REACTIONS OF 4-CHLORO-1-NITROBENZENE WITH *o*-SUBSTITUTED PHENYLACETONITRILES; SYNTHESIS OF 8-CHLORO-1-METHYL(AND METHYLTHIOMETHYL)-6-(2-SUBSTITUTED PHENYL)-4*H*-*s*--TRIAZOLO[4,3-*a*]-1,4-BENZODIAZEPINES

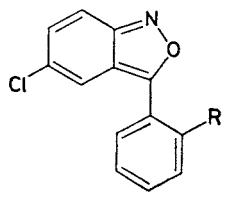
Zdeněk VEJDĚLEK[a], Jiří HOLUBEK[a], Miroslav RYSKA[a], Ivan KORUNA[a], Emil SVÁTEK[a], Miloš BUDĚŠÍNSKÝ[b] and Miroslav PROTIVA[a]

[a] *Research Institute for Pharmacy and Biochemistry, 130 60 Prague 3 and*
[b] *Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, 166 10 Prague 6*

Received February 23rd, 1987

Reactions of 4-chloro-1-nitrobenzene with 2-methyl-, 2-methoxy- and 2-(methylthio)phenylacetonitrile in methanolic potassium hydroxide gave mixtures from which the expected 3-aryl--5-chloro-2,1-benzisoxazoles *Ia—c* were isolated in addition to the 2*H*-indoles *IIIa* and *IIIc* and acridines *VIII* and *IX*. The 2,1-benzisoxazoles were reduced to the 2-aminobenzophenones *XIIa—c* which were transformed *via* the phthalimidoacetamido compounds *XIIIa—c* to 5-aryl-7--chloro-1,3-dihydro-1,4-benzodiazepine-2-ones *XVa—c*. Treatment with phosphorus pentasulfide led to the thiones *XVIa—c* which reacted in boiling butanol either with acetohydrazide or with (methylthio)acetohydrazide to give the title compounds *XVIIa—c* and *XVIIIa—c*. They showed only weak anticonvulsant, incoordinating and central depressant effects.

Some time ago we discussed the possibility of using 3-aryl-5-chloro-2,1-benzisoxazoles[1] as intermediates in the synthesis of the anxiolytic and hypnotic 5-aryl-7--chloro-1,3-dihydro-1,4-benzodiazepin-2-ones[2,3] as well as of the even more active 1-substituted 6-aryl-8-chloro-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepines[4-6]. The utility of the unsubstituted compound *I* (R = H) was clear because this compound is formed in high yields by the base-catalyzed reaction of 4-chloro-1-nitrobenzene with phenylacetonitrile[7-10]. On the other hand, we found that a similar reaction of 4-chloro-1-nitrobenzene with (2-chlorophenyl)acetonitrile results in a mixture from which the desired compound *I* (R = Cl) could be isolated in the yield of only 12% in addition to further four unexpected products which were identified[1]. The course of this reaction attracted our attention and in this paper we are describing our experience in three other *o*-substituted cases starting from (2-methylphenyl)acetonitrile (series *a*), (2-methoxyphenyl)acetonitrile (series *b*), and (2-(methylthio)phenyl)-acetonitrile (series *c*) with the aim at preparing first 5-chloro-3-(2-substituted phenyl)--2,1-benzisoxazoles *Ia*, *Ib*, and *Ic*.



I

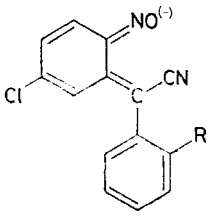
In formulae *I–V, VII, XII, XIII, XV–XVIII*: *a*, R = CH_3; *b*, R = OCH_3; *c*, R = SCH_3

In series *a* we started from 2-methylbenzyl bromide[11] which was transformed to (2-methylphenyl)acetonitrile by treatment with sodium cyanide in dimethyl sulfoxide (60°C) (method[12]; for a different procedure, *cf.* ref.[13]). (2-Methylphenyl)acetonitrile was subjected to treatment with 4-chloro-1-nitrobenzene in a concentrated solution of potassium hydroxide in methanol and in the presence of benzene at 25–30°C (method[1]). After dilution with benzene, the mixture was decomposed with an aqueous solution of ammonium chloride. Evaporation of the organic layer and crystallization of the residue first from a mixture of ethanol and hexane and then from ethanol gave the first two products (empirical formulae on the basis of analyses and mass spectra): the ethanol-soluble compound A, $C_{14}H_{10}ClNO$, m.p. 89–90°C, and the ethanol-insoluble compound B, $C_{23}H_{17}ClN_2$, m.p. 177–178°C. Evaporation of the mother liquors and chromatography of the residue on aluminium oxide gave in the first fractions further amounts of compound A. The more polar fractions could be separated by distillation *in vacuo*. The lower boiling fraction crystallized and represents the minor product C, $C_7H_7NO_3$, m.p. 53–54°C. The higher boiling fraction did not crystallize and represents the other minor product D, $C_{15}H_{12}N_2O_2$, b.p. 197°C/0·1 kPa.

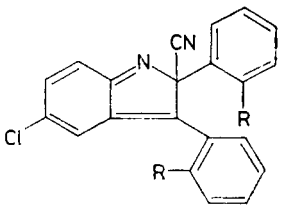
Compound A is the desired 5-chloro-3-(2-methylphenyl)-2,1-benzisoxazole (*Ia*), formed *via* the anion *IIa* (refs[7,14]). The UV, IR, and ^{1}H NMR spectra are in agreement with structure *Ia* which was confirmed by further chemical transformation. Compound *Ia* is the main product of the reaction, the yield being 54%.

The composition of compound B (yield about 10%) indicates the presence of three aromatic rings; ^{1}H NMR spectrum showed the presence of 11 aromatic protons *per* 6 protons of two methyl groups (no further protons are present). The IR spectrum characterized the compound to be a nitrile (ν 2 238 cm^{-1}). These facts are compatible with formulating compound B as the 2*H*-indole derivative *IIIa*. Its formation assumes in addition to the anion *IIa* further intermediates like *IVa* which could be formed from *IIa* by displacement of CN^- with HO^- and by the following Knoevenagel reaction[15]. The rather big difference in the chemical shifts of signals corresponding to the two methyl groups in the two tolyls (2 s at δ 2·75 and 1·50, respectively) could have steric reasons: deflexion of one methyl group out of the

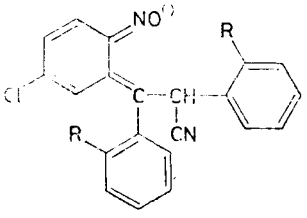
plane of the aromatic ring in this rather crowdy molecule, hindrance of free rotation along the Ar—C bond, different shieldings of the methyl groups by the neighbouring benzene rings. Structure *IIIa* was corroborated by the reduction with lithiumaluminium hydride. Two products were formed: the neutral $C_{22}H_{18}ClN$ and the basic one $C_{23}H_{23}ClN_2$. The former is the indole derivative *Va*, formed from *IIIa* by dis placement of CN^- with H^- and by the shift of the double bonds; its spectra fully confirm this structure and it corresponds to the chloro analogue *V* (R = Cl), described previously[1]. The basic and main product of the reduction has by 6 H more than the starting compound *IIIa* and it is the primary amine *VI*; its UV, IR, and ^{1}H NMR spectra are in agreement with this formulation. The molecule contains two asymmetric centers but the product is homogeneous (*cf.* the singlet of the proton in position 3 in the ^{1}H NMR spectrum); the *trans*-configuration of the aryl groups is probably preferred. The hydrochloride (monohydrate) seems homogeneous after a single crystallization.



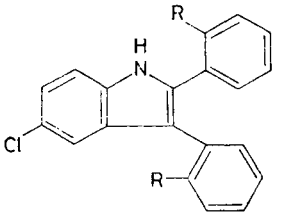
II



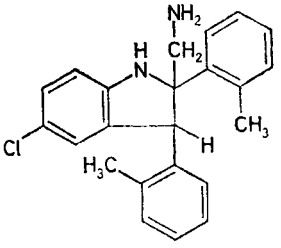
III



IV

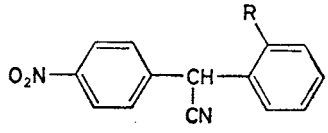


V



VI

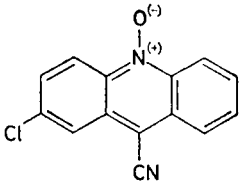
Compound C (minor product) is 4-nitroanisole formed by solvolysis of the starting 4-chloro-1-nitrobenzene; its melting point is in agreement with the literature value[16]. The molecule of compound D (about 10%) contains two aromatic rings (2 and 4 adjacent Ar—H), the nitro group and the nitrile group (IR spectrum). The ^{1}H NMR spectrum settles its structure as that of 2-methyl-4'-nitrodiphenylacetonitrile (*VIIa*). This structure is not surprising; the analogous 4-nitrodiphenylacetonitrile was obtained by reaction of 4-chloronitrobenzene with phenylacetonitrile and potassium hydroxide in pyridine[17].



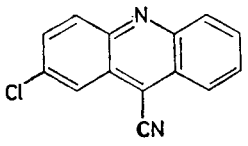
VII

In series *b*, salicylaldehyde was methylated with dimethyl sulfate to 2-methoxybenzaldehyde[18] which was transformed by the crossed Cannizzaro reaction[19] to 2-methoxybenzyl alcohol[18,20] (in analogy to ref.[21]). Treatment with thionyl chloride in benzene gave 2-methoxybenzyl chloride[18,20] which was converted to (2-methoxyphenyl)acetonitrile by reaction with sodium cyanide in dimethyl sulfoxide at 35 to 45°C (analogy[12]); the conditions used for the latter reaction proved more satisfactory then working in aqueous ethanol[20,22] or in dimethylformamide[18]. The reaction of (2-methoxyphenyl)acetonitrile with 4-chloro-1-nitrobenzene was carried out similarly like in series *a* and following products were obtained: compound E (30%), $C_{14}H_7ClN_2O$, m.p. 204–205°C; compound F (27%), $C_{14}H_{10}ClNO_2$, m.p. 67–70°C; compound G (2%), $C_{14}H_7ClN_2$, m.p. 210–211°C.

