PSYCHOTROPIC DERIVATIVES OF 5-PHENYL-7-CHLORO-1,3-DIHYDRO-1,4-BENZODIAZEPIN-2-ONE AND CONTRIBUTION TO THE SYNTHESIS OF ITS 5-(2-CHLOROPHENYL) ANALOGUE*

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Alkylation of 7-chloro-5-phenyl-1,3-dihydro-1,4-benzodiazepin-2-one (*I*) with 2,5-dimethoxyphenacyl bromide and 3-(4-phenylpiperazino)propyl chloride afforded the N-substituted derivatives of nordazepam *III* and *IV*; compound *IV* revealed properties of a potential hypnotic agent. Reaction of 4-chloronitrobenzene with (2-chlorophenyl)acetonitrile in methanolic solutions of alkali hydroxides gave mixtures from which the following compounds were isolated: 5-chloro-3-(2-chlorophenyl)-2,1-benzisoxazole (*VII*), the O-methyloxime *X*, 5-chloro-2,3-bis(2-chlorophenyl)indole (*XI*), 2-chloro-4′-nitrobenzophenone (*XVII*) and 2-chloro-9-cyanoacridine N-oxide (*XX*). A similar reaction of 4-chloronitrobenzene with (2-fluorophenyl)acetonitrile gave compound *XX* as the main product; in smaller amounts 4-nitroanisole, 2-fluoro-4′-nitrobenzophenone (*XVIII*) and 2-chloroacridine-9-carbonitrile (*XXIV*) were obtained. Compound *VII* was reduced to the aminobenzophenone derivative *V* which was transformed *via* the phthalimidoacetyl derivative *VI* to the chlorodemethyldiazepam *II*.

7-Chloro-5-phenyl-1,3-dihydro-1,4-benzodiazepin-2-one (nordazepam) (*I*) (ref.[1-4]) and its N^1-substituted derivatives (ref.[5-7]) are psychotropic agents with anxiolytic activity and with more or less pronounced hypnotic, anticonvulsant and myorelaxant components of action. Some of these components (especially the anticonvulsant one) are much higher with the 5-(2-chlorophenyl) analogue of compound *I* (ref.[2,8,9]), known as chlorodemethyldiazepam or delorazepam *II* (ref.[5-7,10]).

In the first part of the present communication we describe the synthesis of two new N^1-substituted derivatives of nordazepam, compounds *III* and *IV*, which were obtained by alkylation of compound *I* (ref.[2,3]) with 2,5-dimethoxyphenacyl bromide[11] and 3-(4-phenylpiperazino)propyl chloride[12]. Alkylations were carried out in a mixture of toluene and dimethylformamide and with the use of sodium hydride as the reagent for the formation of the amide anion. The synthesis of the Ar-unsubstituted 1-phenacyl derivative of compound *I* was described in a patent[13].

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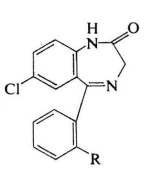
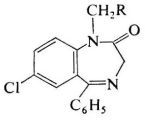
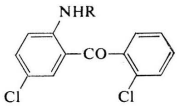
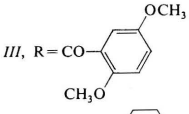


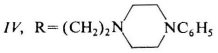
I, R = H
II, R = Cl



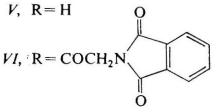




III, R = CO–



IV, R = $(CH_2)_2N$–



V, R = H

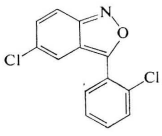
VI, R = $COCH_2N$

In a further part of this paper the attempts at improving the synthetic procedure leading to chlorodemethyldiazepam (*II*) are described. 2-Amino-5,2′-dichlorobenzophenone (*V*) is an intermediate in the synthesis of compound *II*. Its preparation was described only by the reaction of 4-chloroaniline with 2-chlorobenzoyl chloride in the presence of zinc chloride under drastic conditions (220–230°C) and by the following hydrolysis of the intermediate[14,15]. Since the analogous 2-amino-5-chlorobenzophenone (intermediate in the synthesis of nordazepam, *I*) is accessible by a two-step sequence, in which 5-chloro-3-phenyl-2,1-benzisoxazole[16–19] is first obtained by a base-catalyzed reaction of 4-chloronitrobenzene with phenylacetonitrile and this is cleaved in the second step by reduction[20], a similar approach to the dichloro derivative *V* was considered desirable; we were not able to find any report on a similar reaction of 4-chloronitrobenzene with (2-chlorophenyl)acetonitrile[21]. Reactions of phenylacetonitrile and some of its derivatives with nitrobenzene and its 2-, 3- and 4-substituted derivatives were investigated[16,22,23]; the formation of 3-aryl-2,1-benzisoxazoles was found only in the case of 4-substituted nitrobenzenes[16]. 4-Chloronitrobenzene and 4-bromonitrobenzene reacted in this manner; phenylacetonitrile, (4-chlorophenyl)acetonitrile and (4-methoxyphenyl)acetonitrile were used as nitrile components[16]. In our recent paper[24], a successful use of 6,7,8,9-tetrahydro-5*H*-benzocycloheptene-2-acetonitrile in a reaction with 4-chloronitrobenzene was reported.

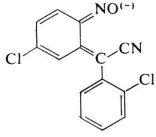
The reaction of 4-chloronitrobenzene with (2-chlorophenyl)acetonitrile[21] was carried out similarly like in the analogous case[16–19], *i.e.* in a concentrated solution of sodium hydroxide or potassium hydroxide in methanol at 25–30°C. With regard to a better solubility of potassium hydroxide in methanol, the work with this hydroxide was easier. After the decomposition of the reaction mixture a heterogeneous product was obtained which was separated by chromatography on aluminium oxide and by fractional crystallization. In addition to the recovered 4-chloronitrobenzene, five substances *A*–*E* were obtained. The products are arranged according to the

increasing polarity: compound *A* (12%), $C_{13}H_7Cl_2NO$, m.p. 142–143°C; compound *B* (15%), $C_{22}H_{15}Cl_3N_2O$, m.p. 128–129°C; compound *C* (25%), $C_{20}H_{12}Cl_3N$, m.p. 177–178°C; compound *D* (5%), $C_{13}H_8ClNO_3$, yellowish, m.p. 101–102°C; compound *E* (20%), $C_{14}H_7ClN_2O$, yellow solid, m.p. 203–204°C. For identification, spectra and chemical transformations were used; in one case an independent and unequivocal synthesis was carried out.

