REACTIONS OF 4-CHLORO-1-NITROBENZENE WITH (3-CHLORO-4-METHOXYPHENYL)ACETONITRILE AND (3,4-DIMETHOXYPHENYL)ACETONITRILE; SYNTHESIS OF 8-CHLORO-1-METHYL (AND METHYLTHIOMETHYL)-6-(3,4-DISUBSTITUTED PHENYL)-4*H*-*s*-TRIAZOLO[4,3-*a*]-1,4--BENZODIAZEPINES

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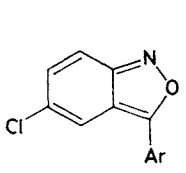
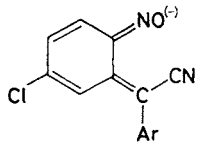
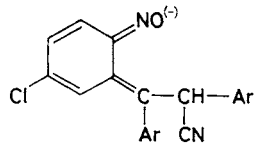
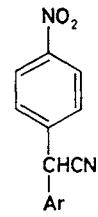
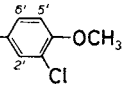
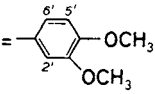
Received June 19th, 1987

Reactions of 4-chloro-1-nitrobenzene with (3-chloro-4-methoxyphenyl)acetonitrile and (3,4--dimethoxyphenyl)acetonitrile in methanolic potassium hydroxide gave the corresponding 3-aryl-5-chloro-2,1-benzisoxazoles *Ia* and *Ib* in good yields; compounds *Va*, *Vb*, *VI*—*VIII*, and *X* were isolated as by-products and identified by means of spectra. Compounds *Ia* and *Ib* were transformed in five steps to the title compounds *XVab* and *XVIab* which were found inactive in tests for central depressant and anticonvulsant activity.

The base-catalyzed reaction of 4-chloro-1-nitrobenzene with phenylacetonitrile and (*p*-substituted phenyl)acetonitriles results in the corresponding 3-aryl-5-chloro-2,1--benzisoxazoles (*I*) (refs[1,2]) which are obtained in high yields. This type of compounds represents useful, and partly very important (*I*, Ar = C_6H_5), starting materials in the synthesis of the anxiolytic, hypnotic, and anticonvulsant 5-aryl-7-chloro--1,3-dihydro-1,4-benzodiazepine-2-ones and 6-aryl-8-chloro-4*H*-*s*-triazolo[4,3-*a*]-1,4--benzodiazepines[3]. In two communications[4,5] we described reactions of 4-chloro-1--nitrobenzene with five (*o*-substituted phenyl)acetonitriles and found the yields on *I* varying from 0 to 54%; their formation was accompanied by several side reactions proceeding via the postulated or proven intermediates *II*—*IV* (refs[1,3,5,6]). Now, we have concluded our investigation by using (3-chloro-4-methoxyphenyl)acetonitrile[7] and (3,4-dimethoxyphenyl)acetonitrile as components in reactions with 4-chloro-1--nitrobenzene. At variance with findings on (*o*-substituted phenyl)acetonitriles, the yields on *Ia* and *Ib* were about 75%; the isolated and identified by-products are probably connected with the intermediates *II*—*IV*. Compounds *Ia* and *Ib* were used as starting materials for the syntheses of the title 4*H*-*s*-triazolo[4,3-*a*]-1,4--benzodiazepines which are described in the present paper.

I *II* *III* *IV*

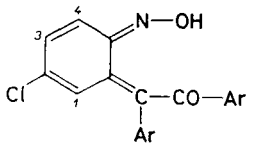
In formulae *I*–*V* and *XI*–*XVI*: *a*, Ar =  *b*, Ar = 

Reaction of 4-chloro-1-nitrobenzene with (3-chloro-4-methoxyphenyl)acetonitrile[7] was carried out similarly like in our previous work[4,5], i.e. in a concentrated solution of potassium hydroxide in methanol at 20–26°C. The reaction mixture was diluted with benzene and decomposed with an aqueous solution of ammonium chloride. The separated solid represents the main part of the main product *Ia*. The working up of the filtrate led to recovery of 15% of 4-chloro-1-nitrobenzene and to a further crop of *Ia* which made its total yield 77%.

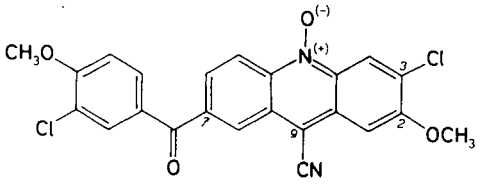
The further benzene fractions were processed to a little soluble minor product (less than 5%) melting at 201–202°C and having the elemental composition $C_{22}H_{16}$. $.Cl_3NO_4$. This composition indicated the presence of three aromatic rings. ^{1}H NMR spectrum proved the presence of 9 aromatic protons per 6 protons of two methoxy groups. The remaining proton could be exchanged for deuterium and was assigned to the fragment C=N—OH (in the IR spectrum band at 1 638 cm^{-1}). The remaining oxygen atom belongs to a conjugated ketone (ν 1 671 cm^{-1}). Formula *Va* was confirmed by the detailed analysis of the ^{1}H NMR spectrum (200 MHz). Compound *Va* is in close relation to the postulated intermediate *IIIa* (ref.[5]) and was probably formed by displacement of the CN anion by the OH anion, and by the following oxidation.

Compound *Va* was followed by a high-melting (m.p. 260–270°C and after resolidification again at 319–321°C) minor yellow product. Its mass spectrum established the elemental composition $C_{23}H_{14}Cl_2N_2O_4$. Typical is the fragment M - 16 corresponding to cleavage of the oxygen atom from an N-oxide. The double melting may correspond to the same phenomenon (thermic deoxygenation of the N-oxide to the tertiary amine). The substance is rather insoluble in common solvents which disabled to record the ^{1}H NMR spectrum. The UV spectrum of a saturated solution in methanol indicates a high degree of conjugation. The IR spectrum evidences the following functional groups: methoxy (ν 1 060 and 1 240 cm^{-1}), N-oxide (1 275 and 1 319 cm^{-1}), ArCOAr (1 665 cm^{-1}), Ar—CN (2 210 cm^{-1}). Taking into

account all the facts available together with the mechanisms of side reactions we already met in this field[4,5], we arrived to the tentative formula *VI*. Its formation could start from the intermediate *II* in which the atom of chlorine is still sufficiently reactive to enable a nucleophilic substitution reaction with a further molecule of (3-chloro-4-methoxyphenyl)acetonitrile. The transformation of the fragment Ar—CH—CN formed in this reaction to the fragment Ar—CO can be explained by the same mechanism like in our preceding communications[4,5]. The nucleophilic cyclization reaction of the oxime to the acridine N-oxide has also its precedents already[4,5]; what is new is the necessity of assuming the formation of the hydride anion as the leaving group.