The compound E was identified as 2-chloroacridine-10-carbonitrile N-oxide (*VIII*) by comparison with the same compound, obtained previously[1] by reaction of (2-chlorophenyl)acetonitrile with 4-chloro-1-nitrobenzene. In the present case, the methoxy group of the intermediate *IIb* disappeared; it was displaced in the proceeding intramolecular nucleophilic cyclization. The compound F is the desired 5-chloro-3-(2-methoxyphenyl)-2,1-benzisoxazole (*Ib*). This formulation was corroborated by UV, IR, and ^{1}H NMR spectra, and by further transformation. The compound G was identified as 2-chloroacridine-10-carbonitrile (*IX*) by comparison with a product isolated previously[1] from the reaction of (2-fluorophenyl)acetonitrile with 4-chloro-1-nitrobenzene. It accompanies the N-oxide *VIII* from which it is formed by deoxygenation. The investigated reactions of 4-chloro-1-nitrobenzene with arylacetonitriles are generally accompanied by oxidation and reduction processes. In addition to the air oxygen, the N-oxide oxygen of *VIII* is probably the most important source of oxygen for the oxidation reactions. Rather different pattern of products in series *a* and *b* is worth mentioning.



VIII



IX

In series *c* we attempted to prepare 2-(methylthio)benzaldehyde from 2-chlorobenzaldehyde by treatment with sodium methanethiolate in boiling 2-ethoxyethanol. Instead of the expected displacement, the Cannizzaro reaction[19] took place and the crystalline product obtained was identified as 2-chlorobenzyl alcohol (*cf.*[23,24]). 2-(Methylthio)benzyl alcohol was then obtained by reduction of 2-(methylthio)benzoic acid[25] with sodium dihydridobis(2-methoxyethoxo)aluminate[26]. The following transformation to 2-(methylthio)benzyl chloride was carried out by treatment with thionyl chloride in benzene without heating (ref.[27] described this transformation by refluxing the mixture in the presence of a small amount of pyridine). (2-(Methylthio)phenyl)acetonitrile was obtained from the chloride by treatment with sodium cyanide in dimethyl sulfoxide with a very high yield; this nitrile was mentioned in ref.[28].

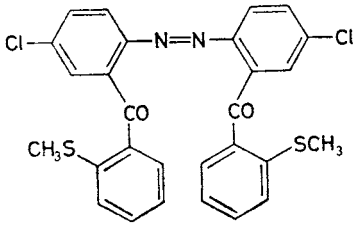
Reaction of (2-(methylthio)phenyl)acetonitrile with 4-chloro-1-nitrobenzene and processing of the mixture of products were carried out similarly like in the preceding series *a* and *b*. First to be isolated was the very insoluble and sharply red compound H (8%), $C_{28}H_{20}Cl_2N_2O_2S_2$, m.p. 270–271°C. Chromatography afforded successively: recovered 4-chloro-1-nitrobenzene (12%); compound J (6%), $C_{23}H_{17}ClN_2S_2$, m.p. 189–190°C; 4-nitroanisole (*cf.* compound C in series *a*) (6%); compound K (27%), $C_{14}H_{10}ClNOS$, m.p. 109–110°C; compound L (36%), $C_{14}H_{11}NO_3S$, m.p. 110 to 111°C.

Elemental composition of compound H indicates the presence of two 4-Cl-C_6H_4-N and two thioanisole residues (2 atoms of chlorine and 2 atoms of sulfur). According to the IR spectrum, there is no CN group but there is the ArCOAr' fragment (ν 1 660 cm^{-1}). The ^1H NMR spectrum shows signals of 10 hydrogen atoms; because there are 20 H atoms in the molecule, this must be symmetrical; the two identical halves of the molecule have the elemental composition $C_{14}H_{10}ClNOS$. The ^1H NMR spectrum proves for each half of the molecule the presence of one SCH_3 group (singlet at 2·44) and of seven aromatic protons (δ 6·88–7·73). The complete analysis of their multiplets leads to the proof of presence of 1,2-disubstituted and 1,2,4-trisubstituted benzene nuclei. Assuming again *IIc* as the common intermediate of all products we have the assignment of the azobenzene structure *X* for compound H. The appearance of the keto group instead of the =C(CN)Ar fragment (*cf. IIc*) has

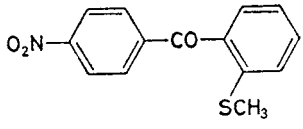
to be explained by displacement of the CN anion with the hydroxide anion and the formation of the azo group is the result of reduction of the nitrogen function contained in *IIc*.

Compound J, according to its elemental composition, must contain one 4-Cl—C_6H_4—N and two thioanisole fragments (one Cl and two S atoms). One CN group (ν 2 230 cm^{-1}) remains in the molecule like in the postulated intermediate *IVc*. The assignment of the 2*H*-indole structure *IIIc* to compound J was corroborated by the ^{1}H NMR spectrum: It confirmed the total number of 17 H atoms in the molecule. Six of them belong to two SCH_3 groups (the signal of one of them is strikingly shifted upfield to 1·90) and the remaining 11 H atoms are aromatic protons; none of them can be exchanged by deuterium. A characteristic feature of this spectrum is the broadening of some signals; it is the already mentioned shifted signal of one of the SCH_3 groups and further signals of six of the aromatic protons where the fine structure of the multiplets disappeared almost completely, which makes the interpretation difficult. Not even recording the spectrum in hexadeuteriodimethyl sulfoxide at 80°C did lead to the sufficient narrowing of the signals. The origin of their broadening is the strongly hindered rotation of both *o*-substituted phenyls in *IIIc* due to their steric proximity and bulkiness of the SCH_3 substituents in *o*-positions which is shown by models. The shielding effects to the hydrogen atom in *o*-position and both hydrogen atoms in *m*-positions of both phenyl residues are incompletely averaged in the course of the hindered rotation which leads to the important broadening of the corresponding six signals. This phenomenon is not so striking with the *para*-standing hydrogen atoms because these are in the axes of rotation. ^{13}C NMR spectrum was also recorded and shows similar anomalies.

Similarly like in series *a*, 4-nitroanisole (about 6%) was isolated from the mother liquors after the indole *IIIc*. Further product to be isolated was compound K, the desired 5-chloro-3-(2-methylthiophenyl)-2,1-benzisoxazole (*Ic*). The spectra fully confirmed this structure assignment. The last was compound L whose molecule contains nitro group (IR), diaryl ketone fragment (IR), methylthio group (^{1}H NMR), and 8 aromatic protons in one 1,2-disubstituted and one 1,4-disubstituted benzene nuclei (IR and ^{1}H NMR). The experimental data result in the assignment of the



X



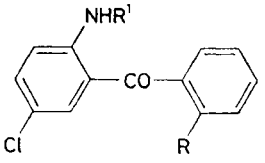
XI

structure of 2-methylthio-4'-nitrobenzophenone (*XI*). This structure has the precedent in our previous study[1] (Cl instead of SCH_3) and the formation of *XI* has to be explained similarly: The precursor of *XI* is the non-isolated nitrile *VIIc* which cleaves the α-proton, the anion formed reacts with air oxygen to give the peroxide anion, which is cleaved to ketone *XI* and the cyanate anion (*cf.* Kornblum[29]).

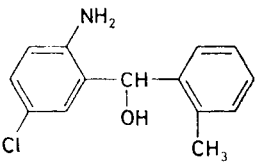
The present work thus confirmed the versatility of pathways which must be considered in reactions of 4-chloro-1-nitrobenzene with substituted phenylacetonitriles in methanolic potassium hydroxide solutions. In addition to the six types of products encountered in the previous work[1], three further types (*III*, *VII*, and *X*) were found in the present study. The three desired 3-aryl-5-chloro-2,1-benzisoxazoles (*Ia*, *Ib*, *Ic*) were obtained in preparatively useful yields which enabled to continue and conclude the planned syntheses of 1-substituted 6-aryl-8-chloro-4*H*-*s*-triazolo[4,3-*a*]-1,4--benzodiazepines.

2,1-Benzisoxazoles *Ia*–*c* were reduced with iron and acetic acid in boiling aqueous ethanol to 2-amino-5-chlorobenzophenones *XIIa*–*c* (analogy[1,7,30]); all three ketones are known and were prepared by different methods: *Ia* (refs[31,32]), *Ib* (refs[31,33]), *Ic* (refs[34,35]). Compound *Ia* was reduced with lithium aluminium hydride in a mixture of ether and benzene and the product was identified as the substituted benzhydrol *XIV*; the same product was obtained by similar reduction of the benzophenone *XIIa*. 2-Aminobenzophenones *XIIa*–*c* were then subjected to treatment with phthalimidoacetyl chloride[36–38] in boiling chloroform and gave the corresponding phthalimido derivatives *XIIIa*–*c*; the first two of them were included in claims of a patent application[39] but any experimental data are missing. Further step of the synthesis was the hydrazinolysis of *XIIIa*–*c* in methanol at 60°C which was accompanied by cyclization to the corresponding 5-aryl-7-chloro-1,3-dihydro-1,4--benzodiazepin-2-ones (*XVa*–*c*) (method[39]). All the three compounds are known and were prepared by different methods: *XVa* (ref.[40]), *XVb* (ref.[40]), *XVc* (refs[34,35]). The method used by us is claimed in the mentioned application[39] for *XVa* and *XVb* but not described.