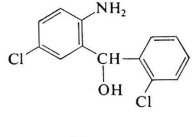
Compound *A* corresponds to the desired 5-chloro-3-(2-chlorophenyl)-2,1-benzisoxazole (*VII*), the precursor of which is evidently the oxime anion *VIII* (*cf.*[16,20]). The UV, IR and ^{1}H-NMR spectra are in agreement with the assigned structure *VII* which was confirmed by chemical transformations. Reduction with iron in acetic acid (for analogy, *cf.*[16,24]) afforded the benzophenone derivative *V*, the identity of which was confirmed by comparison with the authentic substance, prepared differently[14,15]. Reduction of compound *VII* with lithium aluminium hydride gave



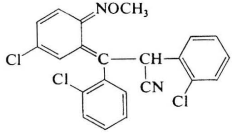
VII



VIII



IX



X

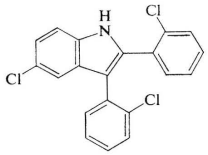
the benzhydrol derivative *IX*; its melting point is identical with that of the product of a reaction of 4-chloroaniline with 2-chlorobenzaldehyde in the presence of phenyldichloroborane and triethylamine, described only after the termination of our experimental work[25]. Reaction of 4-chloronitrobenzene with (2-chlorophenyl)acetonitrile results thus in principle in the desired 2,1-benzisoxazole derivative *VII*; the low yield and the necessity of separating the product from a complicated mixture exclude the possibility of the use of this reaction to preparative purpose.

The empirical composition of the compound *B* shows the presence of three aromatic rings and the IR and ^{1}H-NMR spectra give information about the character of their substitution. The intensive band at 1662 cm^{-1} in the IR spectrum is at-

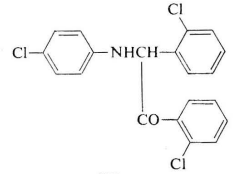
tributed to the C=N fragment of the oxime group and the band at 2250 cm^{-1} belongs evidently to the nitrile group. The ^{1}H-NMR spectrum shows the singlet of a methyl group localized in formula *X* on the oxygen atom of the oxime group. In addition to 11 aromatic protons, this spectrum shows another singlet at 6·03 ppm, corresponding to a methine group adjacent to an aromatic ring. The presence of methoxyl is confirmed by the mass spectrum. It is supposed that the compound *X* could be formed from the benzisoxazole *VII* by the attack of the methoxide anion and by a following reaction of the intermediate benzophenone derivative with an additional molecule of (2-chlorophenyl)acetonitrile by mechanism of the Knoevenagel condensation[26].

Compound *C* can be designated as the main product of the reaction. By its empirical composition, it is not too far from compound *B* differing from it by the absence of the methyl and nitrile groups. The ^{1}H-NMR spectrum shows in addition to the multiplet of aromatic protons a singlet at δ 11·88 ppm, corresponding to the NH group of an indole derivative. The IR spectrum confirms the presence of the NH group by a sharp band at 3420 cm^{-1}. The substance is formulated as 5-chloro-2,3-bis(2-chlorophenyl)indole (*XI*) which was confirmed by its independent preparation from 2,2′-dichlorodeoxybenzoin[27] and 4-chlorophenylhydrazine[28] by means of a Fischer synthesis. The synthesis of 2,3-diarylindoles was described using several methods[29–32]; compound *XI* has not yet been described. An attempt to apply the Koelsch[29] procedure to our case was not successful: heating of 2,2′-dichlorobenzoin[27] with 4-chloroaniline and a small amount of hydrochloric acid to 140–150°C gave the desylaniline derivative *XII* (for analogy, *cf.*[30,33]). Neither heating of 2,2′-dichlorobenzoin with 4-chloroaniline and a greater quantity of hydrochloric acid to higher temperature (150–160°C), nor heating of compound *XII* with aniline and hydrochloric acid did result in indole derivatives; only diketanils *XIII* and *XIV* were formed (for analogy and explanation of the mechanism of formation of such compounds, *cf.*[30]). Heating of 2,2′-dichlorobenzoin[27] with aniline and hydrochloric acid precisely under the Koelsch' conditions[29] did not lead to the formation of the indole derivative but only the diketanil *XV*; the formation of this compound by a different method was already mentioned[34]. Reduction of 2,2′-dichlorodeoxybenzoin[27] with sodium borohydride in ethanol gave the alcohol *XVI* (*cf.*[35]). Structural relation between *X* and *XI* induced the hypothesis that compound *X* could function as precursor of the substance *XI* in the reaction of 4-chloronitrobenzene with (2-chlorophenyl)acetonitrile in methanolic solutions of alkali hydroxides. An attempt to transform compound *X* by the action of methanolic potassium hydroxide at room temperature to the indole derivative *XI* was unsuccessful; compound *X* was recovered. Since the stoichiometry of transformation of compound *X* to substance *XI* presumes a reduction step, the attempt was repeated with the presence of ascorbic acid. In this case a mixture was formed consisting approximately of 40% of the starting compound *X* and 60% of the indole derivative *XI*

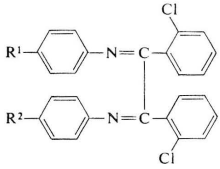
which was isolated from the mixture in pure form. It is possible to consider this result a confirmation of our hypothesis that compound *X* is a precursor of compound *XI*; some other component of the complicated reaction mixture could serve as the reducing agent.