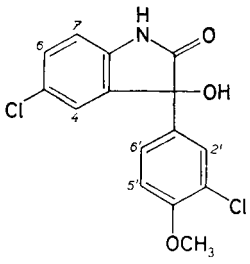


V



VI

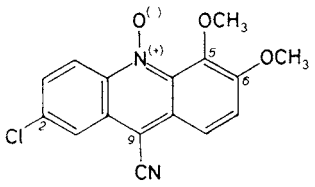
A further minor product (less than 5%) was isolated from the most polar fractions It has the elemental composition $C_{15}H_{11}Cl_2NO_3$ and melts at 217–218°C. Its molecule contains two aromatic rings. The nature of the hydrogen atoms was characterized by the ^{1}H NMR spectrum: 6 aromatic protons, 3 protons of the methoxy group, and the two remaining protons (singlets at δ 6·81 and 10·53) which could be exchanged for deuterium. Structure *VII* was suggested for the compound and the ^{1}H NMR spectrum (200 MHz) is in full agreement. The first of the exchangeable protons is attributed to the Ar—NH—CO fragment in the five-membered ring (in the IR spectrum the band at 1 722 cm^{-1}), the second one to the hydroxyl group with intramolecular hydrogen bond to the adjacent C=O. This compound was probably formed from the intermediate *II* by hydrolysis of the nitrile group to carboxyl, by the following oxidation-reduction process during which the nitrogen



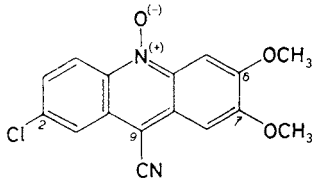
VII

function was reduced and a new oxygen function appeared at the α-carbon atom by the final intramolecular N-acylation.

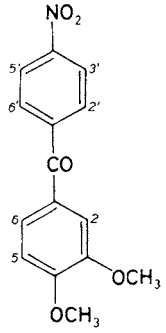
Reaction of 4-chloro-1-nitrobenzene with (3,4-dimethoxyphenyl)acetonitrile was carried out similarly and also the processing of the reaction mixture was similar like in the preceding case. The benzisoxazole *Ib* was obtained by crystallization (and from the first chromatographic fractions) in the yield of 75%. It was followed by a small amount of orange needles melting at 259°C, little soluble in common solvents. It was characterized by the elemental composition $C_{16}H_{11}ClN_2O_3$. Structure assignment can also be only a tentative one because of the lack of the ^{1}H NMR spectrum. The UV spectrum indicates a high degree of conjugation like in a condensed aromatic system. In the mass spectrum, the fragment M − 16 indicates the cleavage of the N-oxide to the corresponding amine. The IR spectrum shows the presence of the conjugated nitrile group (ν 2 213 cm^{-1}), methoxyl and N-oxide groups (bands at 1 235, 1 248, and 1 267 cm^{-1}). On the basis of our experience[4,5] structures of 9-cyanoacridine N-oxides (in our papers[4,5] an erroneous numbering of the acridine system was used, cf. ref.[8]) *VIII* or *IX* are suggested. These compounds could be formed from the intermediate *IIb* by intramolecular nucleophilic cyclization with the hydride anion as the leaving group. Formula *IX* would be preferred on the basis of steric reasons but formula *VIII* is more likely because of the lack of a typical band of the solitary aromatic C—H bond in the region of out-of-plane bending (bands only at 821 and 844 cm^{-1}).



VIII



IX



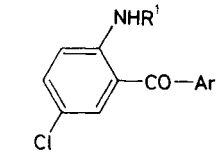
X

Chromatography of the mother liquors recovered again a small amount of 4-chloro-1-nitrobenzene and gave some 4-nitroanisole formed by solvolysis of the starting 4-chloro-1-nitrobenzene (cf. refs[4,5]). Still with benzene the benzophenone *X* was eluted (about 15%); in this case the structure assignment on the basis of the IR and ^{1}H NMR spectra is unequivocal. Similar benzophenones were found in our previous investigations[4,5] and their formation from the intermediate nitriles *IV* was explained by the mechanism proposed by Kornblum[9] for similar compounds con-

taining the 4-nitrobenzyl system(the anions, formed in the alkaline medium, react with air oxygen, and the peroxide anions formed are cleaved to ketones and the cyanate anion).

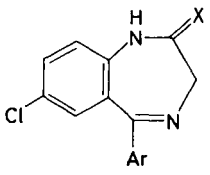
By rechromatography of the most polar fraction (eluted with benzene containing 5% ethanol) the last by-product was isolated which melts at 192–193°C. By its composition $C_{24}H_{22}ClNO_6$, it corresponds to *Va* from the preceding experiment and structure *Vb* is suggested for it. The UV spectrum confirmed the high degree of conjugation and the IR spectrum showed the presence of methoxyl, conjugated ketone, and of the hydrogen-bonded C=N—OH. The ^{1}H NMR spectrum (80 MHz) cannot differentiate the aromatic protons but is not at variance with the proposed structure.