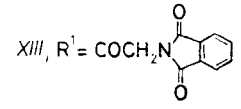
The lactams *XVa*–*c* were transformed to the corresponding thiolactams *XVIa*–*c* by treatment with phosphorus pentasulfide in boiling pyridine (*cf.* ref.[6]); only



XII, R^1 = H

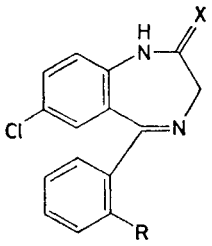


XIV

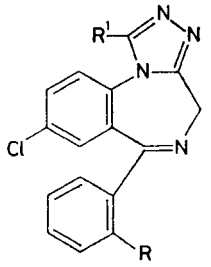


XIII, R^1 = $COCH_2N$

XVIb is known and was prepared similarly[41-43]. The last steps were reactions of the thiones *XVIa–c* with acetohydrazide[44] or (methylthio)acetohydrazide[45] in boiling butanol (method[6,46]) to give the corresponding 6-aryl-8-chloro-1-methyl-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepines *XVIIa–o* and their 1-(methylthiomethyl) analogues *XVIIIa–c*.



XV, X = O
XVI, X = S



XVII, $R^1 = CH_3$
XVIII, $R^1 = CH_2SCH_3$

Compounds *XVIIa*, *XVIIb*, *XVIIIa*, and *XVIIIb* were subjected to preliminary pharmacological screening in mice using four tests: T-1, anticonvulsant activity towards the maximum electroshock; T-2, anticonvulsant activity towards pentetrazole; T-3, incoordinating activity on the rotarod; T-4, inhibition of the spontaneous locomotor activity followed by the photo-cell method (Dews). The compounds were administered orally in the only dose of 1 mg/kg. Test T-1: *XVIIa*, ED_{50} = = 0·75 mg/kg; *XVIIb*, weak activity, protection from the convulsions only in 30% animals; *XVIIIa*, weak activity, protection in 30% animals; *XVIIIb*, weak activity, protection in 30% animals. Test T-2: *XVIIa*, full protective effect; *XVIIb*, *XVIIIa*, *XVIIIb*, marginal effects. Test T-3: *XVIIa*, ataxia in 50% animals; *XVIIb*, *XVIIIa*, *XVIIIb*, marginal effects. Test T-4: *XVIIa*, only mild (statistically insignificant) inhibition of the activity; *XVIIb*, *XVIIIa*, *XVIIIb*, practically inactive. In conclusion, introduction of substituents other than atoms of fluorine or chlorine into the *o*-position of 6-phenyl in 1-substituted 6-aryl-8-chloro-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepines is connected with a strong decrease or with a complete loss of the anticonvulsant, incoordinating, and central depressant activity (*cf.* refs[6,46]).

EXPERIMENTAL

The melting points were determined in a Kofler block and are not corrected; the samples were dried *in vacuo* of about 60 Pa over P_2O_5 at room temperature or at 77°C. The UV spectra (in methanol, λ_{max} in nm ($\log \varepsilon$)) were recorded with a Unicam SP 8 000 spectrophotometer, the IR spectra (mostly in Nujol, ν in cm^{-1}) with Unicam SP 200G and Perkin–Elmer 298 spectrophotometers, ^1H NMR spectra (in C^2HCl_3 unless stated otherwise, δ, J in Hz) mostly with a CW-NMR spectrometer Tesla BS 487 C (80 MHz) and partly on a FT-NMR spectrometer

Varian XL-200 (200 MHz) (^{13}C NMR spectrum with the same instrument at 50·3 MHz), and finally the mass spectra with MCH 1 320 and Varian MAT 44S spectrometers (*m/z* and % given). The homogeneity of the compounds and composition of the mixtures were checked by thin layer chromatography on silica gel (Silufol). The column chromatography was carried out on neutral Al_2O_3 (activity II).

2-Chlorobenzyl Alcohol

2-Chlorobenzaldehyde (14·0 g) was added to a stirred solution of 14·0 g sodium methanethiolate in 90 ml 2-ethoxyethanol and the mixture was refluxed for 4 h. A part of the solvent (70 ml) was evaporated *in vacuo* and the residue was distributed between 100 ml water and 100 ml benzene, the aqueous layer was extracted with further 100 ml benzene, the benzene solutions were combined, washed with 5% NaCl, 5% $NaHCO_3$, dried with Na_2SO_4, and evaporated. The residue was distilled; 6·20 g (41%) product boiling at 135°C/1·6 kPa. The distillate solidified on standing, was recrystallized from hexane (m.p. 68—69°C), and was identified as 2-chlorobenzyl alcohol. Refs[23,24], m.p. 69·5°C, b.p. 242°C.

2-Methoxybenzyl Alcohol

The present procedure is a modification of the published method[18,20]. A solution of 210 g 2-methoxybenzaldehyde and 164 g 37% formaldehyde in 160 ml methanol was added over 70 min to a stirred solution of 258 g 85% KOH in 390 ml methanol at 60—70°C (heating was not necessary) and the misture was then stirred for 3 h and heated to the same temperature. Most of the solvents (500 ml) were distilled off, the cooled residue was distributed between 400 ml water and 200 ml benzene, the aqueous layer was extracted with additional 300 ml benzene (in 3 parts), the extracts were combined, washed with dilute NaCl solution, dried, and evaporated under reduced pressure. The residue was distilled; 200 g (94%), b.p. 93—94°C/130 Pa, n_D^{22} 1·5468. Refs[18,20,27], yield 79 and 82%; b.p. 100—101°C/0·3 kPa, 122—123°C/2 kPa, and 80—82°C/ /13 Pa, respectively; n_D^{21} 1·5470.

2-Methoxybenzyl Chloride

The present procedure is a modification of the published method[18,20]. A stirred solution of 65·0 g 2-methoxybenzyl alcohol in 300 ml benzene was cooled to 2°C and treated at this temperature over 100 min with 72 g $SOCl_2$, added dropwise. The mixture was allowed to stand overnight at room temperature, stirred for 2 h at 45—50°C, the volatile components were distilled off through a column under reduced pressure, and the residue was distilled; 60·7 g (82%), b.p. 110—112°C/2·2 kPa, n_D^{22} 1·5458. Refs[18,20,27], yield 75, 74—79, and 66%; b.p. 101—102°C/ /2 kPa, 88—89°C/0·5 kPa, 52—54°C/13 Pa; n_D^{22} 1·5478. Our distillate solidified on standing to a low-melting solid; ref.[20], m.p. 29—30°C.

2-(Methylthio)benzyl Chloride

A stirred solution of 95·0 g 2-(methylthio)benzyl alcohol[26] in 400 ml benzene was treated over 80 min with 95 ml $SOCl_2$ at 2—6°C, the mixture was stirred for 2 h with cooling, allowed to stand for 17 h at room temperature, the volatile components were distilled off through a column under reduced pressure, the residue was dissolved in a mixture of 100 ml benzene and 75 ml ether, the solution was washed with water, 6% $NaHCO_3$, and water, then it was dried, the solvents were evaporated, and the residue was distilled; 87·6 g (82%), b.p. 130—131°C/2 kPa,

n_D^{22} 1·6040. Ref.[27] described a similar reaction at the boiling point of the mixture and in the presence of a small amount of pyridine; yield 71%, b.p. 75—76°C/13 Pa, n_D^{21} 1·6045.

(2-Methylphenyl)acetonitrile

A stirred suspension of 54 g 94% NaCN in 270 ml dimethyl sulfoxide was treated under cooling (maximum temperature 60°C) with 152 g 2-methylbenzyl bromide[11], added dropwise over 40 min. The mixture was stirred for 2 h at 40—50°C, allowed to stand overnight at room temperature, poured into 2·7 l water, and the product was extracted with ether. The extract was dried ($MgSO_4$), the solvent was evaporated, and the residue was distilled; 101 g (94%), b.p. 112 to 120°C/1·3—1·6 kPa, n_D^{25} 1·5252. Ref.[13] described a similar reaction with KCN in boiling aqueous ethanol and gave the yield of 64%, b.p. 74°C/90 Pa, n_D^{25} 1·5260.

(2-Methoxyphenyl)acetonitrile

A solution of 30 g 94% NaCN in 145 ml dimethyl sulfoxide was prepared by heating to 90°C, it was cooled to 35°C, and the fine suspension formed was treated under stirring with 74·0 g 2-methoxybenzyl chloride in such a rate that the temperature was maintained at 35—45°C. The mixture was stirred at this temperature for 1·5 h (total reaction time 3 h), poured into 600 ml water, and the product was extracted with a 1 : 1 mixture of benzene and ether. The extract was washed with 10% NaCl, dried, and the solvents were evaporated under reduced pressure (maximum bath temperature 75°C). The residue crystallized on cooling: 67·6 g (97%), m.p. 68—69°C. Refs[18,20] (different procedures), yields 91 and 92%; m.p. 70—71 and 68·5°C, respectively.

(2-(Methylthio)phenyl)acetonitrile

2-(Methylthio)benzyl chloride (87·5 g) and 34 g 95% NaCN were reacted in 170 ml dimethyl sulfoxide under similar conditions like in the preceding case. Similar processing with the final distillation gave 78·8 g (95%) product boiling at 115°C/70 Pa, n_D^{23} 1·5860. For C_9H_9NS (163·2) calculated: 66·22% C, 5·56% H, 8·58% N, 19·64% S; found: 66·27% C, 5·62% H, 8·67% N, 19·32% S.

