticataleptic effect in rats against perphenazine-induced catalepsy: compounds *XVIII* and *XXVII* in doses of 50 mg/kg had mild anticataleptic effect. All compounds were devoid of antireserpine activity in the tests of ptosis in mice and gastric ulcers in rats, and of antihistamine activity in the tests in vivo.

Inhibition of binding of 4 nmol $l^{-1}$ [$^3$H]imipramine in the hypothalamus of the rat brain, $IC_{50}$ in nmol $l^{-1}$: *XVII*, 142; *XXVII*, 1 770. Inhibition of binding of 4 nm . $l^{-1}$ [$^3$H]desipramine in the rat hypothalamus ($IC_{50}$ in nmol $l^{-1}$): *XVII*, 718; *XXVII*, 1 216.

Spasmolytic effects on the isolated rat duodenum (concentrations in mg/l reducing the contractions to 50%) against contractions induced by (i) acetylcholine: *XVII*, *XXII*, *XXIII*, and *XXIV*, 1–10; (ii) barium chloride: *XVII*, *XXII*, *XXIII*, and *XXIV*, 1–10.

Blood pressure in normotensive anaesthetized rats: brief and deep drops after the doses D of *XVII*, *XXI*, *XXIII*, and *XXIV*.

Hypoglycaemic effect in rats: *XVII* and *XXII*, mild decrease of blood sugar level after the doses of 30 mg/kg; *XXII*, significant effect at 40 mg/kg.

Diuretic effect in mice: *XVII* at 30 mg/kg increased diuresis by 150%.

In conclusion: Compound *X* (VUFB-16 608) showed anticonvulsant activity against pentetrauole, central depressant and antinociceptive activities. Compound *XVII* (VUFB-16 592) was anticonvulsant in the electroshock test and showed affinity to imipramine and desipramine binding sites in the hypothalamus of rats. Compounds *XXIII*( VUFB-16 586) and *XXVII* (VUFB-16 591) protected also from the convulsant and lethal effects of electroshock. All the effects appear only in relatively high doses and further testing of the compounds was discontinued.

The compounds were also tested for antimicrobial activity in vitro (microorganisms and the minimum inhibitory concentrations in mg/l, unless they exceed 100 mg/l, are given): *Streptococcus β-haemolyticus*, *X* 50, *XVII* 100, *XXII* 100, *XXIV* 100, *XXVII* 50; *Streptococcus faecalis*, *XXII* 100, *XXIII* 100, *XXIV* 100, *XXVII* 100; *Staphylococcus pyogenes aureus*, *XVII* 100, *XVIII* 100, *XXII* 50, *XXIII* 25, *XXIV* 50, *XXVII* 50; *Proteus vulgaris*, *XII* 100; *Trichophyton mentagrophytes*, *X* 50, *XI* 50, *XXI* 50, *XXIII* 50.

## EXPERIMENTAL

The melting points were determined in the Mettler FP-5 melting point recorder or in a Kofler block; the samples were dried in vacuo of about 60 Pa over $P_2O_5$ at room temperature or at a suitably elevated temperature. UV spectra (in methanol, $\lambda_{max}$ in nm (log ε)) were recorded with a Unicam SP 8 000 spectrophotometer, IR spectra (mostly in Nujol, $\tilde{\nu}$ in $cm^{-1}$) with a Perkin–Elmer 298 spectrophotometer, $^1H$ NMR spectra (in $CDCl_3$ unless stated otherwise, δ in ppm, *J* in Hz) with a Tesla BS 487C (80 MHz) spectrometer, and the mass spectra (*m/z*, fragments and/or %) with MCH 1320 and Varian MAT 44S (GC-MS) spectrometers. The homogeneity of the products and composition of the mixtures were checked by thin-layer chromatography (TLC) on silica gel (Silufol). The extracts were dried with $MgSO_4$, $Na_2SO_4$ or $K_2CO_3$ and evaporated under reduced pressure on a rotary evaporator.

D(+)-N-(2-Benzoyl-4-chlorophenyl)-2-(2-hydroxy-1-phenylethylamino)acetamide (*X*)