Compounds *Ia* and *Ib* were reduced with iron and acetic acid in boiling aqueous ethanol to 2-amino-5-chlorobenzophenones *XIa* and *XIb* which were treated with phthalimidoacetyl chloride[10–12] to give derivatives *XIIa* and *XIIb*. Hydrazinolysis was accompanied by cyclization and the corresponding 5-aryl-7-chloro-1,3-dihydro--1,4-benzodiazepine-2-ones *XIIIa* and *XIIIb* were obtained. These lactams were treated with phosphorus pentasulfide in boiling pyridine and gave the thiolactams *XIVa* and *XIVb*. The last steps were reactions of these thiones with acetohydrazide[13] or (methylthio)acetohydrazide[14] in boilig butanol which resulted in the title compounds *XVab* and *XVIab*. Compounds *XIab*–*XVIab* were characterized by spectra which confirmed their structures. The methods used were the same like described in the previous paper[5].



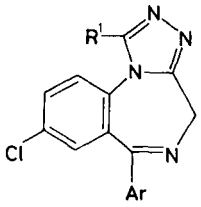
XI, R^1 = H

XII, R^1 = $COCH_2N$ (O, O)



XIII, X = O

XIV, X = S



XV, R^1 = CH_3

XVI, R^1 = CH_2SCH_3

Compounds *XVab* and *XVIab* were pharmacologically evaluated for acute toxicity, central depressant, and anticonvulsant activity in mice (oral administration). Acute toxicity, LD_{50} in mg/kg: *XVa*, >2 500; *XVb*, c. 2 000; *XVIa*, >2 500; *XVIb*, >2 500. In doses of 300 mg/kg *XVa*, *XVIa*, and *XVIb* were inactive in tests for central depressant and anticonvulsant activity. Compound *XVb* in the dose of 300 mg/kg did not inhibit the convulsant activity of pentetrazole but protected the animals in doses of 50–100 mg/kg from the lethal effect of pentetrazole. At 300 mg/kg it was inactive in the electroshock test. In doses higher than 300 mg/kg, the

compound had central depressant effects (inhibition of spontaneous activity and reactivity). Toxic doses brought about ptosis in mice. In comparison with other compounds of the series (cf. ref.[15]), *XVab* and *XVIab* were inactive which is due to the unsuitable substitution in the aromatic ring (Ar in position 6 of the skeleton).

EXPERIMENTAL

The melting points were determined in a Kofler block and they are not corrected; the samples were dried in vacuo of about 60 Pa over P_2O_5 at room temperature or at suitably elevated temperature. 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 a Perkin–Elmer 298 spectrophotometer, ^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), 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 chomatography (TLC) on silica gel (Silufol). The column cromatography was carried out on neutral Al_2O_3 (activity II). The solutions (extracts) were dried with Na_2SO_4 and evaporated on a rotating evaporator.

5-Chloro-3-(3-chloro-4-methoxyphenyl)-2,1-benzisoxazole (*Ia*)

A solution of 40·0 g (3-chloro-4-methoxyphenyl)acetonitrile[7] and 35·4 g 4-chloro-1-nitrobeozene in 100 ml benzene was added dropwise over 95 min to a stirred soolution of 142 g 80%KOH in 280 ml methanol at 20°C. The suspension obtained was stirred for 4 h at room temperature, poured into a stirred solution of 140 g NH_4Cl in 930 ml water, and diluted with 200 ml benzene. The mixture was shaken for 10 min, the solid was filtered, washed with 100 ml water, twice with 100 ml benzene, and dried in vacuo; 40·0 g crude *Ia*, m.p. 181—182°C. Crystallization from benzene gave the pure *Ia*, m.p. 183°C. Mass spectrum: 295, 293 (M^+, $C_{14}H_9Cl_2NO_2$, 88), 278 ($C_{13}H_6Cl_2NO_2$, 21), 258 ($C_{14}H_9ClNO_2$, 100), 250 (79), 187 (43). UV spectrum: 225 (4·29), 272 (4·26), infl. 298 (3·93), 358 (3·39). IR spectrum: 810, 820, 850, 870 (2 adjacent and solitary Ar—H); 1 285 ($ArOCH_3$); 1 500, 1 600, 3 082, 3 100 (Ar); 1 630 (C=N). For $C_{14}H_9Cl_2NO_2$ (294·1) calculated: 57·17% C, 3·08% H, 24·11% Cl, 4·76% N; found: 57·68% C, 3·18% H, 23·88% Cl, 4·66% N.

The benzene layer was separated from the filtrate and the aqueous layer was extracted with 600 ml benzene (in 3 parts), the combined benzene solutions were dried, and evaporated.The residue was extracted twice with 60 ml benzene and the extract gave by evaporation further 3·6 g *Ia*, m.p. 180—182°C. The undissolved part (25 g) was chromatographed on 900 g Al_2O_3. Elution with benzene gave first 5·5 g (15%) recovered 4-chloro-1-nitrobenzene (m.p. 81·5—83°C), which was followed by further 7·1 g *Ia* (m.p. 181—183°C), the total yield on *Ia* being thus 50·7 g (77%). The presence of a small amount of the starting (3-chloro-4-methoxyphenyl)acetonitrile[7] was proven in the immediately following fraction by TLC.

Processing of the following benzene fractions resulted in 3·4 g homogeneous substance which was crystallized from benzene and melted at 201—202°C. It was identified as 2-(2-chloro-5-(hydroxyimino)-1,3-cyclohexadien-6-ylidene)-1,2-bis(3-chloro-4-methoxyphenyl)ethan-1-one (*Va*). Mass spectrum: 463 (M^+, $C_{22}H_{16}Cl_3NO_4$, derived on the basis of fragments), 294 ($C_{14}H_{10}Cl_2NO_2$), 169 ($C_8H_6ClO_2$). UV spectrum (saturated solution): 274. IR spectrum: 828, 880 (2 adjacent and solitary Ar—H); 1 235, 1 271, 1 310 ($ArOCH_3$); 1 500, 1 520, 1 570, 1 590, 1 600 (Ar); 1 638 (C=N—OH); 1 671 (ArCO); 3 310 (O—H··O=C). ^1H NMR spectrum