5-Chloro-3-(2-methylphenyl)-2,1-benzisoxazole (*Ia*)

A solution of 53·6 g 4-chloro-1-nitrobenzene and 45·0 g (2-methylphenyl)acetonitrile in 150 ml benzene was added dropwise over 2·5 h to a stirred solution of 218 g 79% KOH in 430 ml methanol, maintained at 25—30°C. The mixture was stirred for 3 h at room temperature, poured into a solution of 210 g NH_4Cl in 1·4 l water, stirred, and extracted with benzene. The extract was washed with 10% NaCl, dried with $CaCl_2$, and the solvent was evaporated under reduced pressure. The residue was dissolved in a mixture of 20 ml ethanol and 175 ml hexane and allowed to crystallize overnight in the refrigerator. Crude compound A (32·0 g, m.p. 86—88°C) was obtained by filtration, washing with a mixture of benzene and hexane, and by drying *in vacuo*. Processing of the mother liquor gave further 12·2 g crude compound A. The combined products were heated for a short time with 400 ml boiling ethanol and the undissolved part (10·5 g compound B, m.p. 173—175°C) was filtered off. Partial evaporation of the filtrate and crystallization by cooling gave 31·0 g compound A, m.p. 86—88°C. Further amount of this substance was obtained from the first chromatographic fractions (see below); the total yield was 44·8 g (54%) and compound A was identified as *Ia*. Analytical sample, m.p. 89—90°C (hexane or ethanol). Mass spectrum: 243 (M^+, $C_{14}H_{10}ClNO$), 242, 214, 208, 200, 180, 91, 65. UV spectrum: 250 (3·95), 340 (4·03). IR spectrum: 715, 760, 772, 800, 892 (4 and 2 adjacent, and solitary Ar—H);

1 510, 1 545 (Ar); 1 630 (C=N). ^{1}H NMR spectrum: 2·49 s, 3 H ($ArCH_3$); 7·10—7·70 m, 7 H (ArH). For $C_{14}H_{10}ClNO$ (243·7) calculated: 68·99% C, 4·14% H, 14·55% Cl, 5·75% N; found: 68·75% C, 4·13% H, 14·27% Cl, 5·56% N.

The ethanol-insoluble compound B was obtained in a yield of 10·5 g (9%) and was identified as 5-chloro-2,3-bis(2-methylphenyl)-2*H*-indole-2-carbonitrile (*IIIa*). Analytical sample was obtained by crystallization from a hundredfold amount of boiling ethanol, m.p. 177—178°C. Mass spectrum: 357 (M + 1), 356 (M^+, $C_{23}H_{17}ClN_2$, base peak), 355, 341, 340, 306, 305, 204, 203. UV spectrum: 228 (4·28), 312 (4·16). IR spectrum: 762, 840, 882 (4 and 2 adjacent, and solitary Ar—H); 1 520, 1 580, 3 090 (Ar); 1 600 (C=N); 2 238 (R—CN). ^{1}H NMR spectrum: 1·50 s, 3 H and 2·75 s, 3 H (2 $ArCH_3$); 6·80—8·20 m, 11 H (ArH). For $C_{23}H_{17}ClN_2$ (356·8) calculated: 77·42% C, 4·80% H, 9·93% Cl, 7·85% N; found: 77·48% C, 4·76% H, 10·10% Cl, 7·68% N.

Mother liquors after the isolation of the crude *Ia* were evaporated and the residue (40 g) was chromatographed on 1 kg Al_2O_3 using benzene as the eluent. Lrom the first fractions further 13·8 g *Ia* were obtained by crystallization. The more polar fractions were oily and could be distilled. First the low-boiling compound C (2·0 g) was obtained, b.p. 130—150°C/0·3 kPa, and crystallized on standing, m.p. 53—54°C (hexane–ethanol). The compound was identified as 4-nitroanisole. Ref.[16], m.p. 52·5°C.

A little more polar fraction gave by distillation 2·5 g compound D, b.p. 197°C/0·1 kPa, which was identified as 2-(2-methylphenyl)-2-(4-nitrophenyl)acetonitrile (*VIIa*). IR spectrum (film): 743, 841, 857, 869 (4 and 2 adjacent Ar—H); 1 347, 1 520 ($ArNO_2$); 1 591, 1 605, 3 070, 3 100 (Ar); 2 235 (R—CN). ^{1}H NMR spectrum: 2·24 s, 3 H ($ArCH_3$); 5·35 s, 1 H (Ar_2CHCN); 7·20 m, 4 H (4 ArH of *o*-tolyl); 7·42 d, 2 H (H-2 and H-6 of 4-nitrophenyl, J = 8·5); 8·20 d, 2 H (H-3 and H-5 of 4-nitrophenyl, J = 8·5). For $C_{15}H_{12}N_2O_2$ (252·3) calculated: 71·41% C, 4·80% H, 11·11% N; found: 72·03% C, 5·05% H, 10·65% N.

5-Chloro-2,3-bis(2-methylphenyl)-2,3-dihydroindole-2-methaneamine (*VI*)

A solution of 2·5 g *IIIa* in 20 ml benzene was prepared by heating, cooled partly, and added dropwise to a stirred solution of 2·5 g $LiAlH_4$ in 60 ml ether. The mixture was refluxed for 2 h and after cooling decomposed by a slow addition of 10 ml 20% NaOH. After stirring for 30 min the solid was filtered off and washed with 60 ml warm benzene. The filtrate was evaporated under reduced pressure, the residue (2·7 g) was dissolved in 25 ml ether, and the solution was neutralized by a solution of HCl in ether. The precipitated hydrochloride of *VI* was filtered, washed with ether, and dried; 2·0 g (69%). It crystallized from a mixture of aqueous ethanol and ether as the monohydrate, m.p. 174—175°C. Mass spectrum: 362 (M^+, $C_{23}H_{23}ClN_2$, 2·5), 335 (37), 334 (52), 333 (85), 332 ($C_{22}H_{19}ClN$, M — CH_2NH_2, 100), 298 (20), 297 (74), 254 (22), 204 (18). For $C_{23}H_{24}Cl_2N_2 + H_2O$ (417·4) calculated: 66·18% C, 6·28% H, 16·99% Cl, 6·71% N; found: 66·78% C, 6·07% H, 17·32% Cl, 6·44% N.

A suspension of the hydrochloride in water was decomposed with NH_4OH and the base *VI* was isolated by extraction with benzene and ether. The combined extracts were dried and evaporated. The solid base was purified by crystallization from a mixture of ethanol, cyclohexane and hexane, m.p. 143—144°C. UV spectrum: 256 (4·03), 329 (3·46). IR spectrum: 730, 755, 788, 815, 870 (4 and 2 adjacent, and solitary Ar—H); 1 600 (Ar); 3 190, 3 210 (NH_2). ^{1}H NMR spectrum: 1·20 bs, 2 H (NH_2); 1·75 s, 3 H and 2·25 s, 3 H (2 $ArCH_3$); 3·35 and 3·70 ABq, 1 + 1 H (CH_2N, J = 13·0); 4·15 bs, 1 H (NH of dihydroindole); 5·40 s, (H-3); 6·50—7·20 m, 11 H (ArH). For $C_{23}H_{23}ClN_2$ (362·9) calculated: 76·12% C, 6·39% H, 9·77% Cl, 7·72% N; found: 76·46% C, 6·56% H, 10·07% Cl, 7·55% N.

The mother liquor after the *VI* hydrochloride was evaporated, the residue was dissolved in 3 ml benzene, and the solution was treated with 2 ml hexane. Cooling led to crystallization of 0·7 g (30%) neutral 5-chloro-2,3-bis(2-methylphenyl)indole (*V*), m.p. 185—186°C (benzene–hexane). Mass spectrum: 331 (M^+, $C_{22}H_{18}ClN$, 100), 330 (13), 316 (7), 296 (18), 294 (16), 281 (22), 204 (17). UV spectrum: 232 (4·53), 300 (4·14). IR spectrum: 768, 790, 888 (4 and 2 adjacent, and solitary Ar—H); 1 598 (Ar); 3 400 (NH). ^{1}H NMR spectrum ($C^2H_3SOC^2H_3$): 2·00 s, 3 H and 2·18 s, 3 H (2 $ArCH_3$); 7·10—7·60 m, 11 H (11 ArH); 11·70 bs, 1 H (NH). For $C_{22}H_{18}$.ClN (331·8) calculated: 79·62% C, 5·47% H, 10·69% Cl, 4·22% N; found: 79·96% C, 5·39% H, 10·64% Cl, 4·01% N.

5-Chloro-3-(2-methoxyphenyl)-2,1-benzisoxazole (*Ib*)

A stirred solution of 319 g 79% KOH in 630 ml methanol was slowly treated (over 1·5 h) with a solution of 75·0 g (2-methoxyphenyl)acetonitrile and 78·8 g 4-chloro-1-nitrobenzene in 220 ml benzene at 25—32°C. The mixture was stirred at room temperature for 3 h, poured into a solution of 300 g NH_4Cl in 2 l water, and extracted with benzene. The extract was washed with 5% NaCl, dried, and evaporated. The residue (136 g) was dissolved in 100 ml ether, 150 ml hexane were added, and the mixture was allowed for 48 h to crystallize in the refrigerator. The yellow crystals were filtered, washed with ether, and dried; 40·0 g (30%) crude compound E, which was identified as 2-chloroacridine-10-carbonitrile N-oxide (*VIII*), m.p. 204—205°C (benzene). The IR spectrum is identical with that of a sample, obtained previously[1]. Ref.[1], m.p. 203—204°C; in admixture with this authetic substance, the melting point is without depression.

The mother liquors were evaporated and the remaining 90 g oil were chromatographed on 1·5 kg Al_2O_3 using benzene as the eluent. From the first fractions crystallization separated first 7·0 g recovered 4-chloro-1-nitrobenzene, m.p. 82—83°C (benzene–hexane). This was followed by 35·0 g (27%) compound F which was identified as *Ib*, m.p. 69—70°C (ethanol). UV spectrum: 250 (4·07), 256 (4·08), 354 (3·96). IR spectrum: 755, 770, 810, 860 (4 and 2 adjacent, and solitary Ar—H); 1 022, 1 055, 1 260, 1 285, 2 840 ($ArOCH_3$); 1 495, 1 515, 1 545, 1 580, 1 595 (Ar); 1 628 (C=N). ^{1}H NMR spectrum: 3·96 s, 3 H ($ArOCH_3$); 6·90—8·00 m, 7 H (7 ArH). For $C_{14}H_{10}ClNO_2$ (259·7) calculated: 64·75% C, 3·88% H, 13·65% Cl, 5·39% N; found: 64·60% C, 3·84% H, 13·78% Cl, 5·17% N.