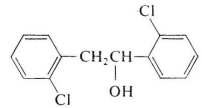
XI



XII

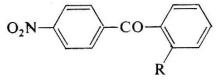


XIII, $R^1 = R^2 = Cl$
XIV, $R^1 = H$, $R^2 = Cl$
XV, $R^1 = R^2 = H$

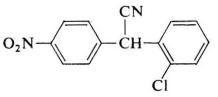


XVI

Compound *D* is a minor product of the reaction. It was possible to derive for it the structure of 2-chloro-4′-nitrobenzophenone (*XVII*). The compound gives a 2,4-dinitrophenylhydrazone of the expected composition. The literature[36] mentioned the ketone *XVII* with doubts on the correctness of its structure. It is assumed that the source of ketone *XVII* in our case was the nitrile *XIX*, the formation of which by reaction of 4-chloronitrobenzene with (2-chlorophenyl)acetonitrile under the conditions used is to be expected. A similar reaction of 4-chloronitrobenzene and phenylacetonitrile leading to (4-nitrophenyl)phenylacetonitrile proceeds in the presence of pyridine and potassium hydroxide[37]. The conversion of nitriles similar to compound *XIX* to ketones (like *XVII*) was carried out by oxidation with chromium trioxide in acetic acid[16]. In our case the oxidation was apparently effected by the air oxygen and a mechanism is proposed similar to that discussed by Kornblum[38] for compounds containing the 4-nitrobenzyl system: the anion, formed in the alkaline medium, reacts with oxygen to give the peroxide anion which is cleaved to ketone and the cyanate anion.



XVII, R = Cl
XVIII, R = F

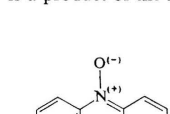


XIX

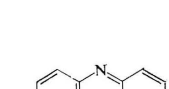
Compound *E* is the second main product of the reaction. Its UV spectrum suggested a polycyclic aromatic system. It contains the nitrile group bound to an aromatic ring ($\nu_{(ArCN)}$ 2218 cm^{-1}) and it is an aromatic N-oxide ($\nu_{(N-O)}$ 1290 cm^{-1}). All the facts prove that we are dealing here with a product of the intramolecular nucleophilic substitution reaction of the intermediate *VIII*, *i.e.* 2-chloro-10-cyanoacridine N-oxide (*XX*). This structure was confirmed by the course of alkaline hydrolysis as well as of reduction of compound *XX* with lithium aluminium hydride. The hydrolysis with ethanolic potassium hydroxide gave a mixture which was separated to two parts on the basis of the solubility in aqueous potassium hydroxide. The insoluble part is the amide which is not homogeneous and consists of a small amount of the N-oxide *XXI* and of the prevailing quantity of the acridinecarboxamide *XXIII*; the hydrolysis is thus accompanied by reduction of the N-oxide. The presence of the N-oxide *XXI* was definitely proven by the mass spectrum, IR spectrum and by the polarographic reduction. The alkali soluble component has the composition $C_{13}H_8ClNO_2$; it is considered to be an equilibrium mixture of tautomers *XXII* and *XXV*. The IR spectrum shows bands at 1642 and 3200 cm^{-1}, ascribed to a keto group conjugated with two aromatic nuclei, and further to a hydroxyl group. The polarographic curve exhibits two reduction waves which indicates the presence of two different fragments N—O. The reduction of compound *XX* with lithium aluminium hydride results in a mixture which was separated to a neutral and a basic component. The neutral product was identified as 2-chloroacridan (*XXVI*). The basic product, giving a crystalline hydrochloride, is the primary amine *XXVII*. The reaction proceeds thus as (*a*) reduction of the N-oxide, (*b*) reduction of the central ring and (*c*) reduction and partly hydrogenolysis of the nitrile group. All the facts are compatible with the structure *XX*. The just described part of the present communication has already been presented in a preliminary form[39].

For comparison an analogous reaction of 4-chloronitrobenzene with (2-fluorophenyl)acetonitrile[40] in methanolic potassium hydroxide was carried out similarly like in the preceding case. A mixture was obtained from which crystallization afforded 60% of the acridine oxide *XX*, being in this case the main product. The mother liquors were evaporated and the residue separated by chromatography on a column of aluminium oxide with further separation of the individual fractions by crystallization and distillation, respectively. There were successively isolated, in addition to the recovered 4-chloronitrobenzene, three compounds, arranged according to the

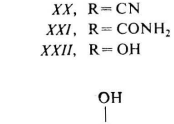
increasing polarity: compound *F* (8%), $C_7H_7NO_3$; compound *G* (2%), $C_{13}H_8FNO_3$; compound *H* (4%), $C_{14}H_7ClN_2$. The most polar product was a further quantity of compound *XX*, the yield of which increased to 73%. The fluorinated analogues of the benzisoxazole derivative *VII* and of the indole derivative *XI* were not isolated at all. A small change in the structure of the starting arylacetonitrile results thus in an important change of the pattern of products. The fluorine atom is much more suitable than the chlorine atom for the intramolecular substitution reaction of the intermediate (2-fluorophenyl analogue of *VIII*) leading to the acridine oxide *XX*. Compound *F* is a product of the nucleophilic reaction of 4-chloronitrobenzene with



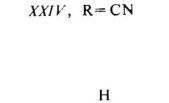
XX, R = CN
XXI, R = $CONH_2$
XXII, R = OH



XXIII, R = $CONH_2$
XXIV, R = CN



XXV



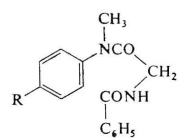
XXVI, R = H
XXVII, R = CH_2NH_2

methanol and was identified as 4-nitroanisole[41]. Compound *G* is 2-fluoro-4'-nitrobenzophenone (*XVIII*), *i.e.* the fluorine analogue of compound *D* (*XVII*). Its formation proceeded probably in the same way as discussed for *D*. Compound *H* has the UV spectrum typical for condensed aromatic systems. The IR spectrum shows a band of the aromatic nitrile group (2220 cm^{-1}) and the compound is transformed by reaction with hydrogen peroxide in acetic acid at 100–110°C to the N-oxide *XX*. All the facts show clearly the identity of compound *H* as 2-chloroacridine-9-carbonitrile (*XXIV*). It is apparently formed by reduction of the primarily resulting N-oxide *XX* directly in the reaction mixture.