(200 MHz): 3·97 s, 3 H (OCH_3); 4·01 s, 3 H (OCH_3); 7·02 d, 2 H (in a 2 : 1 mixture of C^2HCl_3 and $C_6{}^2H_6$ the doublets of both hydrogens are separated to signals at δ 6·76 and 6·70) (H-5 in Ar-2 and H-5 in Ar-1, J(5, 6 in Ar-2) = J(5, 6 in Ar-1) = 8·6); 7·56 (protons H-3, H-1, and H-4 afford an ABX spectrum whose parameters were verified by the simulated spectrum calculation), 1 H (H-1, J(1, 3) = 2·6); 7·58, 1 H (H-3, J(3, 4) = 8·5; J(3, 1) = 2·6); 7·63 dd, 1 H (H-6 in Ar-2, J(6, 5 in Ar-2) = 8·6; J(6, 2 in Ar-2) = 2·2); 7·87 d, 1 H (H-2 in Ar-2, J(2, 6 in Ar-2) = 2·2); 7·88 dd, 1 H (H-6 in Ar-1, J(6, 5 in Ar-1) = 8·6; J(6, 2 in Ar-1) = 2·3); 8·05 d, 1 H (H-2 in Ar-1, J(2, 6 in Ar-1) = 2·3); 8·76, 1 H (H-4, J(4, 3) = 8·5); 11·40 s, 1 H =NOH). For $C_{22}H_{16}Cl_3NO_4$ (464·7) calculated: 56·86% C, 3·47% H, 22·89% Cl, 3·01% N; found: 57·00% C, 3·43% H, 22·77% Cl, 2·94% N.

Further benzene fractions yielded 1·25 g of a yellow minor product which crystallized from a mixture of chloroform and ethanol in prisms melting at 260—270°C, resolidifying by further heating in the form of thin needles which melt at 319—321°C. The substance is tentatively assigned to be 3-chloro-7-(3-chloro-4-methoxybenzoyl)-2-methoxyacridine-9-carbonitrile N-oxide (*VI*). Mass spectrum: 452 (M^+, $C_{23}H_{14}Cl_2N_2O_4$), 436 ($C_{23}H_{14}Cl_2N_2O_3$), 297 ($C_{15}H_6ClN_2O_3$), 281 ($C_{15}H_6ClN_2O_2$), 169 ($C_8H_6ClO_2$), 155 (C_8H_8ClO). UV spectrum (saturated solution): 290 (high), 376, 397. IR spectrum (KBr): 773, 815, 846, 856, 887 (2 adjacent and solitary Ar—H); 1 060, 1 240 ($ArOCH_3$); 1 275, 1 319 (N—O); 1 500, 1 569, 1 593, 3 095 (Ar); 1 620 (C=N); 1 665 (ArCOAr'); 2 210 (ArCN). For $C_{23}H_{14}Cl_2N_2O_4$ (453·3) calculated: 60·94% C, 3·11% H, 6·18% N; found: 60·71% C, 3·14% H, 6·22% N.

The elution was continued with a mixture of benzene with 7·5% ethanol which resulted in 3·4 g of the most polar component of the mixture crystallizing in needles from benzene containing 1% ethanol and melting at 217—218°C. It was identified as 5-chloro- 3-(3-chloro-4-methoxyphenyl)-3-hydroxyindole-2(3*H*)-one (*VII*). Mass spectrum: 323 (M^+, $C_{15}H_{11}Cl_2NO_3$), 295 ($C_{14}H_{11}Cl_2NO_2$), 294 ($C_{14}H_{10}Cl_2NO_2$), 280 ($C_{13}H_8Cl_2NO_2$), 260 ($C_{14}H_{11}ClNO_2$), 169 ($C_8H_6ClO_2$), 154 (C_7H_5ClNO). UV spectrum: 259 (4·05), infl. 301 (3·19). IR spectrum (KBr): 811, 828 (2 adjacent and solitary Ar—H); 1 063 (C—OH); 1 176, 1 261 ($ArOCH_3$); 1 500, 1 600, 1 618 (Ar); 1 722 (in $CHCl_3$ 1 726) (CONHAr in a 5-membered ring); 3 300 (OH and/or NH in H bonds). ^{1}H NMR spectrum (200 MHz, $C^2H_3SOC^2H_3$): 3·82 s, 3 H (OCH_3); 6·81 s, 1 H (NH); 6·92 d, 1 H (H-5', J(5', 6') = 8·2); 7·04 dd, 1 H (H-6, J(6, 7) = 8·6; J(6, 4) = 1·9); 7·10 dd, 1 H (H-7, J(7, 6) = 8·6; J(7, 4) = c. 0·4); 7·15 d, 1 H (H-2', J(2', 6') = 2·2); 7·32 dd, 1 H(H-6', J(6', 5') = 8·2; J(6', 2') = 2·2); 7·37 dd, 1 H (H-4, J(4, 6) = 1·9; J(4, 7) = c. 0·4); 10·43 s, 1 H (OH). For $C_{15}H_{11}Cl_2NO_3$ (324·1) calculated: 55·57% C, 3·42% H, 21·88% Cl, 4·32% N; found: 56·01% C, 3·34% H, 21·60% Cl, 4·21% N.

5-Chloro-3-(3,4-dimethoxyphenyl)-2,1-benzisoxazole (*Ib*)

A solution of 53·6 g (3,4-dimethoxyphenyl)acetonitrile and 61·0 g 4-chloro-1-nitrobenzene in 100 ml benzene was added dropwise over 105 min to a stirred solution of 218 g 80% KOH in 430 ml methanol at 25—30°C. The mixture was stirred for 3 h at room temperature, poured into a solution of 220 g NH_4Cl in 1 400 ml water, diluted with 250 ml benzene, shaken for several minutes, and the suspension was filtered. The solid was washed with 100 ml 1 : 1 mixture of benzene and hexane and dried in vacuo; 32·0 g fraction A, m.p. 130—135°C. The filtrate was extracted wih benzene, the extract was washed wih 250 ml 5% NaCl, dried with $CaCl_2$, and evaporated. The residue was extracted with 140 ml ethanol at room temperature under stirring, the suspension was allowed to stand overnight in a refrigerator, filtered, the solid was washed with 100 ml ice-cold ethanol, and dried; 33·0 g fraction B, m.p. 127—130°C. Because TLC showed for fractions A and B similar composition, they were combined and chromatographed on 1·3 kg Al_2O_3. Benzene eluted in the first fractions 59·6 g homogeneoüs *Ib*, m.p. 143—144°C