From a further fraction 2·0 g (2%) of the yellow compound G were obtained, m.p. 206—207°C (chloroform–ethanol). The substance was identified as 2-chloroacrdine-10-carbonitrile (*IX*); ref.[1], m.p. 204—205°C (the mixture with the present substance melts without depression), the IR spectrum is identical with that of *IX*, described previously[1].

5-Chloro-3-(2-(methylthio)phenyl)-2,1-benzisoxazole (*Ic*)

The reaction of 72·3 g 4-chloro-1-nitrobenzene and 78·5 g (2-(methylthio)phenyl)acetonitrile in 200 ml benzene by treatment with a solution of 290 g 79% KOH in 575 ml methanol was carried out similarly like in the preceding cases, and the reaction mixture was similarly processed. The starting 4-chloro-1-nitrobenzene was recovered; 8·4 g. The following products were isolated:

Compound H, 4,4′-dichloro-2,2′-bis(2-(methylthio)benzoyl)azobenzene (*X*), yield approximately 8%, red crystals which are rather insoluble in common solvents, m.p. 270—271°C (pyridine). Mass spectrum: 550 (M^+, $C_{28}H_{20}Cl_2N_2O_2S_2$). UV spectrum (saturated solution in methanol): 238, 240. IR spectrum: 740, 750, 760, 798, 850, 890 (4 and 2 adjacent, and solitary Ar—H); 1 240, 1 260, 1 270 (CO); 1 560, 1 581, 3 080 (Ar); 1 660 (ArCOAr′). ^{1}H NMR spectrum (C^2H_3.SOC^2H_3, 200 MHz): 2·49 s, 3 H (SCH_3); 6·88 d, 1 H (H-6, $J(6, 5) = 8·7$); 7·07 ddd, 1 H (H-4′,

$J(4', 3') = 8{\cdot}0$; $J(4', 5') = 6{\cdot}4$; $J(4', 6') = 1{\cdot}6$); 7·17 bdd, 1 H (H-3', $J(3', 4') = 8{\cdot}0$; $J(3', 5') = = 1{\cdot}6$; $J(3', 6') \leq 0{\cdot}5$); 7·46 bdd, 1 H (H-6', $J(6', 5') = 8{\cdot}1$; $J(6', 4') = 1{\cdot}6$; $J(6' 3') \leq 0{\cdot}5$); 7·53 ddd, 1 H (H-5', $J(5', 6') = 8{\cdot}1$; $J(5', 4') = 6{\cdot}4$; $J(5', 3') = 1{\cdot}6$); 7·64 dd, 1 H (H-5, $J(5, 6) = = 8{\cdot}7$; $J(5, 3) = 2{\cdot}3$); 7·73 d, 1 H (H-3, $J(3, 5) = 2{\cdot}3$). For $C_{28}H_{20}Cl_2N_2O_2S_2$ (551·6) calculated: 61·00% C, 3·65% H, 12·85% Cl, 5·08% N, 11·62% S; found: 61·65% C, 3·82% H, 12·70% Cl, 5·20% N, 11·43% S.

Compound J, 5-chloro-2,3-bis(2-methylthiophenyl)-2*H*-indole-2-carbonitrile (*IIIc*), yield approximately 6%, yellow prisms, m.p. 189—190°C (ethanol or chloroform–ethyl acetate). Mass spectrum: 420 (M^+, $C_{23}H_{17}ClN_2S_2$, 42), 405 (M — CH_3, 100), 256 (33), 224 (23), 177 (28), 111 (28), 75 (37). UV spectrum: 241 (4·43), infl. 254 (4·31), infl. 300 (4·06), 310 (4·06), 323 (4·04), 377 (3·91). IR spectrum: 750, 835, 874 (4 and 2 adjacent, and solitary Ar—H); 1 527, 1 586, 3 060 (Ar); 2 235 (R—CN). ^{1}H NMR (200 MHz): 1·89 bs, 3 H (SCH_3); 2·49 s, 3 H (SCH_3); 6·95 ddd, 1 H (H-4″ or H-4′, $J = 8{\cdot}0$; 5·6; 2·8); 7·35 dd, 1 H (H-4, $J(4, 6) = 2{\cdot}1$; $J(4, 7) \approx 0{\cdot}4$); 7·32 ddd, 1 H (H-4′ or H-4″, $J = 8{\cdot}1$; 6·9; 1·3); 7·46 dd, 1 H (H-6, $J(6, 7) = 8{\cdot}3$; $J(6, 4) = 2{\cdot}1$); 7·76 dd, 1 H (H-7, $J(7, 6) = 8{\cdot}3$; $J(7, 4) \approx 0{\cdot}4$); 7·15—7·46 bm, 5 H and 8·24 bd, 1 H (remaining ArH). ^{13}C NMR spectrum (C^2HCl_3): 16·65 and 17·89 (broad signal) (2 SCH_3); 117·08 (CN); 122·94, 123·28, 125·19, 127·16, 129·31 (broad signal), 129·82, 129·99 (broad signal), 130·55, 130·82, 131·64 and 145·79 (11 —CH=); 127·58 (broad signal), 133·01 (broad signal), 133·16, 137·18, 143·61, 145·83 and 183·22 (7 >C=; three remaining quaternary carbons could not be reliably detected). For $C_{23}H_{17}ClN_2S_2$ (421·0) calculated: 65·61% C, 4·07% H, 8·44% Cl, 6·65% N, 15·23% S; found: 65·11% C, 4·08% H, 9·02% Cl, 6·28% N, 14·63% S.

Compound K, *Ic*, yield approximately 27%, yellowish needles, m.p. 109—110°C (cyclohexane or ethanol). Mass spectrum: 275 (M^+, $C_{14}H_{10}ClNOS$, 93), 260 (62), 240 (45), 228 (79), 225 (86), 200 (57), 196 (57), 45 (100). UV spectrum: 241 (4·25), 340 (4·01). IR spectrum: 745, 775, 818, 861, 864 (4 and 2 adjacent, and solitary Ar—H); 1 519, 1 545, 1 565, 1 589, 3 048, 3 065 (Ar); 1 634 (C=N). ^{1}H NMR spectrum: 2·48 s, 3 H (SCH_3); 7·10—7·70 m, 7 H (7 ArH). For $C_{14}H_{10}$·.ClNOS (275·7) calculated: 60·99% C, 3·65% H, 12·86% Cl, 5·09% N, 11·68% S; found: 60·82% C, 3·66% H, 12·96% Cl, 4·93% N, 11·41% S.

Compound L, 2-methylthio-4′-nitrobenzophenone (*XI*), yield approximately 36%, m.p. 110—111°C (ethanol or cyclohexane). Mass spectrum: 273 (M^+, $C_{14}H_{11}NO_3S$, 66), 258 (100), 212 (48), 184 (41), 151 (66), 78 (38). UV spectrum: 263 (4·31), 356 (3·34). IR spectrum: 740, 750, 775, 855, 868 (4 and 2 adjacent Ar—H); 1 352, 1 525 ($ArNO_2$); 1 560, 1 580, 1 605, 3 065, 3 110 (Ar); 1 660 (ArCOAr′). ^{1}H NMR spectrum: 2·45 s, 3 H (SCH_3); 7·10—7·60 m, 4 H (4 ArH of the thioanisole residue); 7·90 d, 2 H (H-2 and H-6 in 4-nitrophenyl, $J = 8{\cdot}5$); 8·30 d, 2 H (H-3 and H-5 in 4-nitrophenyl, $J = 8{\cdot}5$). For $C_{14}H_{11}NO_3S$ (273·3) calculated: 61·52% C, 4·06% H, 5·12% N, 11·73% S; found: 61·60% C, 4·05% H, 4·83% N, 11·86% S.

2-Amino-5-chloro-2 -methylbenzophenone (*XIIa*)

Ia (39·7 g) was added to a mixture of 29 g Fe, 55 ml ethanol, 30 ml water, and 80 ml acetic acid, and the mixture was refluxed for 2 h. After cooling to 70°C it was diluted with 220 ml benzene, stirred for 15 min, filtered, and the solid was washed with 120 ml warm benzene. From the filtrate the benzene layer was separated, washed with diluted NaCl solution, 5% $NaHCO_3$, and with water, dried with $CaCl_2$, and evaporated. The residue was dissolved in a warm mixture of 10 ml ethanol and 10 ml benzene, the solution was treated with 50 ml hexane, and was allowed to stand overnight at room temperature. A small quantity of separated solid was filtered off, the filtrate was evaporated, and distilled; 35·3 g (88%) yellow *XIIa*, b.p. 178°C/0·13 kPa. Refs[31,32], m.p. 50—55°C, and b.p. 130—140°C/2·7 Pa, respectively.

2-Amino-5-chloro-2'-methoxybenzophenone (*XIIb*)

Ib (32·0 g) was similarly reduced with the mixture of 18 g Fe and 50 ml acetic acid in 33 ml ethanol and 16 ml water. The mixture was similarly processed and the crude product was crystallized from a mixture of 20 ml benzene and 30 ml hexane by standing for 48 h in the refrigerator; 24·0 g (75%) yellow crystals, m.p. 82–83°C. UV spectrum: 233 (4·43), 263 (3·88), 390 (3·82). IR spectrum: 760, 830, 902 (4 and 2 adjacent, and solitary Ar—H); 1 242, 2 835 ($ArOCH_3$); 1 538, 1 580, 1 600 (Ar); 1 614 (NH_2); 1 630 (ArCOAr'); 3 345, 3 495 (NH_2). ^{1}H NMR spectrum: 3·80 s, 3 H (OCH_3); 6·40 bs, 2 H (NH_2); 6·60–7·60 m, 7 H (7 ArH). For $C_{14}H_{12}ClNO_2$ (261·7) calculated: 64·25% C, 4·62% H, 13·55% Cl, 5·35% N; found: 64·00% C, 4·61% H, 13·62% Cl, 5·08% N. Literature gave different m.p.: 81–83°C (ref.[31]), 64–65°C (ref.[33]).