A solution of 6·0 g 2-(2-iodoacetamido)-5-chlorobenzophenone[22] in 150 ml acetone was treated with a solution of 6·0 g D(−)-2-amino-2-phenylethanol[23] in 20 ml acetone and with 7·2 g $K_2CO_3$ and the mixture was stirred for 4 h at room temperature. After standing overnight it was refluxed for 1 h. After cooling the inorganic salts were filtered off and the filtrate was evaporated in vacuo. The residue was dissolved in 150 ml benzene, the solution was washed with water, filtered, and shaken with 120 ml 10% methanesulfonic acid. The aqueous solution and the separated oily methanesulfonate were combined, made alkaline with $NH_4OH$ and the base was isolated by extraction with chloroform. The extract was washed with water, dried, and evaporated. The residue was chromatographed on a column of 70 g neutral $Al_2O_3$ (activity II). Elution with benzene and a 1 : 1 mixture of benzene and chloroform removed the less polar components. The first fraction, eluted with chloroform (1·4 g, 8%) represented the crystalline *X*, m.p. 132°C (ethanol). $[\alpha]_D^{20} = +52{\cdot}4°$ (*c* = 1, ethanol). UV spectrum: 239 (4·42), 331 (3·48). IR spectrum: 705, 718, 760, 812, 830, 860, 890 (5 and 2 adjacent and solitary Ar–H); 1 069 ($CH_2OH$); 1 520 1 670 (CONH); 1 575, 1 597, 3 060 (Ar); 1 655 (ArCOAr'); 3 245, 3 340, 3 360 (NH, OH). $^1H$ NMR spectrum: 2·20 bs, 1 H (NH of amino); 3·10 and 3·48 2 d, 1 + 1 H ($COCH_2N$, $J = 13{\cdot}0$); 3·60 bs, 1 H (OH); 3·70 m, 3 H ($ArCHCH_2O$); 7·20 s, 5 H ($C_6H_5$ of phenylglycinol); 7·30–7·80 m, 7 H ($COC_6H_5$, H-3, and H-5); 8·60 d, 1 H (H-6, $J = 8{\cdot}0$); 11·80 bs, 1 H (ArNH). For $C_{23}H_{21}ClN_2O_3$ (408·9) calculated: 67·56% C, 5·18% H, 8·67% Cl, 6·85% N; found: 67·51% C, 5·32% H, 8·58% Cl, 6·70% N.

*Hydrogen oxalate monohydrate*, m.p. 131–132°C (ethanol). For $C_{25}H_{21}N_2O_6 + H_2O$ (498·9) calculated: 58·10% C, 4·87% H, 6·85% Cl, 5·42% N; found: 58·16% C, 4·81% H, 7·01% Cl, 5·44% N.

N-(2-Benzoyl-4-chlorophenyl)-2-(2-hydroxy-2-phenylethylamino)acetamide (*XI*)

A similar reaction of 14·6 g 2-(2-iodoacetamido)-5-chlorobenzophenone[22] with 5·0 g 2-amino-1--phenylethanol[25], and 6·05 g $K_2CO_3$ in 140 ml acetone and a similar processing (without chromatography) gave 5·3 g of crystalline *XI*, m.p. 148—150°C (ethanol). UV spectrum: 238·5 (4·74), 330 (3·48). IR spectrum: 705, 751, 810, 840, 860, 895 (5 and 2 adjacent and solitary Ar—H); 1 132 (CHOH); 1 506, 1 600, 3 040, 3 060 (Ar); 1 568, 1 673 (ArNHCOR); 1 634 (ArCOAr'); 3 215, 3 320, 3 518 (NH, OH). $^1$H NMR spectrum: 2·70 bs, 2 H (NH and OH of amino alcohol); 2·82 d, 2 H ($NCH_2$ of aminoethanol, $J$ = 6·0); 3·35 s, 2 H ($COCH_2N$); 4·82 t, 1 H (ArCH—O, $J$ = 6·0); 7·00—7·80 m, 12 H (ArH); 8·60 d, 1 H (H-6, $J$ = 8·0); 11·75 bs, 1 H (ArNH). For $C_{23}H_{21}ClN_2O_3$ (408·9) calculated: 67·56% C, 5·18% H, 8·67% Cl, 6·85% N; found: 67·30% C, 5·31% H, 8·70% Cl, 6·74% N.

*Hydrogen maleate hemihydrate*, m.p. 92—93°C (ethanol–ether). For $C_{27}H_{25}ClN_2O_7$ + 0·5 $H_2O$ (533·9) calculated: 60·73% C, 4·91% H, 6·64% Cl, 5·25% N; found: 61·05% C, 4·91% H, 6·86% Cl, 5·33% N.