For termination of the synthesis of chlorodemethyldiazepam (*II*) there was used an analogy of the Podešva's[42] very advantageous synthesis of 7-chloro-1-methyl-

-5-phenyl-1,3-dihydro-1,4-benzodiazepin-2-one (diazepam) consisting in a reaction of 5-chloro-2-methylaminobenzophenone with phthalimidoacetyl chloride and in the following hydrazinolysis of the product obtained, which is followed by ring-closure to the cyclic Schiff base. For compound *II*, this sequence was claimed to protection but not described in a patent[3], concerning especially nordazepam (*I*). We describe the reaction of 2-amino-5,2′-dichlorobenzophenone (*V*) with phthalimidoacetyl chloride[43–45] and the isolation and characterization of the intermediate *VI* which was then subjected to hydrazinolysis in methanol at 65°C and gave *II*. After termination of our work, even this synthesis was described in a further patent[9] without solation of the intermediate *VI*.

Now, attempts will be mentioned aiming at preparing 7-chloro-1-methyl-5-phenyl--1,3-dihydro-1,4-benzodiazepin-2-one (diazepam) or its dechloro analogue by using the Bischler–Napieralski reaction. We reported already about an unsuccessful attempt to cyclize hippuric acid anilide with a mixture of polyphosphoric acid and phosphoryl chloride at 100 – 110°C to a dechlorodemethyl analogue of diazepam[46]. The American authors[47] mentioned a failure of an attempt to cyclize hippuric acid 4-chloroanilide with polyphosphoric acid. On the other hand, Kaegi[48] was able to cyclize 4-chloro--N-(2-benzamidoethyl)-N-methylaniline with a mixture of phosphorus pentoxide and phosphoryl chloride to 7-chloro-1-methyl-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine (medazepam) and Sternbach[49] characterized this reaction as a very useful one for preparative purpose. By reactions of hippuric acid with N-methylaniline and 4-chloro-N-methylaniline[50] in the presence of phosphorus trichloride the N-methylanilides *XXVIII* and *XXIX* have now been prepared and their cyclization has been attempted by heating with phosphoryl chloride. The desired 1,4-benzodiazepine derivatives were not obtained and it is thus necessary to conclude that the Bischler–Napieralski reaction is suitable only for the synthesis of the 2-deoxo compounds of the medazepam type.

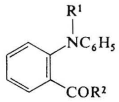


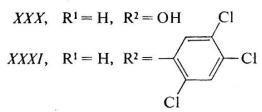
XXVIII, R = H
XXIX, R = Cl

The last attempt aimed at the synthesis of 1-phenyl-2,4-dihydro-1*H*-1,4-benzodiazepin-3,5-dione. N-Phenylanthranilic acid (*XXX*) (ref.[51]) was obtained in excellent yield by a reaction of 2-iodobenzoic acid[52] with aniline in a boiling aqueous solution of potassium hydroxide in the presence of copper and transformed by a described procedure[53] *via* 1-phenyl-2*H*-3,1-benzoxazin-4-one (*XXXV*) to the nitrile-acid *XXXII*. A mild alkaline hydrolysis of this compound gave the amide *XXXIII*,

whereas the energetic alkaline hydrolysis leads to the di-acid *XXXIV* (ref.[53]). In connection with this work, 2,4,5-trichlorophenyl ester *XXXI* was prepared by a reaction of the acid *XXX* with 2,4,5-trichlorophenol and N,N'-dicyclohexylcarbodiimide in dichloromethane as a potential "active ester" of the acid *XXX*. The product does not react with glycine in aqueous pyridine and is stable when crystallized from boiling aqueous ethanol. In the case of the nitrile-acid *XXXII*, thermic reaction could directly lead to the mentioned 1,4-benzodiazepin-3,5-dione derivative. Compound *XXXII*, when heated to the melting point (about 135°C), undergoes really an exothermic reaction (carried out at 150°C), but the melt solidifies quickly to a high-melting (337–339°C) solid, isomeric with the starting compound (the same product was obtained by boiling the amide-acid *XXXIII* with acetic anhydride). In addition to transformation to the desired benzodiazepindione it was necessary to consider the more probable cyclization to a 9-acridanone derivative with the simultaneous hydration of the nitrile group to the amide one, *i.e.* with the formation of the amide *XXXVI*. The bands at 1634, 1671 and in the region 3200–3500 cm^{-1} in the IR spectrum were not a sufficient basis for distinguishing whether a combination of fragments ArCOAr and $RCONH_2$ or the fragment ArCONHCOR is present. For this reason the compound was subjected to alkaline hydrolysis under drastic conditions. A carboxylic acid was formed indicating by its composition that the hydrolysis effected only the substitution of the NH_2 group by a hydroxyl group. If the starting compound had the structure of the amide *XXXVI*, the resulting acid would be compound *XXXVII*. The ^{1}H-NMR spectrum is in agreement with this view but the atypical position of the band of the keto group in conjugation with two aromatic nuclei in the IR spectrum at 1610 cm^{-1} admitted further doubts. The synthesis of the acid *XXXVII* was described in the literature[54] by cyclization of the di-acid *XXXIV* with sulfuric acid but the melting point of the product was not reported. We carried out this cyclization and found the product to be identical with our substance. Since the literature[54] characterizes better the methyl ester *XXXVIII*, we prepared also this compound from the acid *XXXVII*, obtained by both methods, and could again find the identity of the products (the melting point found by us is much higher than the literature[54] value). In this case, even the position of the band in the IR spectrum corresponding to the keto group (1640 cm^{-1}) is closer to the expected value. The product of the thermic reaction of the nitrile-acid *XXXII* is thus 9-oxoacridan-10-acetamide (*XXXVI*) which is hydrolyzed to 9-oxoacridan-10-acetic acid (*XXXVII*). After the termination of our experiment, further attention was paid to the acid *XXXVII* (ref.[55,56]) and a new way of formation of the methyl ester *XXXVIII* was noted[56]. Properties of an antiviral compound were described for the sodium salt of the acid *XXXVII* (ref.[57]). Reaction of the amide *XXXVI* with sodium hydride in dimethylformamide followed by the treatment with 3-dimethylaminopropyl chloride gave a basic amide, having evidently the structure *XXXIX*. As a potential intermediate, the diphenylamide *XL* was prepared by a reaction of diphenyl-