2-Amino-5-chloro-2'-(methylthio)benzophenone (*XIIc*)

Crude *Ic* (contaminated with *IIIc*) (5·2 g) was reduced similarly with 3·5 g Fe in a mixture of 5·2 ml ethanol, 2·5 ml water, and 8 ml acetic acid. The product (5·3 g yellow oil) was heated with 7 ml ethanol which induced crystallization. Recrystallization from 8 ml ethanol separated first 1·3 g *IIIc* and gave then 2·0 g *XIIc*, m.p. 100–100·5°C (hexane). Refs[34,35], m.p. 100 to 100·5°C.

2-Amino-5-chloro-2'-methylbenzhydrol (*XIV*)

A) A solution of 1·0 g *Ia* in 8 ml benzene was added dropwise to a stirred solution of 0·8 g $LiAlH_4$ in 30 ml ether and the mixture was refluxed for 1 h. After cooling the stirred mixture was decomposed by a slow addition of 3·2 ml 20% NaOH, after stirring for 30 min the solid was filtered off, it was washed with benzene, and the filtrate was evaporated. The residue (1·1 g) crystallized from 6 ml cyclohexane; 0·85 g (84%), m.p. 108–109°C (cyclohexane). UV spectrum: 244 (3·97), 300 (3·39). IR spectrum: 754, 812, 885 (4 and 2 adjacent, and solitary Ar—H); 1 010, 1 020 (CHOH); 1 480 (Ar); 1 620 ($ArNH_2$); 3 160 (OH); 3 380, 3 450 (NH_2). ^{1}H NMR spectrum: 2·18 s, 3 H ($ArCH_3$); 3·00 bs, 1 H (OH); 3·90 bs, 2 H (NH_2); 5·80 s, 1 H (Ar_2CH—O); 6·52 d, 1 H (H-3, J = 8·5); 6·70 d, 1 H (H-6, J = 2·0); 7·01 q, 1 H (H-4, J = 8·5; 2·0); 7·20 m, 4 H (4 ArH of 2-tolyl). For $C_{14}H_{14}ClNO$ (247·7) calculated: 67·88% C, 5·70% H, 14·31% Cl, 5·65% N; found: 68·39% C, 5·66% H, 14·20% Cl, 5·53% N.

B) *XIIa* (1·0 g) was similarly reduced with 1·0 g $LiAlH_4$ in 45 ml boiling ether. Similar processing gave 0·87 g (86%) *XIV*, m.p. 108–109°C (cyclohexane), identical with the product obtained under *A*); direct comparison with TLC and no depression of the melting point of both samples in mixture.

5-Chloro-2'-methyl-2-(phthalimidoacetamido)benzophenone (*XIIIa*)

A solution of 25·0 g *XIIa* in 125 ml chloroform was treated with 23 g phthalimidoacetyl chloride[36–38], and the mixture was refluxed for 8 h. After standing overnight most of the ethanol was distilled off and the residue (72 g) was treated under stirring with 120 ml ethanol. The suspension formed was allowed to stand overnight in the refrigerator, the product was filtered, washed first with a cold mixture of 5 ml chloroform and 30 ml ethanol and then with 50 ml cold ethanol, and dried *in vacuo*; 42·7 g (97%) product, m.p. 166–168°C. Analytical sample, m.p. 168–169°C (chloroform–ethanol). UV spectrum: 217 (4·73), 231 (4·63), 263 (4·13), infl. 291 (3·65), 340 (3·58). IR spectrum: 764, 835, 898 (4 and 2 adjacent, and solitary Ar—H); 1 510 (Ar); 1 580, 1 715 (RCONHAr); 1 640 (ArCOAr'); 1 715, 1 770 (1,2-$Ar(CO)_2N$); 3 210 (NH). ^{1}H NMR

spectrum: 2·20 s, 3 H ($ArCH_3$); 4·63 s, 2 H ($COCH_2N$); 7·10—8·00 m, 10 H (ArH with the exception of H-3); 8·72 d, 1 H (H-3, $J = 8·5$); 11·85 bs, 1 H (NH). For $C_{24}H_{17}ClN_2O_4$ (432·9) calculated: 66·59% C, 3·96% H, 8·19% Cl, 6·47% N; found: 66·36% C, 3·93% H, 8·32% Cl, 6·16% N.

5-Chloro-2'-methoxy-2-(phthalimidoacetamido)benzophenone (*XIIIb*)

A similar reaction of 18·8 g *XIIb* with 16·2 g phthalimidoacetyl chloride[36-38] in 100 ml chloroform gave 32·0 g (99%) crude *XIIIb*, m.p. 184—186°C. Analytical sample, m.p. 185—186°C (ethanol–chloroform). UV spectrum: 233 (4·65), 237 (4·64), 265 (4·15), infl. 271 (4·10), 305 (3·74), 330 (3·81). IR spectrum: 722, 759, 844, 862, 875 (4 and 2 adjacent, and solitary Ar—H); 1 495, 1 585, 1 600 (Ar); 1 520, 1 700 (RCONHAr); 1 650 (ArCOAr'); 1 720, 1 774 (1,2-Ar$(CO)_2$N); 2 840 ($ArOCH_3$); 3 250 (NH). ^{1}H NMR spectrum: 3·78 s, 3 H (OCH_3); 4·65 s, 2 H ($COCH_2N$); 6·90—7·60 m, 6 H (H-4, H-6, H-3', H-4', H-5', H-6'); 7·70—8·00 m, 4 H (4 ArH of phthalyl); 8·70 d, 1 H (H-3); 11·85 bs, 1 H (NH). For $C_{24}H_{17}ClN_2O_5$ (448·9) calculated: 64·22% C, 3·82% H, 7·90% Cl, 6·24% N; found: 64·28% C, 3·85% H, 8·06% Cl, 6·15% N.

5-Chloro-2'-(methylthio)-2-(phthalimidoacetamido)benzophenone (*XIIIc*)

Was prepared similarly from 2·0 g *XIIc* and 1·61 g phthalimidoacetyl chloride[36-38] in 10 ml chloroform; 3·1 g (93%), m.p. 198·5—199°C (chloroform–ethanol). UV spectrum: 238 (4·66), infl. 265 (4·20), infl. 273 (4·10), 348 (3·71). IR spectrum: 720, 753 (Ar—H); 1 513, 1 580, infl. 1 690 (CONH); 1 650 (ArCOAr'); 1 718, 1 772 (1,2-Ar$(CO)_2$N); 3 030, 3 045, 3 105 (Ar); 3 210, 3 220 (NH). For $C_{24}H_{17}ClN_2O_4S$ (464·9) calculated: 62·00% C, 3·69% H, 7·63% Cl, 6·02% N, 6·90% S; found: 62·22% C, 3·75% H, 7·76% Cl, 6·04% N, 6·95% S.

7-Chloro-5-(2-methylphenyl)-1,3-dihydro-1,4-benzodiazepin-2-one (*XVa*)

A suspension of 75 g *XIIIa* in 1·25 l methanol was treated with 62 ml 18% N_2H_4, the mixture was heated to 60°C, and stirred for 3 h at this temperature. After cooling to room temperature and standing overnight in the refrigerator, the separated phthalylhydrazine was filtered off, the filtrate was evaporated *in vacuo*, the residue was stirred with a solution of 25 ml NH_4OH in 300 ml water, separated by decantation, and this extraction procedure was repeated once more. The solid product was now filtered, washed with a solution of 30 ml NH_4OH in 150 ml water, with water alone, and it was dried *in vacuo*; 49 g (99%), m.p. 182—183°C (acetone). UV spectrum: 225 (4·57), infl. 247 (4·15), 317 (3·31). IR spectrum: 750, 820, 833, 885 (4 and 2 adjacent, and solitary Ar—H); 1 480, 1 520, 3 040 (Ar); 1 615 (Ar—C=N); 1 680 (CONH); 3 170 (NH). ^{1}H NMR spectrum ($C^2H_3SOC^2H_3$): 1·91 s, 3 H ($ArCH_3$); 4·20 s, 2 H ($COCH_2N$); 6·90 d, 1 H (H-6, $J = 2·0$); 7·25 m, 5 H (H-9 and 4 ArH of 2-tolyl); 7·59 q, 1 H (H-8, $J = 8·5$; 2·0); 10·80 bs, 1 H (NH). Ref.[40], m.p. 180—181°C.

7-Chloro-5-(2-methoxyphenyl)-1,3-dihydro-1,4-benzodiazepin-2-one (*XVb*)

A similar reaction of 29·2 g *XIIIb* with 24 ml 18% N_2H_4 in 470 ml methanol and similar processing gave 17·5 g (90%) *XVb*, m.p. 206—207°C (aqueous ethanol). UV spectrum: 229 (4·64), infl. 250 (4·26), 305 (3·57). IR spectrum (KBr): 757, 770, 835, 883 (4 and 2 adjacent, and solitary Ar—H); 1 020, 1 240, 2 835 ($ArOCH_3$); 1 480, 1 594 (Ar); 1 611 (Ar—C=N); 1 680 (CONH); 3 060, 3 110, 3 225 (NH). ^{1}H NMR spectrum: 3·53 s, 3 H (OCH_3); 4·40 s, 2 H ($COCH_2N$); 6·80—7·60 m, 7 H (7 ArH); 10·25 bs, 1 H (NH). Ref.[40], m.p. 206—207°C.