N-(2-Benzoyl-4-chlorophenyl)-2-(3-hydroxy-2-phenylpropylamino)acetamide (*XII*)

A similar reaction of 14·7 g 2-(2-iodoacetamido)-5-chlorobenzophenone[22] with 5·6 g 3-amino--2-phenylpropanol[26], and 6·0 g $K_2CO_3$ in 120 ml acetone and a similar processing gave 9·7 g (62%) of crude oily *XII* which slowly crystallized, m.p. 100—101°C (ethanol). UV spectrum: 239 (4·44), 331 (3·47). IR spectrum: 710, 754, 810, 830, 897 (5 and 2 adjacent and solitary Ar—H); 1 042 ($CH_2OH$); 1 493, 1 593, 3 040, 3 080 (Ar); 1 567, 1 700 (ArNHCOR); 1 630 (ArCOAr'); 3 305, 3 340, 3 480 (NH, OH). $^1$H NMR spectrum: 2·20 flat band, 2 H (NH and OH of amino alcohol); 3·00 m, 3 H ($ArCHCH_2$); 3·30 s, 2 H ($COCH_2N$); 3·85 d, 2 H ($CH_2O$, $J$ = 6·0); 7·18 s, 5 H ($C_6H_5$ in the phenylpropanolamine part); 7·20—7·80 m, 7 H ($COC_6H_5$, C-3, and C-5); 8·55 d, 1 H (H-6, $J$ = 8·0); 11·35 bs, 1 H (ArNHCO). For $C_{24}H_{23}ClN_2O_3$ (422·9) calculated: 68·16% C, 5·48% H, 8·38% Cl, 6·62% N; found: 68·58% C, 5·52% H, 8·16% Cl, 6·51% N.

*Hydrogen maleate*, m.p. 140—141°C (ethanol). For $C_{28}H_{27}ClN_2O_7$ (539·0) calculated: 62·39% C, 5·05% H, 6·58% Cl, 5·20% N; found: 62·50% C, 4·96% H, 6·57% Cl, 5·05% N.

D(+)-N-(2-Benzoyl-4-chlorophenyl)-2-(1-hydroxy-1-phenyl--2-propylamino)acetamide (*XIII*)

A solution of 9·5 g 2-(2-iodoacetamido)-5-chlorobenzophenone[22] in 30 ml chloroform was treated with a solution of 7·2 g D(+)-norpseudoephedrine[27,28] in 50 ml chloroform and 7·9 g $K_2CO_3$, the mixture was stirred for 5 h at room temperature and refluxed for 1 h. After cooling the mixture was filtered, the filtrate was partly evaporated and allowed to crystallize; 2·8 g (28%) of *XIII*, m.p. 205°C (ethanol–chloroform), $[\alpha]_D^{20}$ = +78·56° ($c$ = 1, $CHCl_3$). UV spectrum: 240 (4·44), 327 (3·46). IR spectrum: 708, 751, 766, 810, 830, 870 (5 and 2 adjacent and solitary Ar—H); 1 103 (CHOH); 1 510, 1 600, 3 030, 3 065 (Ar); 1 568, 1 675 (NHCOR), 1 635 (ArCOAr'); 3 200, 3 280, 3 550 (NH, OH). $^1$H NMR spectrum ($CD_3SOCD_3$): 0·75 d, 3 H ($CH_3$, $J$ = 6·0); 2·72 m, 1 H (NCH); 3·10 and 3·38 ABq, 1 — 1 H ($COCH_2N$, $J$ = 17·5); 4·34 d, 1 H (CH—O, $J$ = 7·0); 7·10—7·90 m, 12 H (2 $C_6H_5$, H-3, and H-5); 8·29 d, 1 H (H-6). For $C_{24}H_{23}ClN_3O_2$ (422·9) calculated: 68·16% C, 5·48% H, 8·38% Cl, 6·62% N; found: 68·01% C, 5·34% H, 8·79% Cl, 6·46% N.

*Methanesulfonate*, m.p. 117—120°C (ethanol–ether). For $C_{25}H_{27}ClN_2O_4S$ (519·0) calculated: 57·85% C, 5·24% H, 6·83% Cl, 5·40% N, 6·18% S; found: 57·97% C, 5·49% H, 6·76% Cl, 5·07% N, 6·09% S.

N-(2-Benzoyl-4-chlorophenyl)-2-(2-cyano-2-propylamino)acetamide (*XIV*)