amine with the methyl ester chloride of succinic acid[58]; its alkaline hydrolysis gave the diphenylamide-acid *XLI*. The preparation of this compound by reaction of diphenylamine with succinic anhydride was described previously[59].





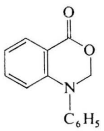
XXX, $R^1 = H$, $R^2 = OH$

XXXI, $R^1 = H$, $R^2 =$

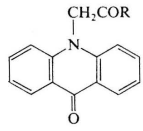
XXXII, $R^1 = CH_2CN$, $R^2 = OH$

XXXIII, $R^1 = CH_2CONH_2$, $R^2 = OH$

XXXIV, $R^1 = CH_2COOH$, $R^2 = OH$



XXXV



XXXVI, $R = NH_2$

XXXVII, $R = OH$

XXXVIII, $R = OCH_3$

XXXIX, $R = NH(CH_2)_3N(CH_3)_2$

$(C_6H_5)_2NCOCH_2CH_2COOR$

XL, $R = CH_3$

XLI, $R = H$

Some of the compounds prepared were submitted to pharmacological testing oriented especially to the expected central activities. Compound *III* (VÚFB-9506) is nontoxic for mice until the oral dose of 2 g/kg. In the rotarod test in mice it brings about ataxia only in relatively high oral doses; $ED_{50} = 280$ mg/kg (maximum effect in 2 h after the administration). In an oral dose of 400 mg/kg it has not anticonvulsant effect in mice against pentetrazole and in the test of corneal electroshock.

Compound *IV* (VÚFB-9069) exhibited in preliminary tests properties of a potential hypnotic agent and was evaluated more thoroughly. In all tests it was administered orally in the form of suspensions. In the test of acute toxicity in mice, it has not lethal effect until the dose of 1 kg/g. Doses higher than 200 mg/kg bring about depression, sleep and loss of the righting reflex. Phenobarbital, used for comparison, brought about loss of the righting reflex at doses higher than 100 mg/kg and nitrazepam[5,6] at doses higher than 400 mg/kg. Also in rats, the doses until 1 g/kg have not lethal activity. Lower doses, however, elicit depression, decrease of locomotor

activity and decrease of the muscular tone but not sleep or loss of the righting reflex. In dogs a dose of 50 mg/kg has a taming effect but does not act hypnotically. In the rhesus monkeys (*M. mulatta*) a dose of 10 mg/kg does not influence the behaviour; a dose of 100 mg/kg decreases the locomotor activity in 1 h after the administration; a dose of 200 mg/kg strongly decreases the locomotion and brings about ataxia; the ataxia after a dose of 400 mg/kg lasts for 18 h (after 40 h the muscular tone is again normalized). For evaluation of the hypnotic effect, the loss of the righting reflex in mice was observed; the ED_{50} in the interval of 1·5—4 h after the administration are 200—220 mg/kg. The maximum of the effect is attained in 2—3 h after the administration; higher doses exhibit an effect lasting longer than 30 h. Phenobartbital in the same test is about twice as active but its higher doses (200 mg/kg) are already toxic. In the rotarod test in mice, the compound brings about ataxia; ED_{50} = 31 mg/kg (90 min after the administration) (for phenobarbital, ED_{50} = 23·7 mg/kg, for nitrazepam 1078 mg/kg). The influence on the total activity of mice was evaluated in the test of Ther; ED_{50} = 60 mg/kg (2—4 h after the administration) (phenobarbital has approximately equal activity and nitrazepam is more active in 2 h after the administration but its effect disappears quickly). In the test of antagonization of pentetrazole convulsions in mice the dose PD_{50} for compound *IV* is 7·0 mg/kg, for phenobarbital 16 mg/kg and for nitrazepam 1·25 mg/kg. In the test for anticonvulsant activity against the corneal electroshock the PD_{50} = 91·5 mg/kg for compound *IV*, for phenobarbital 18·1 mg/kg and for nitrazepam 8·0 mg/kg. Until the dose of 60 mg/kg compound *IV* does not exhibit catalepsy in rats. The central activity of compound *IV* is quite clear but in comparison with nitrazepam it is less active and its evaluation was discontinued.

Compound *XXVI* (VÚFB-14·027) had the LD_{50} in mice higher than 2·5 g/kg; only this very high dose brings about ataxia. In a dose of 300 mg/kg it decreases significantly the spontaneous motility in mice.

Compound *XXXV* (VÚFB-6775) has the LD_{50} = 2 g/kg for mice. A dose of 300 mg/kg has a significant antiinflammatory effect in the tests of kaolin and carrageenan edema; in the test of adjuvant arthritis, the effect is weak (Dr J. Grimová, pharmacological department of this institute).

Compound *XXXVI* (VÚFB-6765) has the LD_{50} = 5 g/kg (mice); in a dose of 800 mg/kg it prolongs the thiopental sleeping time in mice to 200% of the control value; it has an anticonvulsant effect in the tests of pentetrazole convulsions in mice (PD_{50} = 72 mg/kg) and strychnine convulsions (PD_{50} = 82 mg/kg); it brings about ataxia in the rotarod test in mice (ED_{50} = = 350 mg/kg); it inhibits the spontaneous activity of mice (ED_{50} = 140 mg/kg).