(benzene) UV spectrum: 220 (4·45), 259 (4·06), 266 (4·04), 373 (4·23). IR spectrum: 808, 853 (2 adjacent and solitary Ar—H); 1 018, 1 131, 1 237, 1 258, 2 825 ($ArOCH_3$); 1 500, 1 515, 1 585, 1 600 (Ar); 1 631 (C=N). ^{1}HNMR spectrum: 3·98 s, 3 H (OCH_3); 4·00 s, 3 H (OCH_3); 7·00 d, 1 H (H-5′, J = 8·5); 7·20 q, 1 H (H-6′, J = 8·5; 2·5); c. 7·48 m, 3 H (H-6, H-7, H-2′); 7·70 bs, 1 H (H-4). For $C_{15}H_{12}ClNO_3$ (289·7) calculated: 62·20% C, 4·17% H, 12·23% Cl, 4·84% N; found: 62·54% C, 4·20% H, 12·26% Cl, 4·78% N.

Further elution with benzene gave 4·8 g (5%) orange needles, m.p. 259°C (chloroform–ethanol–benzene), very little soluble in common solvents. It was tentatively assigned to be 2-chloro-5,6-dimethoxyacridine-9-carbonitrile N-oxide (*VIII*). Mass spectrum: 316, 314 (M^+, $C_{16}H_{11}ClN_2O_3$, 100), 298 ($C_{16}H_{11}ClN_2O_2$). UV spectrum: 252 (4·34), 290 (4·84), 418 (4·20), 454 (4·07). IR spectrum: 821, 844 (2 adjacent and solitary Ar—H); 1 235, 1 248 ($ArOCH_3$); 1 267 (N—O); 1 490, 1 528, 1 570, 1 600 (Ar); 1 620 (C=N); 2 213 (ArCN). For $C_{16}H_{11}ClN_2O_3$ (314·7) calculated: 61·05% C, 3·52% H, 11·26% Cl, 8·90% N; found: 61·13% C 3·49% H, 11·60% Cl, 8·94% N.

The filtrate after fraction B was evaporated and the residue (36 g) was chromatographed on 1 kg Al_2O_3. In the first fractions benzene eluted further 6·0 g *Ib* (m.p. 142—144°C), its total yield being thus 65·6 g (75%). Crystallization of a further fraction separated 0·3 g recovered 4-chloro-1-nitrobenzene and 1·1 g (2%) 4-nitroanisole (cf. refs[4,5]). Elution with benzene gave finally 15·0 g (17%) 3,4-dimethoxy-4′-nitrobenzophenone (*X*), m.p. 174—175°C (benzene). UV spectrum: 269 (4·26), 323 (3·92). IR spectrum: 848, 869 (2 adjacent and solitary Ar—H); 1 226, 1 278 ($ArOCH_3$); 1 340, 1 515 ($ArNO_2$); 1 574, 1 588, 3 010, 3 070, 3 080, 3 100 (Ar); 1 643 (ArCOAr′). ^{1}H NMR spectrum: 3·98 s, 3 H (OCH_3); 4·00 s, 3 H (OCH_3); 6·92 d, 1 H (H-5, J = 8·5); 7·33 q, 1 H (H-6, J = 8·0; 2·0); 7·52 d, 1 H (H-2, J = 2·0); 7·90 d, 2 H (H-2′ and H-6′, J = 8·5); 8·38 d, 2 H (H-3′ and H-5′, J = 8·5). For $C_{15}H_{13}NO_5$ (287·3) calculated: 62·71% C, 4·56% H, 4,88% N; found: 62·30% C, 4·56% H, 4·66% N.

The elution was continued with benzene containing 5% ethanol and gave 8·0 g amorphous substance. It was rechromatographed on 210 g Al_2O_3, using again benzene as eluent. The amorphous middle fractions (4·4 g) were combined and heated with 120 ml ethanol which resulted in crystallization of 4·0 g compound assigned to be 2-(2-chloro-5-(hydroxyimino)-1,3-cyclohexadien-6-ylidene)-1,2-bis(3,4-dimethoxyphenyl)ethan-1-one (*Vb*), m.p. 192—193°C (chloroform–ethanol or acetonitrile). Mass spectrum: 457, 455 (M^+, $C_{24}H_{22}ClNO_6$, 5), 165 ($C_9H_9O_3$, 100). UV spectrum: infl. 230 (4·52), infl. 262 (4·34), 285 (4·30), infl. 346 (3·91). IR spectrum: 835, 858, 882, 890 (2 adjacent and solitary Ar—H); 1 025, 1 265 ($ArOCH_3$); 1 512, 1 580, 1 593 (Ar); 1 619 (C=N—OH); 1 672 (ArCO—C=C); 3 220 (N—OH··O=C). ^{1}H NMR spectrum: 3·96 s, 6 H (2 OCH_3); 3·99 s, 6 H (2 OCH_3); 6·80—7·70 m, 9 H (9 ArH). For $C_{24}H_{22}ClNO_6$ (455·9) calculated: 63·22% C, 4·86% H, 7·80% Cl, 3·07% N; found: 63·23% C, 4·90% H, 8·07% Cl, 2·91% N.