A mixture of 15·3 g 2-(2-chloroacetamido)-5-chlorobenzophenone[29], 9·0 g NaI and 150 ml acetone was refluxed for 1 h. After cooling, NaCl was filtered off, the filtrate was treated with 6·0 g 2-aminopropane-2-carbonitrile[30] and 10 g $K_2CO_3$ and the mixture was refluxed for 8 h. After cooling it was filtered and the filtrate was evaporated. The residue was crystallized from 30 ml acetone. The first part of the precipitated solid was filtered off and the filtrate was allowed to crystallize; 1·0 g (6%) of *XIV*, m.p. 121–123°C (ethanol). UV spectrum: 238 (4·44), infl. 258 (4·22), 335 (3·50). IR spectrum: 707, 752, 780, 804, 894 (5 and 2 adjacent and solitary Ar—H); 1 636 (ArCOAr'); 1 566, 1 694 (ArNHCOR); 2 220 (R—CN); 3 060 (Ar); 3 250 (NH). $^1$H NMR spectrum: 1·48 s, 6 H (2 $CH_3$); 2·21 bt, 1 H (NH in the aliphatic part, $J$ = 7·0); 3·50 d, 2 H ($COCH_2N$, $J$ = 7·0); 7·20–7·70 m, 7 H ($C_6H_5$, H-3, and H-5); 8·60 d, 1 H (H-6, $J$ = 9·0); 11·40 bs, 1 H (ArNHCO). For $C_{19}H_{18}ClN_3O_2$ (355·8) calculated: 64·13% C, 5·10% H, 9·96% Cl, 11·81% N; found: 64·09% C, 5·19% H, 10·09% Cl, 11·72% N.

N-(6-Chloro-2-oxo-4-phenyl-1*H*-3-quinolinyl)pyridinium Iodide (*XV*)

A stirred mixture of 2·4 g 1-aminocyclohexane-1-carboxamide[31], 5·9 g 2-(2-iodoacetamido)-5-chlorobenzophenone[22], 50 ml benzene, and 10 ml pyridine was heated to 60°C and after cooling the yellow crystals (4·7 g, 69%) were filtered. The substance crystallized from a mixture of dimethylformamide and ethanol and did not melt until 340°C. The structure *XV* was assigned on the basis of analysis and of the IR spectrum. UV spectrum: 235 (4·68), infl. 275 (4·02), 355 (3·78). IR spectrum (KBr): 700, 713, 765, 835, 881 (5, 4, and 2 adjacent and solitary Ar—H); 1 472 (Ar); 1 623 (C=C in conjugation); 1 655, 1 676 (NHCO of lactam); 3 020, 3 225 (NH). For $C_{20}H_{14}ClIN_2O$ (460·7) calculated: 52·13% C, 3·06% H, 27·56% I, 6·08% N; found: 52·10% C, 3·05% H, 27·89% I, 6·16% N.

2,3'-Dichlorobenzhydrol (*XVI*)

Grignard reagent was prepared by reaction of 11·7 g 3-bromo-1-chlorobenzene and 1·68 g Mg in 380 ml ether and was treated under stirring at 5–10°C with a solution of 7·88 g 2-chlorobenzaldehyde in 235 ml tetrahydrofuran, added dropwise. After standing overnight the mixture was decomposed under stirring with dilute hydrochloric acid, the organic layer was washed with 5% $NaHCO_3$, dried, and distilled; 13·2 g (93%) of *XVI*, b.p. 146°C/33 Pa. Ref.[32], b.p. 183–185°C/0·53 kPa.

N,N-Dimethyl-2-(2,3'-dichlorobenzhydryloxy)ethylamine (*XVII*)

A solution of 10·0 g *XVI* in 50 ml toluene was treated with 5·0 g 80% NaH (suspension in oil) and under stirring the solution of 8·5 g 2-dimethylaminoethyl chloride in 15 ml toluene was added dropwise. The mixture was refluxed for 5 h and after cooling decomposed with water. The organic layer was washed with water, and the basic product was extracted into dilute hydrochloric acid. The aqueous layer was made alkaline with $NH_4OH$ and the product was extracted with ether. Evaporation of the extract gave 11·1 g (87%) of crude oily *XVII*. It was dissolved in ethanol and the solution was neutralized with a solution of 4·1 g oxalic acid dihydrate in ethanol. Addition of ether resulted in crystallization of 11·6 g hydrogen oxalate, m.p. 116·5 to 117°C (ethanol–ether). Mass spectrum: 323 ($M^+$, $C_{17}H_{19}Cl_2NO$, 0·005), 235 ($C_{13}H_9Cl_2$, 0·6), 199 ($C_{13}H_8Cl$, 2·3), 165 ($C_{13}H_9$, 8), 111 ($C_6H_4Cl$, 1), 73 ($C_4H_{11}N$, 18), 58 (100). $^1$H NMR spectrum ($CD_3SOCD_3$): 2·70 s, 6 H ($N(CH_3)_2$); 3·28 bt, 2 H ($CH_2N$); 3·68 bt, 2 H ($CH_2O$); 5·80 s, 1 H ($Ar_2CHO$); 7·30 m, 7 H and 7·65 m, 1 H (ArH). For $C_{19}H_{21}Cl_2NO_5$ (414·3) calculated: 55·08% C, 5·12% H, 3·38% N; found: 55·17% C, 5·11% H, 3·59% N.