Compound *XXXIX* (VÚFB-6792): LD_{50} = 5 g/kg (mice, orally); potentiates the thiopental sleep in mice (D_2 = 390 mg/kg); inhibits in mice the pentetrazole (PD_{50} = 390 mg/kg) as well as strychinne convulsions (PD_{50} = 380 mg/kg); brings about ataxia in the rotarod test in mice (ED_{50} = 500 mg/kg) and inhibits the spontaneous activity of mice (ED_{50} = 350 mg/kg).

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's 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) were recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (mostly in Nujol) with a Unicam SP 200G spectrophotometer, ^{1}H-NMR spectra (mostly in $CDCl_3$) with a Tesla BS 487C (80 MHz) spectrometer (a small part with a ZKR 60, Zeiss-Jena, spectrometer) and the mass spectra with the MS 902 (AEI) spectrometer The homogeneity of the compounds was checked by thin layer chromatography on silica gel (Silufol). The column chromatography was carried out on neutral Al_2O_3 (activity II).

7-Chloro-1-(2,5-dimethoxyphenacyl)-5-phenyl-1,3-dihydro-1,4-benzodiazepin-2-one (*III*)

A mixture of 5·4 g *I* (ref.[2,3]), 65 ml toluene, 40 ml dimethylformamide and 0·8 g NaH was stirred for 1·5 h at 60°C, treated at room temperature over 10 min with a solution of 5·2 g 2,5-dimethoxyphenacyl bromide[11] in 25 ml dimethylformamide, and refluxed under stirring for 2 h. After standing overnight the mixture was decomposed with 300 ml water and extracted with toluene. The extract was dried with Na_2SO_4, filtered with charcoal and evaporated under reduced pressure. The residue crystallized after mixing with ether; 6·0 g (67%), m.p. 173—176°C. Analytical sample, m.p. 183—185°C (ethanol). UV spectrum: λ_{max} 227 nm (log ε 4·64). infl. 250 nm (4·36), 330 nm (3·75). IR spectrum: 700, 740, 745, 822, 870 (5 and 2 adjacent and solitary Ar—H), 1220 (CO), 1560 (Ar), 1610 (C=N), 1670 (CON), 1680 cm^{-1} (ArCO). ^{1}H-NMR spectrum (ZKR 60): δ 6·80—7·80 (m, 11 H, Ar—H), 5·15 (ABq, 2 H, J = 19·0 Hz, $ArCOCH_2$), 4·86 and 3·92 (2 d, J = 11·0 Hz, 2 H, $COCH_2N$=), 3·84 and 3·75 (2 s, 6 H, 2 OCH_3). For $C_{25}H_{21}ClN_2O_4$ (448·9) calculated: 66·88% C, 4·72% H, 7·90% Cl, 6·24% N; found: 66·88% C, 4·97% H, 7·72% Cl 6·11% N.

7-Chloro-5-phenyl-1-[3-(4-phenylpiperazino)propyl]-1,3-dihydro-1,4-benzodiazepin-2-one (*IV*)

A mixture of 23·1 g *I* (ref.[2,3]), 100 ml dimethylformamide and 2·4 g NaH was stirred for 25 min and treated over 10 min with a solution of 22·4 g 3-(4-phenylpiperazino)propyl chloride[12] in 10 ml dimethylformamide, added dropwise. The mixture was stirred and heated for 1·5 h to 120—125°C, cooled and decomposed by a slow addition of 200 ml water. It was extracted with benzene, the extract was dried with K_2CO_3, filtered with charcoal and the filtrate evaporated *in vacuo*. The residue was dissolved in 100 ml ethanol and the solution acidified with 7·0 ml hydrochloric acid; the precipitated hydrochloride was filtered, washed with ethanol and dried *in vacuo*; 30 g (69%), m.p. 251—257°C. Analytical sample, m.p. 254—257°C (aqueous ethanol). For $C_{28}H_{30}Cl_2N_4O$ (509·5) calculated: 66·01% C, 5·93% H, 13·92% Cl, 11·00% N; found: 66·28% C, 5·90% H, 13·85% Cl, 11·27% N.

Reaction of 4-Chloronitrobenzene with (2-Chlorophenyl)acetonitrile

A solution of 35·6 g 4-chloronitrobenzene and 35·8 g (2-chlorophenyl)acetonitrile[21] in 100 ml benzene was added dropwise over 2 h to a stirred solution of 142 g KOH (containing 79% KOH, 6% K_2CO_3 and 15% H_2O) in 280 ml methanol at 25°C. The mixture was stirred for 2 h at room temperature, poured into a solution of 135 g NH_4Cl in 900 ml water and extracted with benzene. The extract was dried with $CaCl_2$, filtered with charcoal and evaporated. The residue (60·5 g) was chromatographed on a column of 1·5 kg Al_2O_3. Elution with hexane recovered 7·5 g 4-chloronitrobenzene, m.p. 82—84°C. Elution with a mixture 1 : 1 of hexane and benzene gave 17·9 g mixture of compounds *A* and *B* which was separated by fractional crystallization from ethanol (compound *A* crystalizes first). Continuation of the elution with the same mixture of solvents gave 16·3 g mixture of compounds *C* and *D* separated by crystallization from a mixture of chloroform and hexane (compound *C* crystallizes out and compound *D* remains in the mother liquor). The chromatography was terminated by elution with benzene giving 12 g compound *E*.