7-Chloro-5-(2-methylthiophenyl)-1,3-dihydro-1,4-benzodiazepin-2-one (*XVc*)

It was prepared similarly from 3·1 g *XIIIc* and 2·5 ml 18% N_2H_4 in 50 ml methanol; 1·90 g (91%), m.p. 183—184°C. Refs[34,35], m.p. 184—185°C.

7-Chloro-5-(2-methylphenyl)-1,3-dihydro-1,4-benzodiazepin-2-thione (*XVIa*)

A mixture of 25·0 g *XVa*, 21·6 g P_2S_5, and 175 ml pyridine (content of H_2O 0·08%) was stirred and refluxed for 45 min in nitrogen atmosphere. After cooling the mixture was poured into a solution of 300 g NaCl in 1 l water at 7—14°C, the suspension was stirred for 20 min, the precipitated *XVIa* was filtered, washed with water, and dried *in vacuo*. This crude product (23·5 g) was dissolved in 1·2 l dichloromethane, a small quantity of undissolved material was filtered off, the filtrate was filtered through a column of 50 g Al_2O_3 which was washed with 1 l dichloromethane. The combined filtrates were evaporated, the residue (19·5 g) was heated with 40 ml ethanol, the suspension was cooled, the product was filtered, washed with a cold mixture of 42 ml ethanol and 18 ml hexane, and dried *in vacuo*; 17·1 g (65%), m.p. 240—241°C (ethanol–chloroform). UV spectrum: 302 (4·38), inflexes 272 (3·94) and 340 (3·68). IR spectrum: 750, 780, 890 (4 and 2 adjacent, and solitary Ar—H); 1 375 (CSNH); 1 520, 1 580 (Ar); 1 614 (Ar—C=N); 2 660 (NH). ^{1}H NMR spectrum ($C^2H_3SOC^2H_3$): 1·95 s, 3 H ($ArCH_3$); 4·65 s, 2 H (CS—CH_2—N); 6·95 d, 1 H (H-6, J = 2·0); 7·25 m, 4 H (4 ArH of 2-tolyl); 7·40 d, 1 H (H-9, J = 8·5); 7·67 q, 1 H (H-8, J = 8·5; 2·0); 12·62 bs, 1 H (NH). For $C_{16}H_{13}ClN_2S$ (300·8) calculated: 63·88% C, 4·36% H, 11·79% Cl, 9·31% N, 10·66% S; found: 64·37% C, 4·40% H, 11·68% Cl, 9·13% N, 10·85% S.

7-Chloro-5-(2-methoxyphenyl)-1,3-dihydro-1,4-benzodiazepin-2-thione (*XVIb*)

It was prepared similarly from 17·0 g *XVb* and 14·0 g P_2S_5 in 115 ml pyridine; 9·50 g (53%), m.p. 218—220°C. Refs[41—43], yield 38%, m.p. 222—224°C.

7-Chloro-5-(2-(methylthio)phenyl)-1,3-dihydro-1,4-benzodiazepin-2-thione (*XVIc*)

It was prepared similarly from 1·90 g *XVc* and 1·50 g P_2O_5 in 15 ml pyridine; 1·30 g (65%), m.p. 231—232°C (ethanol–chloroform). UV spectrum: 305 (4·38), infl. 342 (3·75). IR spectrum: 745, 832, 881 (4 and 2 adjacent, and solitary Ar—H); 1 379 (CSNH); 1 530, 1 583, 1 600, 3 045; (Ar); 1 620 (Ar—C=N); 2 650 (NH). For $C_{16}H_{13}ClN_2S_2$ (332·9) calculated: 57·73% C, 3·94% H, 10·65% Cl, 8·42% N, 19·26% S; found: 57·87% C, 3·99% H, 10·80% Cl, 8·25% N, 19·16% S.

8-Chloro-6-(2-methylphenyl)-1-methyl-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepine (*XVIIa*)

A mixture of 6·0 g *XVIa*, 5·0 g acetohydrazide[44], and 140 ml butanol was stirred and refluxed for 8 h in nitrogen atmosphere. Butanol was evaporated *in vacuo*, the residue was distributed between 70 ml chloroform and 80 ml water, the organic layer was separated, dried with Na_2SO_4, and evaporated. The residue was crystallized from ethyl acetate; 5·4 g (84%), m.p. 228—229°C. UV spectrum: 221 (4·60), inflexes 240 (4·15) and 285 (3·41). IR spectrum: 760, 820, 830, 885 (4 and 2 adjacent, and solitary Ar—H); 1 480, 1 540 (Ar); 1 610 (Ar—C=N). ^{1}H NMR spectrum: 1·90 s, 3 H ($ArCH_3$); 2·61 s, 3 H (1-CH_3); 4·18 d, 1 H and 5·50 d, 1 H (2 H-4, J = 13·0); c. 7·25 m, 5 H (H-7 and 4 ArH of 2-tolyl); 7·48 d, 1 H (H-10, J = 8·5); 7·68 q, 1 H (H-9, J = = 8·5; 2·0). For $C_{18}H_{15}ClN_4$ (322·8) calculated: 66·98% C, 4·68% H, 10·98% Cl, 17·36% N; found: 66·39% C, 4·79% H, 10·92% Cl, 16·84% N.

8-Chloro-6-(2-methoxyphenyl)-1-methyl-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepine (*XVIIb*)

It was prepared similarly from 5·1 g *XVIb* and 4·0 g acetohydrazide[44] in 115 ml boiling butanol; 3·9 g (72%), m.p. 223—224°C (ethyl acetate). UV spectrum: 297 (3·53), infl. 242·5 (4·16). IR spectrum: 744, 752, 820, 842, 889 (4 and 2 adjacent, and solitary Ar—H); 1 237, 1 311 ($ArOCH_3$); 1 485, 1 550, 1 579, 3 025, 30 41, 3 060 (Ar); 1 611 (Ar—C=N). ^{1}H NMR spectrum: 2·60 s, 3 H (1-CH_3); 3·40 s, 3 H (OCH_3); 4·08 d, 1 H and 5·40 d, 1 H (2 H-4, J = 13·0); 6·78 bd, 1 H (H-3′, J = 8·0); 7·00 dt, 1 H (H-5′, J = 8·0; 1·0); 7·21 d, 1 H (H-7, J = 2·0); 7·25—7·60 m, 4 H (H-9, H-10, H-4′, H-6′). For $C_{18}H_{15}ClN_4O$ (338·8) calculated: 63·81% C, 4·46% H, 10·47% Cl, 16·54% N; found: 63·70% C, 4·40% H, 10·76% Cl, 16·89% N.

8-Chloro-6-(2-methylthiophenyl)-1-methyl-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepine (*XVIIc*)

It was pepared similarly from 0·50 g *XVIc* and 0·3 g acetohydrazide[44] in 20 ml butanol; 0·45 g (87%), m.p. 171—172°C (ethyl acetate). UV spectrum: inflexes 245 (4·25) and 290 (3·37). IR spectrum: 750, 758, 820, 840 (Ar—H); 1 480, 1 530, 1 565 (Ar); 1 610 (Ar—C=N); 1 628 (C=N in triazole). ^{1}H NMR spectrum: 2·11 s, 3 H (SCH_3); 2·60 s, 3 H (1-CH_3); 4·15 d, 1 H and 5·48 d, 1 H (2 H-4, J = 13·0); 7·10—7·70 m, 7 H (7 ArH). For $C_{18}H_{15}ClN_4S$ (354·9) calculated: 60·92% C, 4·26% H, 9·99% Cl, 15·79% N, 9·04% S; found: 61·18% C, 4·35% H, 10·23% Cl, 15·98% N, 9·14% S.

8-Chloro-6-(2-methylphenyl)-1-(methylthiomethyl)-4*H*-*s*-triazolo[4,3-*a*]-
-1,4-benzodiazepine (*XVIIIa*)

A mixture of 3·0 g *XVIa*, 3·2 g methyl thioacetohydrazide[45] and 80 ml butanol was stirred and refluxed for 8 h in nitrogen atmosphere. The solvent was evaporated *in vacuo*, the residue was diluted with 60 ml water, and extracted with chloroform. The extract was washed with water, dried, and evaporated. The residue was crystallized from ethyl acetate; 3·0 g (81%), m.p. 207 to 208°C (benzene). UV spectrum: 222 (4·57), inflexes 242 (4·17) and 283 (3·38). IR spectrum: 750, 843, 857, 862 (4 and 2 adjacent, and solitary Ar—H); 1 482, 1 530, 1 564 (Ar); 1 609 (Ar—C=N). ^{1}H NMR spectrum: 1·95 s, 3 H ($ArCH_3$); 2·10 s, 3 H (SCH_3); 3·84 d, 1 H and 4·15 d, 1 H (1-CH_2S, J = 13·0); 4·18 d, 1 H and 5·52 d, 1 H (2 H-4, J = 13·0); 7·20 m, 5 H (H-7 and 4 ArH of 2-tolyl); 7·60 q, 1 H (H-9, J = 8·5; 2·0); 7·80 d, 1 H (H-10, J = 8·5). For $C_{19}H_{17}ClN_4S$ (368·9) calculated: 61·86% C, 4·65% H, 9·61% Cl, 15·19% N, 8·69% S; found: 62·25% C, 4·70% H, 9·61% Cl, 15·17% N, 8·90% S.