2,3′-Dichlorobenzhydryl Chloride (*XIX*)

A mixture of 20 g *XVI*, 40 ml toluene, and 10 g $SOCl_2$ was stirred and refluxed for 2·5 h. After standing overnight, the mixture was distilled; 18·3 g (85%) of *XIX*, b.p. 104—106°C/66 Pa. IR spectrum (film): 690, 750, 790, 890 (4 and 3 adjacent and solitary Ar—H); 1 433, 1 450, 1 477, 1 576, 1 600 (Ar). $^1$H NMR spectrum: 6·54 s, 1 H ($Ar_2CHCl$); 7·10—7·70 m, 8 H (ArH). For $C_{13}H_9Cl_3$ (271·6) calculated: 57·49% C, 3·35% H, 39·16% Cl; found: 57·77% C, 3·43% H, 38·82% Cl.

1,2-Bis(2-chlorophenyl)-1,2-bis(3-chlorophenyl)ethane (*XX*)

A solution of 8·0 g 2-(4-methyl-1-piperazinyl)ethanol[33] in 40 ml dioxane was treated with 5·0 g 80% NaH and under stirring the solution of 10·0 g *XIX* in 20 ml toluene was added. The mixture was refluxed for 5 h, allowed to stand overnight, diluted with ether, and decomposed with water. The organic layer was washed with dilute hydrochloric acid, with 5% $NaHCO_3$, dried, and evaporated. The residue crystallized from a mixture of acetone and heptane; 4·4 g (51%) of *XX*, m.p. 177—180°C (chloroform–heptane). Mass spectrum: 470 ($M^+$, $C_{26}H_{18}Cl_4$, 0·3), 235 ($C_{13}H_9Cl_2$, 100), 200 ($C_{13}H_9Cl$, 15), 199 ($C_{13}H_8Cl$, 15), 165 ($C_{13}H_9$, 47). $^1$H NMR spectrum: 5·20 s and 5·40 s, 1 + 1 H (2 $Ar_2CH$); 6·70—7·50 m, 16 H (ArH). For $C_{26}H_{18}Cl_4$ (472·2) calculated: 66·12% C, 3·84% H, 30·04% Cl; found: 65·86% C, 3·77% H, 29·77% Cl.

1-(2-(2,3′-Dichlorobenzhydryloxy)ethyl)-4-methylpiperazine (*XVIII*)

A mixture of 26·3 g *XIX*, 14·0 g 2-(4-methyl-1-piperazinyl)ethanol[33], and 20 g $K_2CO_3$ was stirred and heated for 11 h to 150°C. After cooling it was diluted with water and extracted with ether. The basic product was transferred into dilute hydrochloric acid. The aqueous layer was made alkaline with $NH_4OH$ and the crude base *XVIII* was isolated by extraction with ether; 4·6 g (13%). It was transformed to the bis(hydrogen oxalate), m.p. 187—189°C (ethanol). Mass spectrum: 378 ($M^+$, $C_{20}H_{24}Cl_2N_2O$, 0·1), 347 ($C_{19}H_{19}Cl_2NO$, 0·4), 235 ($C_{13}H_9Cl_2$, 2·5), 199 ($C_{13}H_8Cl$, 4·2), 143 ($C_7H_{15}N_2O$, 10), 126 ($C_7H_{14}N_2$, 18), 113 ($C_6H_{13}N_2$, 100), 100 ($C_5H_{12}N_2$, 10), 70 ($C_4H_8N$, 55). For $C_{24}H_{28}Cl_2N_2O_9$ (559·4) calculated 51·52% C, 5·06% H, 12·67% Cl, 5·01% N; found: 51·43% C, 5·10% H, 12·56% Cl, 5·12% N.

1-(2,3′-Dichlorobenzhydryl)perhydroazepine (*XXI*)

A mixture of 9·0 g *XIX*, 16·5 g perhydroazepine, and 30 ml dioxane was refluxed for 11 h. After cooling it was diluted with 5% NaOH and extracted with ether. From the organic layer the basic product was transferred into dilute hydrochloric acid, the aqueous layer was made alkaline with $NH_4OH$ and the base *XXI* was isolated by extraction with ether; 4·4 g (40%). The base was neutralized with HCl in a mixtue of ethanol and ether and gave the hydrochloride, m.p. 188 to 191°C (ethanol–ether). $^1$H NMR spectrum ($CD_3SOCD_3$): 1·30—2·00 bm, 8 H (4 $CH_2$ in positions 3, 4, 5, 6 of perhydroazepine); 3·15 bm, 4 H ($CH_2NCH_2$); 6·00 bs, 1 H ($Ar_2CHN$); 7·40 m, 5 H and 7·92 m, 1 H, and 8·80 m, 1 H (H-3, H-4, H-5, H-6, H-4′, H-5′, and H-6′); 8·02 bs, 1 H (H-2′). For $C_{19}H_{22}Cl_3N$ (370·8) calculated: 61·54% C, 5·99% H, 28·68% Cl, 3·78% N; found: 62·03% C, 5·89% H, 28·70% Cl, 3·67% N.