Compound *A*, 5-chloro-3-(2-chlorophenyl)-2,1-benzisoxazole (*VII*), yield approximately 12%, needles, m.p. 142—143°C (hexane–benzene). Mass spectrum, *m/e* (%): 263 (M^+ corresponding to $C_{17}H_7Cl_2NO$, 40), 228 (100), 200 (70), 111 (40), 75 (30). UV spectrum: λ_{max} 247 nm (log ε 3·98), 254·5 nm (4·00), 336 nm (4·08). IR spectrum: 752, 764, 780, 809, 864 (4 and 2 adjacent and solitary Ar—H), 1523, 1557, 1600 (Ar), 1640 cm^{-1} (C=N). ^{1}H-NMR spectrum consists only of a multi-

plet in the region of aromatic protons. For $C_{13}H_7Cl_2NO$ (264·1) calculated: 59·11% C, 2·68% H, 26·85% Cl, 5·30% N; found: 59·12% C, 2·70% H, 26·33% Cl, 5·08% N.

Compound *B*, 2-chloro-6-[1,2-*bis*(2-chlorophenyl)-2-cyanoethylidene]-5-(methoxyimino)-1,3--cyclohexadiene (*X*), yield approximately 15%, needles, m.p. 128—129°C (benzene–hexane). Mass spectrum, *m/e* (%): 428·0260 (M^+ corresponding to $C_{22}H_{15}Cl_3N_2O$, 33), 393·0511 (67), 361·0319 (67), 224·0269 (33), 138·9945 (100), 111 (67). UV spectrum: λ_{max} 267 nm (log ε 3·88), infl. 290 nm (3·71). IR spectrum: 750, 762, 824, 832, 882 (4 and 2 adjacent and solitary Ar—H), 1 115, 1 137 (C—O), 1 312 (N—O), 1 597 (Ar), 1 662 (C=N), 2 250 (R—CN), 3 030, 3 060 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 6·70—7·60 (m, 8 H, Ar—H), 7·15 (mcs, J = 2·5 Hz, 1 H, 1-H of cyclohexadiene), 6·95 (mcd, J = 8·5; 2·5 Hz, 1 H, 3-H of cyclohexadiene), 6·40 (d, J = 8·5 Hz, 1 H, 4-H of cyclohexadiene), 6·03 (s, 1 H, Ar—CH—CN), 4·03 (s, 3 H, $NOCH_3$). For $C_{22}H_{15}Cl_3N_2O$ (429·7) calculated: 61·49% C, 3·52% H, 24·74% Cl, 6·53% N; found: 61·58% C, 3·40% H, 24·80% Cl, 6·66% N.

Compound *C*, 5-chloro-2,3-bis(2-chlorophenyl)indole (*XI*), yield approximately 25%, prisms, m.p. 177—178°C (benzene–hexane). Mass spectrum, *m/e* (%): 371·0041 (M^+ corresponding to $C_{20}H_{12}Cl_3N$, 85), 301 (100), 266 (29), 264 (44). UV spectrum: λ_{max} 302 nm (log ε 4·19). IR spectrum: 743, 757, 769, 777, 800, 879 (4 and 2 adjacent and solitary Ar—H), 1 300, 1 319 (C—N), 1 492, 1 574, 1 600, 3 065 (Ar), 3 420 cm^{-1} (NH). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 11·88 (s, 1 H, NH), 7·00—7·50 (m, 11 H, Ar—H). For $C_{20}H_{12}Cl_3N$ (372·7) calculated: 64·50% C, 3·24% H, 28·50% Cl, 3·76% N; found: 65·10% C, 3·25% H, 28·01% Cl, 3·72% N.

Compound *D*, 2-chloro-3′-nitrobenzophenone (*XVII*), yield approximately 5%, yellowish prisms, m.p. 101—102°C (benzene–hexane). Mass spectrum, *m/e* (%): 261·0188 (M^+ corresponding to $C_{13}H_8ClNO_3$, 42), 180 (11), 150 (71), 141 (89), 139 (100), 114 (100), 104 (55), 76 (100). UV spectrum: λ_{max} 265 nm (log ε 4·27). IR spectrum: 740, 750, 772, 860 (4 and 2 adjacent Ar—H)$_t$ 1 296, 1 310, 1 350, 1 520, 1 526 (NO_2), 1 597, 1 605, 3 048, 3 080, 3 108 (Ar), 1 674 cm^{-1} (ArCOAr). ^{1}H-NMR spectrum: δ 8·22 (d, J = 8·5 Hz, 2 H, 3′,5′-H_2), 7·88 (d, J = 8·5 Hz, 2 H, 2′,6′-H_2), 7·40 (m, 4 H, Ar—H of chlorophenyl). For $C_{13}H_8ClNO_3$ (261·7) calculated: 59·67% C, 3·08% H, 13·55% Cl, 5·36% N; found: 59·95% C, 3·10% H, 13·65% Cl, 5·79% N.

2,4-*Dinitrophenylhydrazone*, m.p. 244°C (acetone–ethanol). For $C_{19}H_{12}ClN_5O_6$ (441·8) calculated: 51·64% C, 2·74% H, 8·02% Cl, 15·85% N; found: 51·77% C, 2·76% H, 8·17% Cl, 15·98% N.

Compound *E*, 2-chloro-10-cyanoacridine N-oxide (*XX*), yield approximately 20%, yellow, m.p. 203—204°C (benzene). Mass spectrum, *m/e*: 254 (M^+ corresponding to $C_{14}H_7ClN_2O$), 238 (M — 16). UV spectrum: λ_{max} 277 nm (log ε 4·82), 373 nm (3·49), 373 nm (3·49), 394 nm (3·81), 421 nm (3·96), 447·5 nm (4·11). IR spectrum (KBr): 757, 774, 822, 870 (4 and 2 adjacent and solitary Ar—H), 1 290 (N—O), 1 534, 1 572, 3 065, 3 105 (Ar), 1 620 (C=N), 2 218 cm^{-1} (Ar—CN). Polarographic reduction in 0·5M-HCl in two waves with $E_{1/2}$ —0·10 and —0·48 V (against saturated calomel electrode). For $C_{14}H_7ClN_2O$ (254·7) calculated: 66·03% C, 2·77% H, 13·92% Cl, 11·00% N; found: 66·15% C, 2·77% H, 13·99% Cl, 11·15% N.