8-Chloro-5-(2-methoxyphenyl)-1-(methylthiomethyl)-
4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepine (*XVIIIb*)

Prepared similarly like *XVIIIa* from 3·0 g *XVIb* and 3·0 g methylthioacetohydrazide[45] in 80 ml butanol; 2·50 g (69%), m.p. 191—192°C (benzene). UV spectrum: 226 (4·46), 301 (3·56), infl. 247 (4·21). IR spectrum: 745, 750, 820, 860 (4 and 2 adjacent, and solitary Ar—H); 1 110, 1 238, 1 255 ($ArOCH_3$); 1 485, 1 530, 1 600, 3 010, 3 043, 3 063 (Ar); 1 613 (Ar—C=N), ^{1}H NMR spectrum: 2·18 s, 3 H (SCH_3); 3·50 s, 3 H (OCH_3); 3·85 d, 1 H and 4·12 d, 1 H (1-CH_2S, J = = 13·0); 4·12 d, 1 H and 5·50 d, 1 H (2 H-4, J = 13·0); 6·80—7·70 m, 6 H (H-7, H-9, and 4 ArH of methoxyphenyl); 7·80 d ,1 H (H-10, J = 8·5). For $C_{19}H_{17}ClN_4OS$ (384·9) calculated: 59·29% C, 4·45% H, 9·21% Cl, 14·56% N, 8·33% S; found: 59·38% C, 4·44% H, 9·50% Cl, 14·99% N, 8·46% S.

8-Chloro-6-(2-methylthiophenyl)-1-(methylthiomethyl)-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepine (*XVIIIc*)

Prepared similarly like *XVIIIa* from 0·64 g *XVIc* and 0·63 g methylthioacetohydrazide[45] in 20 ml butanol; 0·60 g (78%), m.p. 178—179°C (ethyl acetate). UV spectrum: inflexes 250 (4·26) and 300 (3·31). IR spectrum: 748, 820, 855 (4 and 2 adjacent, and solitary Ar—H), 1 485, 1 530, 1 565, 1 585, 3 015, 3 050 (Ar), 1 610 (Ar—C=N). ^{1}H NMR spectrum: 2·10 s, 3 H ($ArSCH_3$); 2·13 s, 3 H (SCH_3 in the 1-side chain): 3·68 d, 1 H and 4·02 d, 1 H (1-CH_2S, J = 13·0); 4·11 d, 1 H and 5·45 d, 1 H (2 H-4, J = 13·0); 7·12 d, 1 H (H-7, J = 2·5); c. 7·30 m, 4 H (4 ArH of (methylthio)phenyl); 7·55 dd, 1 H (H-9, J = 8·5; 2·5); 7·82 d, 1 H (H-10, J = 8·5). For $C_{19}H_{17}ClN_4S_2$ (400·9) calculated: 56·91% C, 4·27% H, 8·84% Cl, 13·98% N, 16·00% S; found: 56·90% C, 4·33% H, 9·13% Cl, 14·00% N, 15·98% S.

The authors wish to thank their colleagues at the Institute for Pharmacy and Biochemistry for their contributions to the work described: Dr J. Metyš (pharmacological data), Mrs J. Komancová, Mrs V. Šmídová and Mr M. Čech (elemental analyses), and Mrs A. Hrádková (recording of the UV *and* IR *spectra).*

REFERENCES

1. Vejdělek Z., Rajšner M., Dlabač A., Ryska M., Holubek J., Svátek E., Protiva M.: Collect. Czech. Chem. Commun. *45*, 3593 (1980).
2. Sternbach L. H. in the book: *The Benzodiazepines* (S. Garattini, E. Mussini and L. O. Randall, Eds), p. 1. Raven Press, New York 1973.
3. Sternbach L. H. in the book: *Benzodiazepines Today and Tomorrow* (R. G. Priest, U. Vianna Filho, R. Amrein and M. Skreta, Eds), p. 5. MTP Press, Lancaster (England) 1980.
4. Rudzik A. D., Hester J. B. jr, Tang A. H., Straw R. N., Friis W.: Ref. 2, p. 285.
5. Moffett R. B.: Lect. Heterocycl. Chem. *3*, S-123 (1976); *5th Int. Congr. Heterocycl. Chem., Ljubljana, Yugoslavia, July 1975*; Abstr. p. 10.
6. Vejdělek Z. J., Metyš J., Protiva M.: Collect. Czech. Chem. Commun. *48*, 123 (1983).
7. Davis R. B., Pizzini L. C., J. Org. Chem. *25*, 1884 (1960).
8. Davis R. B. (University of Notre Dame): U.S. 3,156,704 (Appl. 12. 04. 60); Chem. Abstr. *62*, 2743 (1965).
9. Cilieanu-Bibian S., Belu D., Cuiban F. (Ministry of Petroleum and Chemical Industry of Romania): Belg. 670, 674 (Rom. Appl. 09. 10.64); Chem. Abstr. *65*, 13715 (1966).
10. Heidrich H. J., Henker S., Roehnert H.: Ger. (G.D.R.) 61,265 (Appl. 15. 02. 67); Chem. Abstr. *70*, 37806 (1969).
11. Atkinson A. F. J., Thorpe J. F.: J. Chem. Soc. *91*, 1695 (1907).
12. Friedman L., Shechter H.: J. Org. Chem. *25*, 877 (1960).
13. Overberger C. G., Mulvaney J. E.: J. Am. Chem. Soc. *81*, 4697 (1959).
14. Walker G. N.: J. Org. Chem. *27*, 1929 (1962).
15. Jones G.: Org. React. *15*, 205 (1967).
16. Večeřa M., Gasparič J., Churáček J., Borecký J.: *Chemické tabulky organických sloučenin*, p. 521. Published by SNTL — Nakladatelství technické literatury, Prague 1975.
17. Neresheimer H., Ruppel W. (I. G. Farbenind. A.-G.): Ger. 603,622 (11. 10, 34); U.S. 2,080,057 (11. 05. 37); Chem. Abstr. *29*, 817 (1935); *31*, 4830 (1937).
18. Société Belge de l'Azote et des Produits Chimiques du Marly S. A.: Neth. Appl. 6,514,447 (Br. Appl. 11. 11. 64); Chem. Abstr. *65*, 10569 (1966).
19. Geissman T. A.: Org. React. *2*, 94 (1944).

20. Horii Z., Tsuji J., Inoi T.: Yakugaku Zasshi *77*, 252 (1957); Chem. Abstr. *51*, 8671 (1957).
21. Davidson D., Weiss M.: Org. Synth., Coll. Vol. *2*, 590 (1943).
22. Horii Z., Satoda I., Inoi T. (Nippon New Drug Co.): Japan 7166 (1956), 22. 08. 56; Chem. Abstr. *52*, 9210 (1958).
23. Raikow P. N., Raschtanow J.: Oester. Chem.-Ztg. *5*, 169 (1902); Chem. Zentralbl. *1902*, I, 1212.
24. Shoesmith J. D., Slater R. H.: J. Chem. Soc. *1926*, 214.
25. Kucsman A., Kremmer T.: Acta Chim. Hung. *34*, 75 (1962).
26. Protiva M., Rajšner M., Trčka V., Vaněček M., Němec J., Šedivý Z.: Collect. Czech. Chem. Commun. *40*, 3904 (1975).
27. Grice R., Owen L. N.: J. Chem. Soc. *1963*, 1947.
28. Christiaens L., Renson M.: Bull. Soc. Chim. Belg. *79*, 235 (1970); Chem. Abstr. *73*, 3726 (1970).
29. Kornblum N.: Angew. Chem. *87*, 797 (1975).
30. Vejdělek Z., Rajšner M., Svátek E., Holubek J., Protiva M.: Collect. Czech. Chem. Commun. *44*, 3604 (1979).
31. Sternbach L. H., Fryer R. I., Metlesics W., Sach G., Stempel A.: J. Org. Chem. *27*, 3781 (1962).
32. Richter S. B., Mayer D. D. (Velsicol Chemical Corp.): U.S. 3,422,199 (Appl. 01. 05. 67); Chem. Abstr. *71*, 91055 (1969).
33. Kolbah D., Blaževič N., Hannoun M., Kajfež F., Kovač T., Rendič S., Šunjić V.: Helv. Chim. Acta *60*, 265 (1977).
34. Keller O., Steiger N., Sternbach L. H. (Hoffmann-La Roche Inc.): U.S. 3,121,103 (Czech. Appl. 20. 10. 61); Chem. Abstr. *61*, 5671 (1964).
35. Keller O., Steiger N., Sternbach L. H. (F. Hoffmann-La Roche et Co.): Belg. 632,685 (U.S. Appl. 28. 05. 62); Chem. Abstr. *62*, 577 (1965).
36. Balenović K., Bregant N., Cerar D., Tkalčić M.: J. Org. Chem. *16*, 1308 (1951); Chem. Abstr. *46*, 3005 (1952).
37. Foye W. O., Lange W. E.: J. Am. Pharm. Assoc. *45*, 742 (1956).
38. King F. E., Clark-Lewis J. W., Wade R., Swindin W. A.: J. Chem. Soc. *1957*, 873.
39. Podešva C. (Delmar Chemicals Ltd.): Neth. Appl. 6,500,446 (Brit. Appl. 14. 01. 64); Chem. Abstr. *64*, 5120 (1966).
40. Sternbach L. H., Fryer R. I., Metlesics W., Reeder E., Sach G., Saucy G., Stempel A.: J. Org. Chem. *27*, 3788 (1962).
41. Archer G. A., Sternbach L. H.: J. Org. Chem. *29*, 231 (1964).
42. Archer G. A., Metlesics W., Reeder E., Sternbach L. H. (F. Hoffmann-La Roche et Co.): Belg. 620,773 (U.S. Appl. 28. 07. 61); Chem. Abstr. *59*, 10094 (1963).
43. Reeder E., Sternbach L. H. (Hoffmann-La Roche Inc.): U.S. 3,109,843 (Appl. 21. 06. 62); Chem. Abstr. *60*, 2994 (1964).
44. Curtius T., Hofmann T. S.: J. Prakt. Chem. [2] *53*, 524 (1896).
45. Rose F. L., Wilson B. R. (Imperical Chemical Industries Ltd.): Brit. 782,420 (04. 09. 57); Chem. Abstr. *52*, 2907 (1958).
46. Hester J. B. jr, Rudzik A. D., Kamdar B. V.: J. Med. Chem. *14*, 1078 (1971).

Translated by the author (M.P.).