1-(2,3′-Dichlorobenzhydryl)-4-methylpiperazine (*XXII*)

A similar reaction of 8·0 g *XIX* with 13·0 g 1-methylpiperazine in a boiling mixture of 20 ml chloroform and 10 ml dioxane (24 h of refluxing) and similar processing gave 9·4 g (95%) of oily *XXII*.

*Dihydrochloride*, m.p. 252—255°C (ethanol). Mass spectrum: 334 ($M^+$, $C_{18}H_{20}Cl_2N_2$), 275 ($C_{15}H_{11}Cl_2N$), 263 ($C_{14}H_{10}Cl_2N$), 165 ($C_5H_{11}N_2$). For $C_{18}H_{22}Cl_4N_2$ (408·2) calculated 34·74% Cl, 6·86% N; found: 34·82% Cl, 7·07% N.

*Bis(hydrogen maleate)*, m.p. 108—110°C (ethanol–ether). For $C_{26}H_{28}Cl_2N_2O_8$ (567·5) calculated: 55·03% C, 4·98% H, 12·49% Cl, 4·94% N; found: 54·87% C, 5·02% H, 12·03% Cl, 5·07% N.

1-(2,3'-Dichlorobenzhydryl)-4-(2-hydroxyethyl)piperazine (*XXIII*)

A similar reaction of 9·2 g *XIX* with 18 g 2-(1-piperazinyl)ethanol in 30 ml refluxing dioxane (23 h) gave 10·6 g (86%) of oily *XXIII*.

*Dihydrochloride*, m.p. 221·5—222·5°C (ethanol–ether). Mass spectrum: 364 ($M^+$, $C_{19}H_{22}Cl_2$: $N_2O$), 333 ($C_{18}H_{19}Cl_2N_2$), 235 ($C_{13}H_9Cl_2$), 199 ($C_{13}H_8Cl$), 165 ($C_{13}H_9$), 129 ($C_7H_{13}N_2O$). For $C_{19}H_{24}Cl_4N_2O$ (438·3) calculated: 52·07% C, 5·53% H, 32·36% Cl, 6·39% N; found 52·17% C, 5·55% H, 32·08% Cl, 6·48% N,

1-(2,3'-Dichlorobenzhydryl)-4-(3-hydroxypropyl)piperazine (*XXIV*)

A similar reaction of 9·0 g *XIX* with 19·2 g 3-(1-piperazinyl)propanol[35] in 30 ml refluxing dioxane (19 h) gave 12·1 g (96%) of oily *XXIV*.

*Bis(hydrogen maleate)*, m.p. 130·5—132·5°C (ethanol–ether). Mass spectrum: 378 ($M^+$, $C_{20}H_{24}Cl_2N_2O$), 333 ($C_{18}H_{19}Cl_2N_2$), 235 ($C_{13}H_9Cl_2$), 199 ($C_{13}H_8Cl$), 165 ($C_{13}H_9$). For $C_{24}H_{28}Cl_2N_2O_5 + 0{\cdot}5\ H_2O$ (504·5) calculated: 57·14% C 5·81% H, 14·05% Cl, 5·55% N; found: 57·11% C, 5·45% H, 13·85% Cl, 5·59% N.

2,3'-Dichlorobenzophenone (*XXV*)

A solution of 5·3 g $CrO_3$ in a mixture of 7 ml water and 32 ml acetic acid was added dropwise to a stirred and refluxing solution of 10·0 g *XVI* in 45 ml acetic acid over 20 min. The mixture was refluxed for 1 h, cooled, poured into water, and extracted with ether. The extract was washed with dilute NaOH and water, dried, and distilled; 8·7 g (89%) of *XXV*, b.p. 92—94°C/33Pa. UV spectrum: 251 (4·15), infl. 287 (3·28). IR spectrum (film): 700, 747, 773, 900 (4 and 3adjacent and solitary Ar—H); 1 570, 1 590, 3 060 (Ar); 1 676 (ArCOAr'). $^1$H NMR spectrum: 7·20 to 7·90 m, 8 H (ArH). For $C_{13}H_8Cl_2O$ (251·1) calculated: 62·18% C, 3·22% H, 28·23% Cl; found: 62·40% C, 3·28% H, 27·95% Cl.