2-Amino-5,3′-dichloro-4′-methoxybenzophenone (*XIa*)

Ia (12·2 g) was added to a mixture of 6·6 g powdered Fe, 12·2 ml ethanol, 6·6 ml water, and 18 ml acetic acid, which was preheated to 55°C. The mixture was stirred until the exothermic reaction was finished and then it was refluxed for 2 h. At 60°C it was diluted with 100 ml benzene, the undissolved material was filtered off, washed with 200 ml warm benzene, the filtrates were washed with warm water and with 5% $NaHCO_3$, dried, and evaporated; 12·0 g (98%) of the almost homogeneous yellow product, m.p. 150—152°C. Analytical sample, m.p. 153—154°C (benzene–cyclohexane). UV spectrum: 236 (4·46), 277 (4·03), 390 (3·80). IR spectrum: 825, 831, 860 (2 adjacent and solitary Ar—H); 1 235, 1 255, 1 279 ($ArOCH_3$); 1 496, 1 562, 1 580, 1 605 (Ar); 1 590 ($ArNH_2$); 1 628 (ArCOAr′); 3 375, 3 487 (NH_2). ^{1}H NMR spectrum: 3·98 s, 3 H

(OCH_3); 5·86 bs, 2 H (NH_2); 6·62 d, 1 H (H-3, J = 8·5); 6·92 d, 1 H (H-5', J = 8·5); 7·20 dd, 1 H (H-4, J = 8·5; 2·0); 7·35 d, 1 H (H-6, J = 2·0); 7·52 dd, 1 H (H-6', J = 8·5; 2·0); 7·71 d, 1 H (H-2', J = 2·0). For $C_{14}H_{11}Cl_2NO_2$ (296·2) calculated: 56·77% C, 3·74% H, 23·95% Cl, 4·73% N; found: 56·87% C, 3·75% H, 23·69% Cl, 4·52% N.

2-Amino-5-chloro-3',4'-dimethoxybenzophenone (*XIb*)

A similar reaction of 60·0 g *Ib* with 33 g Fe in 60 ml ethanol, 30 ml water, and 90 ml acetic acid gave 59·5 g (98%) crude *XIb*, m.p. 124·5—126°C. Analytical sample, m.p. 126—127°C (benzene–hexane). UV spectrum: 237 (4·47), 280 (3·85), 309 (3·76), 390 (3·81). IR spectrum: 770, 800, 868, 890 (2 adjacent and solitary Ar—H); 1 130, 1 217 ($ArOCH_3$); 1 513, 1 538, 1 575, 1 585, 3 005, 3 015, 3 080 (Ar); 1 619 ($ArNH_2$); 1 632 (ArCOAr'), 3 365, 3 475 (NH_2). ^{1}H NMR spectrum: 3·90 s, 3 H (OCH_3); 3·94 s, 3 H (OCH_3); 5·78 bs, 2 H (NH_2); 6·62 d, 1 H (H-3, J = 8·5); 6·85 bd, 1 H (H-6', J = 8·5); 7·20 m, 3 H (H-4, H-2', and H-5'); 7·40 d, 1 H (H-6, J = 2·5). For $C_{15}H_{14}ClNO_3$ (291·7) calculated: 61·76% C, 4·83% H, 12·15% Cl, 4·80% N; found: 62·24% C, 4·89% H, 12·44% Cl, 4·56% N.

5,3'-Dichloro-4'-methoxy-2-(phthalimidoacetamido)benzophenone (*XIIa*)

A solution of 40 g *XIa* in 200 ml chloroform was treated with 34·0 g 93% phthalimidoacetyl chloride[10-12] and the mixture was stirred and refluxed for 7 h. Chloroform was distilled off, the warm residue was treated with 200 ml ethanol, the mixture was heated for 30 min to 60°C, then cooled under stirring for 2 h in an ice bath, the solid was filtered, washed with ethanol and ether, and dried in vacuo; 65·2 g (theoretical), m.p. 188—190°C. Analytical sample, m.p. 190—191°C (chloroform–ethanol). UV spectrum: infl. 232 (4·65), 293 (4·11), infl. 337 (3·48). IR spectrum: 760, 785, 811, 829, 845, 900 (4 and 2 adjacent, and solitary Ar—H); 1 237, 1 266 ($ArOCH_3$); 1 500, 1 580, 1 592, 3 020, 3 060, 3 100 (Ar); 1 511, 1 644 (CONH, ArCOAr'); 1 720, 1 778 (1,2-Ar$(CO)_2$N); 3 290 (NH). For $C_{24}H_{16}Cl_2N_2O_5$ (483·3) calculated: 59·64% C, 3·34% H, 14·67% Cl, 5·80% N; found: 59·60% C, 3·37% H, 14·80% Cl, 5·41% N.

5-Chloro-3',4'-dimethoxy-2-(phthalimidoacetamido)benzophenone (*XIIb*)

A similar reaction of 59·0 g *XIb* with 56·0 g 82% phthalimidoacetyl chloride[10-12] in 250 ml chloroform and a similar processing gave 95·5 g (99%) product, m.p. 243—244°C. Analytical sample, m.p. 245°C (chloroform–benzene–ethanol). UV spectrum (saturated solution): 291, 320, infl. 235. IR spectrum: 753, 775, 818, 820, 828, 880, 893 (4 and 2 adjacent, and solitary Ar—H); 1 260, 1 273, 1 300 ($ArOCH_3$); 1 511, 1 532, 1 700 ArNHCOR); 1 582, 1 600 (Ar); 1 650 (ArCOAr'); 1 718, 1 772 (1,2-Ar$(CO)_2$N); 3 330 (NH). For $C_{25}H_{19}ClN_2O_6$ (478·9) calculated: 62·70% C, 4·00% H, 7·40% Cl, 5·85% N; found: 62·88% C, 4·18% H, 7·38% Cl, 6·10% N.

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

A suspension of 66·0 g *XIIa* in 1 l methanol was treated with 50 ml 18% N_2H_4, the mixture was heated to 60—65°C, and stirred for 3 h at this temperature. It was then cooled, allowed to stand overnight in the refrigerator, the solid was filtered, and washed with 150 ml acetone. It was suspended in a solution of 80 ml NH_4OH in 700 ml water, stirred for 1 h at room temperature, filtered, washed with dilute NH_4OH and water, and dried; 41·0 g,m.p. 271—273°C. The combined filtrates were filtered with charcoal, the filtrate was evaporated in vacuo, the residue was treated with a solution of 30 ml NH_4OH and 150 ml water, and the undissolved product was filtered, washed with dilute NH_4OH and water, and was dried in vacuo; 2·5 g, m.p. 263—265°C. Both

products were combined (total yield 43·5 g, 95%) and a sample was crystallized from pyridine, m.p. 272–273°C. UV spectrum: 231 (4·60), inflexes at 260 (4·17), 276 (3·93), 296 (3·89). IR spectrum: 822, 830, 839, 895, 909 (2 adjacent and solitary Ar—H); 1 275 ($ArOCH_3$); 1 560, 1 597, 3 080, 3 088 (Ar); 1 609 (C=N); 1 682 (NHCO in the ring); 3 125, 3 220 (NH). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): 3·90 s, 3 H (OCH_3); 4·12 s, 2 H ($COCH_2N$); 7·00–7·80 m, 6 H (6 ArH); 10·60 bs, 1 H (ArNHCO). For $C_{16}H_{12}Cl_2N_2O_2$ (335·2) calculated: 57·33% C, 3·61% H, 21·16% Cl, 8·36% N; found: 57·29% C, 3·62% H, 21·00% Cl, 8·21% N.