2,3'-Dichlorobenzophenone Oxime (*XXVI*)

A mixture of 8·3 g *XXV*, 11·5 g hydroxylamine hydrochloride, and 40 ml pyridine was stirred and refluxed for 48 h. After cooling it was poured in water and extracted with ether. The extract was washed with dilute hydrochloric acid, 5% $NaHCO_3$, dried, and evaporated. The residue was crystallized from a mixture of acetone and heptane; 8·1 g (92%) of *XXVI*, m.p. 109—112°C (chloroform–heptane). UV spectrum: 250 (4·09). IR spectrum: 700, 710, 746, 776, 860 (4 and 3 adjacent and solitary Ar—H); 1 575, 3 068 (Ar); 1 675 (C=N of oxime); in $CCl_4$: 1 580, 3 065 (Ar); 1 689 (C=N of oxime); 3 300 (OH of oxime). $^1$H NMR spectrum: 7·30—7·90 m (ArH and OH). For $C_{13}H_9Cl_2NO$ (266·1) calculated: 58·67% C, 3·42% H, 26·64% Cl, 5·26% N; found: 58·95% C, 3·47% H, 26·68% Cl, 5·29% N.

2,3'-Dichlorobenzophenone O-(2-Dimethylaminoethyl)oxime (*XXVII*)

A solution of 7·7 g *XXVI* in 50 ml toluene was treated with 5·0 g 80% NaH which was followed by a solution of 6·3 g 2-dimethylaminoethyl chloride in 10 ml toluene. The mixture was stirred and refluxed for 4 h. After standing overnight it was decomposed with water, from the organic layer the basic product was transferred into dilute hydrochloric acid, the aqueous layer was made alkaline with $NH_4OH$ and the base was extracted with ether. Processing of the extract gave 8·1 g (83%) of oily *XXVII*.

*Hydrochloride*, m.p. 162—164°C (ethanol–ether–heptane). Mass spectrum: 336 ($M^+$, $C_{17}H_{18}Cl_2N_2O$, 0·1), 250 ($C_{13}H_{10}Cl_2N$, 2·2), 199 ($C_{13}H_8Cl$, 0·5), 177 ($C_{13}H_7N$, 0·4), 137 ($C_7H_4ClN$, 0·3), 111 ($C_6H_4Cl$, 5), 58 (100). UV spectrum: 259 (4·11). IR spectrum: 695, 740, 788, 884, 890 (4 and 3 adjacent and solitary Ar—H); 985, 1 043 (=N—O—C); 1 475, 1 560, 1 590, 3 010, 3 055 (Ar); 1 602 (C=N); 2 430, 2 508, 2 560, 2 580 ($NH^+$). For $C_{17}H_{19}Cl_3N_2O$ (373·7) calculated: 54·63% C, 5·13% H, 28·46% Cl, 7·50% N; found: 54·83% C, 5·32% H, 28·40% Cl, 7·50% N.

*The authors wish to thank their colleagues at the Research Institute for Pharmacy and Biochemistry for their contributions to the present study: Mrs J. Komancová and Mrs V. Šmídová (elemental analyses); Mrs A. Hrádková and Mrs Z. Janová (recording of the spectra); Mrs H. Bezděková (measurement of the optical rotation); Mrs J. Ezrová, Mrs J. Horáková, and Mrs E. Šulcová (pharmacology and biochemical pharmacology); Dr V. Holá (microbiological screening).*

REFERENCES

1. Sternbach L. H., Randall L. O., Gustafson S. R. in: *Medicinal Chemistry. 4. Psychopharmacological Agents* (M. Gordon, Ed.), Vol. 1, p. 137. Academic Press, New York 1964.
2. Randall L. O., Schallek W., Sternbach L. H., Ning R. Y. in: *Medicinal Chemistry. 4. Psychopharmacological Agents* (M. Gordon, Ed.), Vol. 3, p. 175. Academic Press, New York 1974.
3. Sternbach L. H. in: *Benzodiazepines Today and Tomorrow* (R. G. Priest, U. V. Filho, R. Amrein and M. Skreta, Eds), p. 5. MTP Press, Lancaster (U.K.) 1980.
4. Rudzik A. D., Hester J. B., Jr., Tang A. H., Straw R. N., Friis W. in: *The Benzodiazepines* (S. Garattini, E. Mussini and L. O. Randall, Eds), p. 285. Raven Press, New York 1973.
5. Moffett R. B.: Lectures Heterocycl. Chem. *3*, S-123 (1976); *5th Int. Congr. Heterocycl. Chem., Ljubljana, Yugoslavia, July 1975.*
6. Hirai K., Ishiba T., Sugimoto H., Fujishita T., Tsukinoki Y., Hirose K.: J. Med. Chem. *24*, 20 (1981).
7. Fujimoto M., Tsukinoki Y., Hirose K., Hirai K., Okabayashi T.: Chem. Pharm. Bull. *28*, 1374 (1980).
8. Fujimoto M., Tsukinoki Y., Hirose K., Kuruma K., Konaka R., Okabayashi T.: Chem. Pharm. Bull. *28*, 1378 (1980).
9. Hirose K., Matsushita A., Eigyo M., Jyoyama H., Fujita A., Tsukinoki Y., Shiomi T., Matsubara K.: Arzneim.-Forsch. *31*, 63 (1981).
10. Owen R. T.: Drugs Future *7*, 169 (1982); *8*, 282 (1983); *9*, 226 (1984).
11. Ballabio M., Caccia S., Garattini S., Guiso G., Reginato R.: Arzneim.-Forsch. *33*, 959 (1983).
12. Souto M.: Drugs Future *9*, 501 (1984).
13. Stenger A., Charveron M., Briley M.: J. Pharmacol. *15*, 249 (1984).
14. Golovenko N. Ya., Totrova M. Yu., Rudenko O. P., Povolotskaya O. P.: Khim.-Farm. Zh. *20*, 806 (1986).

15. Sethy V. H., Daenzer C. L., Russell R. R.: J. Pharm. Pharmacol. *35*, 194 (1983).
16. Konishi M., Mori Y., Hirai K.: J. Chromatogr. *229*, 355 (1982).
17. Anonym: Drugs Future *9*, 522 (1984); *10*, 602 (1985), *11*, 626 (1986); *12*, 729 (1987).
18. Greve H. G., Resah K. (Cassella Farbwerke Mainkur AG): Ger. Offen. 2,322,779; Chem. Abstr. *80*, 36874 (1974).
19. Mouzin G. Cousse H., Stenger A., Casadio S. (Pierre Fabre S. A.): Eur. Pat. Appl. 299; Japan 79 36, 238; Chem. Abstr. *91*, 20092 (1979).
20. Mouzin G., Cousse H. (Pierre Fabre S. A.): Fr. Demande 2,492,818; Chem. Abstr. *97*, 163504 (1982).
21. Kulkarni Y. D., Sharma V. L., Dua P. R., Shanker G.: Indian J. Pharm. Sci. *44*, 1 (1982); Chem. Abstr. *97*, 144501 (1982).
22. Bell S. C., McCaully R. J., Childress S. J.: J. Heterocycl. Chem. *4*, 647 (1967).
23. Apresella L., Lamanna A.: Farmaco, Ed. Sci. *8*, 212 (1953); Chem. Abstr. *48*, 3921 (1954).
24. Vogl O., Pöhm M.: Monatsh. Chem. *83*, 541 (1952); Chem. Abstr. *47*, 2696 (1953).
25. Slotta K. H., Heller H.: Ber. Dtsch. Chem. Ges. *63*, 1024 (1930).
26. Gensler W. J., Dheer S. K.: J. Org. Chem. *46*, 4051 (1981).
27. Sicher J., Pánková M.: Collect. Czech. Chem. Commun. *20*, 1409 (1955).
28. Nagai W. N., Kaneo S.: Justus Liebigs Ann. Chem. *470*, 157 (1929).
29. Sternbach L. H., Fryer R. I., Metlesics W., Reeder E., Sach G., Saucy G., Stempel A.: J. Org. Chem. *27*, 3788 (1962).
30. Clarke H. T., Bean H. J.: Org. Synth., Coll. Vol. *2*, 29 (1943).
31. Schipper E., Chinery E.: J. Org. Chem. *26*, 4480 (1961).
32. Faith H. E., Bahler M. E., Florestano H. J.: J. Am. Chem. Soc. *77*, 543 (1955).
33. Cymerman-Craig J., Harrisson R. J., Tate M. E., Thorp R. H., Ladd R.: Aust. J. Chem. *9*, 89 (1956); Chem. Abstr. *50*, 12924 (1956).
34. Protiva M., Jílek J.: Chem. Listy *42*, 145 (1948); Protiva M., Jílek J., Kolínský J., Řeřicha V., Urban J.: Collect. Czech. Chem. Commun. *13*, 326 (1948).
35. Zawisza T., Machoń Z., Kuczyński L.: Acta Pol. Pharm. *22*, 477 (1965).
36. Haller H. L., Bartlett P. D., Drake N. L., Newman M. S., Cristol S. J., Eaker C. M., Hayes R. A., Kilmer G. W., Magerlein B., Mueller G. P., Schneider A., Wheatley W.: J. Am. Chem. Soc. *67*, 1591 (1945).

Translated by the author (M. P.).