7-Chloro-5-(3,4-dimethoxyphenyl)-1,3-dihydro-1,4-benzodiazepin-2-one (*XIIIb*)

A mixture of 70·0 g *XIIb*, 800 ml pyridine, 200 ml ethanol, and 80 ml 18% N_2H_4 was stirred for 2·5 h at 60–65°C. The volatile components were evaporated in vacuo, the residue was stirred for 20 min with a solution of 80 ml NH_4OH in 700 ml water, the solid was filtered off, and its extraction with a similar dilute aqueous ammonia was repeated once more. The solid was filtered again, washed with dilute NH_4OH, water, and ethanol, and the dried crude product was crystallized by dissolving in 1·2 l boiling pyridine, evaporation of a part of the solvent, and by keeping the residue in the refrigerator overnight. The product was filtered and the mother liquors were processed giving totally 47·5 g (90%) *XIIIb*, m.p. 286–288°C. Recrystallization of a sample from pyridine did not raise the melting point. UV spectrum: 248 (4·33), 316 (3·93). IR spectrum: 770, 820, 837, 873, 892 (2 adjacent and solitary Ar—H); 1 150, 1 250, 1 270 ($ArOCH_3$); 1 510, 1 560, 1 580, 1 593 (Ar); 1 603 (C=N); 1 676 (CONH in the ring); 3 080, 3 120, 3 215 (NH). For $C_{17}H_{15}ClN_2O_3$ (330·8) calculated: 61·73% C, 4·58% H, 10·72% Cl, 8·47% N; found: 61·74% C, 4·60% H, 11·08% Cl, 8·39% N.

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

A mixture of 13·4 g *XIIIa*, 10·2 g P_2S_5, and 135 ml pyridine was stirred and refluxed for 45 min in nitrogen atmosphere. After cooling, the mixture was poured at 5°C into a stirred solution of 230 g NH_4Cl in 850 ml water. It was stirred for 30 min, the precipitated solid was filtered, washed with water, and dried in vacuo. It was extracted with 300 ml hot dimethylformamide (100°C), the mixture was filtered with charcoal, and the filtrate was evaporated; 10·5 g (75%), m.p. 260–262°C. Analytical sample, m.p. 262–263°C (pyridine–ethanol). UV spectrum: 300 (4·32), infl. 235 (4·26). IR spectrum: 834, 870 (2 adjacent and solitary Ar—H); 1 276 ($ArOCH_3$); 1 370 (CSNH); 1 501, 1 522, 1 580, 1 595, 3 000, 3 054, 3 085 (Ar); 1 603 (C=N); 3 120 (NH). For $C_{16}H_{12}Cl_2N_2OS$ (351·3) calculated: 54·71% C, 3·44% H, 20·19% Cl, 7·98% N, 9·12% S; found: 54·91% C, 3·42% H, 20·13% Cl, 7·66% N, 9·21% S.

7-Chloro-5-(3,4-dimethoxyphenyl)-1,3-dihydro-1,4-benzodiazepin-2-thione (*XIVb*)

A mixture of 24·6 g *XIIIb*, 19·0 g P_2S_5, and 250 ml pyridine was stirred and refluxed for 45 min under nitrogen. After cooling, the mixture was poured into a solution of 420 g NaCl in 1·5 l water at 4°C, the mixture was stirred for 30 min, the solid was filtered, washed with water, and dried in vacuo. This crude product (23·8 g) was suspended in dichloromethane, the suspension was brought on a column of 45 g Al_2O_3, and the product was eluted with 3·8 l dichloromethane. Evaporation of the eluates gave 20·0 g (78%) purified *XIVb*, m.p. 240–242°C. Analytical sample, m.p. 243–244°C (pyridine). UV spectrum: 305 (4·39), infl. 235 (4·25). IR spectrum (KBr): 770, 809, 838, 878 (2 adjacent and solitary Ar—H); 1 255, 1 274, 2 835 ($ArOCH_3$); 1 365, 1 480 (CSNH); 1 510, 1 572, 1 590, 3 050 (Ar). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): 3·75 s, 3 H OCH_3); 3·78 s, 3 H (OCH_3); 4·50 bs, 2 H ($CSCH_2N$); 6·78 dd, 1 H (H-6', J = 8·0; 1·5); 6·97 d,

1 H (H-5′, J = 8·0); 7·25 d, 1 H (H-2′, J = 1·5); 7·29 d, 1 H (H-6, J = 2·5); 7·36 d, 1 H(H-9, J = 8·5); 7·65 dd, 1 H (H-8, J = 8·5; 2·5); 12·48 bs, 1 H (ArNHCS). For $C_{17}H_{15}ClN_2O_2S$ (346·8) calculated: 58·87% C, 4·36% H, 10·22% Cl, 8·08% N, 9·24% S; found: 58·76% C, 4·42% H, 10·28% Cl, 7·88% N, 9·17% S.

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

A stirred mixture of 5·02 g *XIVa*, 2·95 g acetohydrazide[13], 110 ml butanol, and 20 ml pyridine was refluxed for 6 h in nitrogen atmosphere. The warm mixture was filtered with charcoal, the filtrate was diluted with 40 ml chloroform, washed with water several times, dried, and evaporated. The residue was boiled for several minutes with 10 ml ethyl acetate, allowed to stand overnight in the refrigerator, and filtered; 3·50 g (63%), m.p. 237–239°C. Recrystallization from a mixture of chloroform and ethyl acetate gave the pure product, m.p. 239–240°C. UV spectrum: 225 (4·58), 285 (3·91), 298 (3·92), infl. 245 (4·28). IR spectrum: 834, 900 (2 adjacent and solitary Ar—H); 1 277 ($ArOCH_3$); 1 505, 1 538, 1 562, 1 598, 3 017, 3 053, 3 070, 3 093 (Ar); 1 608 (C=N). ^{1}H NMR spectrum: 2·65 s, 3 H (C—CH_3); 3·95 s, 3 H (OCH_3); 6·90 d, 1 H and 4·08 d, 1 H (ABq, =C—CH_2—N=, J = 13·0); 6·80–7·80 m, 6 H (6 ArH). For $C_{18}H_{14}Cl_2N_4O$ (373·2) calculated: 57·92% C, 3·78% H, 19·00% Cl, 15·01% N; found: 57·65% C, 3·87% H, 19·05% Cl, 14·70% N.

8-Chloro-6-(3,4-dimethoxyphenyl)-1-methyl-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepine (*XVb*)

A stirred mixture of 5·2 g *XIVb*, 2·95 g acetohydrazide[13], and 110 ml butanol was refluxed for 7·5 h under nitrogen and processed similarly like in the preceding case; 3·52 g (64%), m.p. 218 to 219°C (chloroform–ethyl acetate). UV spectrum: 316 (3·89), infl. 245 (4·30). IR spectrum: 770, 790, 805, 835, 874 (2 adjacent and solitary Ar—H); 1 125, 1 145, 1 230, 1 250, 1 270 ($ArOCH_3$); 1 484, 1 510, 1 530, 1 560, 1 575, 1 590, 3 000, 3 020, 3 050, 3 080 (Ar). ^{1}H NMR spectrum: 2·60 s, 3 H (C—CH_3); 3·88 s, 3 H (OCH_3); 3·90 s, 3 H (OCH_3); 4·02 d, 1 H and 5·40 d, 1 H (ABq, =C—CH_2—N=, J = 13·0); 6·90 d, 1 H and 6·75 d, 1 H (ABq, H-5′ and H-6′, J = 8·5); 7·39 bs, 1 H (H-2′); 7·44 d, 1 H, (H-10, J = 8·5); 7·50 d, 1 H (H-7, J = 3·0); 7·69 dd, 1 H (H-9, J = 8·5; 3·0). For $C_{19}H_{17}ClN_4O_2$. (368·8) calculated: 61·87% C, 4·65% H, 9·61% Cl, 15·19% N; found: 61·42% C, 4·77% H, 9·85% Cl, 15·14% N.

8-Chloro-6-(3-chloro-4-methoxyphenyl)-1-(methylthiomethyl)-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepine (*XVIa*)

The reaction of 2·70 g *XIVa* with 2·50 g (methylthio)acetohydrazide[14] in a boiling mixture of 80 ml butanol and 10 ml pyridine was carried out similarly like in the preparation of *XVa*. Similar processing gave 3·0 g (89%) *XVIa*, m.p. 224–225°C (chloroform–ethyl acetate). UV spectrum: 225 (4·56), 284 (3·92), 298 (3·92), infl. 246 (4·30). IR spectrum: 839, 881 (2 adjacent and solitary Ar—H); 1 271 ($ArOCH_3$); 1 500, 1 530, 1 567, 1 600, 3 020, 3 055, 3 075, 3 085 (Ar); 1 610 (C=N). For $C_{19}H_{16}Cl_2N_4OS$ (419·3) calculated: 54·41% C, 3·85% H, 16·91% Cl, 13·36% N, 7·65% S; found: 54·04% C, 3·92% H, 17·07% Cl, 12·77% N, 7·72% S.

8-Chloro-6-(3,4-dimethoxyphenyl)-1-(methylthiomethyl)-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepine (*XVIb*)

Similar reaction of 1·4 g *XIVb* with 1·20 g (methylthio)acetohydrazide[14] in 60 ml boiling butanol gave 1·60 g crude *XVIb*, which crystallized from a mixture of chloroform and ethyl acetate as a 2 : 1 solvate with ethyl acetate; 1·30 g (70%), m.p. 150–152°C. Mass spectrum: 414 (M^+,

$C_{20}H_{19}ClN_4O_2S$), 368 (100), 367. UV spectrum: 317 (3·87), infl. 246 (4·30). IR spectrum: 770, 795, 830, 875 (2 adjacent and solitary Ar—H); 1 260, 1 275 ($ArOCH_3$); 1 515, 1 565, 1 575, 1 590, 3 050, 3 080 (Ar); 1 730 (RCOOR′ of ethyl acetate). ^{1}H NMR spectrum: 1·28 t, 1·5 H (0·5 CH_3 of ethyl in ethyl acetate); 2·08 s, 1·5 H (0·5 CH_3CO of ethyl acetate); 2·10 s, 3 H (CH_3S); 3·81 s, 6 H (2 OCH_3); 4·30 d, 1 H and 3·90 d, 2 H (ABq, S—CH_2—C and 0·5 CH_2 of ethyl acetate, J = 13·0); 5·48 d, 1 H and 4·00 d, 1 H (ABq, =C—CH_2—N=, J = 13·0); 6·87 s, 2 H (H-5′ and H-6′), 7·38 bs, 1 H (H-2′); 7·52 d, 1 H (H-7, J = 2·5); 7·68 dd, 1 H (H-9, J = 8·5; 2·5); 7·86 d, 1 H (H-10, J = 8·5). For $C_{20}H_{19}ClN_4O_2S$ + 0·5 $C_4H_8O_2$ (459·0) calculated: 57·57% C, 5·05% H, 7·73% Cl, 12·21% N, 6·99% S; found: 57·39% C, 5·17% H, 8·03% Cl, 12·16% N, 7·10% S.

The authors thank their colleagues at the Research Institute for Pharmacy and Biochemistry for the co-operation: Dr J. Schlanger (mass spectra), Mrs A. Hrádková (recording of the UV *and* IR *spectra), Dr S. Wildt (pharmacological screening), Mrs J. Komancová, Mrs V. Šmídová, and Mrs J. Kropáčová (elemental analyses).*

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Translated by the author (M.P.).