2-Amino-5,2′-dichlorobenzophenone (*V*)

A) VII (14·0 g) was added to a mixture of 14 ml ethanol, 7 ml water, 21 ml acetic acid and 7·6 g iron powder at 60—70°C. The mixture was refluxed for 2 h, diluted with 60 ml benzene, filtered and the solid washed with 60 ml warm benzene. The filtrate was separated, the benzene layer was washed with water and 5% Na_2CO_3, dried with $CaCl_2$, filtered and evaporated. The residue was diluted with 4 ml benzene, treated with 8 ml hexane and 2 ml ethanol, and the solution kept overnight in a refrigerator; 13·0 g (92%), m.p. 84—86°C. Analytical sample. m.p.

87—88°C (ethanol–hexane). UV spectrum: λ_{max} 233·5 nm (log ε 4·36), infl. 260 nm (3·90), 389 nm (3·84). IR spectrum: 820, 883 (2 adjacent and solitary Ar—H), 1 535, 1 596 (Ar), 1 620 (ArCOAr), 3 320, 3 430 cm^{-1} (NH_2). ^{1}H-NMR spectrum: δ 7·00—7·50 (m, 6 H, 4,6,3′,4′,5′,6′-H_6), 6·59 (d, J = 8·5 Hz, 1 H, 3-H), 6·40 (bs, 2 H, NH_2).

B) 4-Chloroaniline (250 g) was treated with 822 g 2-chlorobenzoyl chloride and 330 g $ZnCl_2$ according to the reported procedure[14,15] and the product was hydrolyzed for 18 h with a boiling mixture of 710 ml acetic acid, 480 ml water and 980 ml sulfuric acid giving 266 g (51%) crude *V*, m.p. 83—85°C. Recrystallization from ether–hexane gave *V*, m.p. 87—88°C, identical with the product prepared according to *A*, The literature[14] reported the m.p. 88—89°C.

2-Amino-5,2′-dichlorobenzhydrol (*IX*)

A solution of 0·25 g *VII* in 3 ml benzene was added dropwise to a stirred solution of 0·2 g $LiAlH_4$ in 10 ml ether and the mixture was refluxed for 30 min. After cooling it was decomposed with 0·8 ml 20% NaOH, the solid was filtered off, washed with benzene and the filtrate was evaporated; 0·24 g (95%), m.p. 98—100°C. Analytical sample, m.p. 99—100°C (cyclohexane). IR spectrum: 756, 814, 830, 888 (4 and 2 adjacent and solitary Ar—H), 1 100 (CHOH), 1 490, 1 578, 1 600, 3 014, 3 047, (Ar), 1 618 ($ArNH_2$), 3 210 (OH), 3 335, 3 405 cm^{-1} (NH_2). ^{1}H-NMR spectrum: δ 7·10 to 7·50 (m, 4 H, Ar—H of the chlorophenyl), 6·98 (mcd, J = 8·5; 2·5 Hz, 1 H, 4-H), 6·79 (mcs, J = 2·5 Hz, 1 H, 6-H), 6·52 (*d*, J = 8·5 Hz, 1 H, 3-H), 6·01 (s, 1 H, Ar—CH—Ar), 3·68 (s, disappears after D_2O, 3 H, NH_2 and OH). For $C_{13}H_{11}Cl_2NO$ (268·1) calculated: 58·23% C; 4·13% H, 26·45% Cl, 5·22% N; found: 58·50% C, 4·31% H, 26·17% Cl, 4·93% N. After the termination of our work, the preparation of *IX* by a different method has been reported[25] and the m.p. of 101—102°C given (no analytical data).

5-Chloro-2,3-bis(2-chlorophenyl)indole (*XI*)

A) A mixture of 3·9 g 4-chlorophenylhydrazine[28], 7·6 g 2,2′-dichlorodeoxybenzoin[27], 50 ml ethanol and 0·6 ml acetic acid was refluxed for 2 h and the solvent was evaporated *in vacuo*. The residue was dissolved in ether, the solution was washed with 1 : 15 dilute hydrochloric acid, saturated NaCl, 10% $NaHCO_3$ and water, dried ($MgSO_4$) and evaporated. The residue was dissolved in benzene and chromatographed on a column of 300 g Al_2O_3. The first fractions (5·8 g), obtained by elution with benzene, represent the homogeneous hydrazone (glassy substance). It was dissolved in 5 ml ethanol, the solution treated with 80 ml 3M-ethanolic HCl and refluxed for 1 h in nitrogen atmosphere. After cooling the separated NH_4Cl was filtered off, the filtrate was poured into 500 ml water and the product extracted with chloroform. The extract was washed with a dilute solution of $NaHCO_3$ and saturated NaCl, dried (Na_2SO_4) and evaporated *in vacuo*. The residue was dissolved in 5 ml boiling benzene and the product crystallized on cooling; 5·0 g (49%), m.p. 174—176°C. Recrystallization from benzene–hexane gave *XI*, m.p. 176—177°C which was found identical with the above mentioned product (mixed m.p., TLC, green and blue colouration of a solution in H_2SO_4 after the addition of $NaNO_2$, ^{1}H-NMR spectrum, analysis).

B) *X* (1·0 g) was dissolved in a warm mixture of 2 ml benzene and 1 ml methanol, the solution was cooled and added dropwise over 20 min to a stirred solution of 3·0 g KOH in 6 ml methanol containing 50 mg ascorbic acid (room temperature). The mixture was stirred for 2 h, poured into 40 ml 20% NH_4Cl, extracted with benzene, the extract was washed with NaCl solution, dried and evaporated. The residue was crystallized from a mixture of benzene and hexane. The inhomogeneous product (mixture of needles and thick prisms) was mechanically separated.

The needles (258 mg) represent the starting *X*, m.p. 128—129°C (benzene–hexane). The prisms (405 mg) crystallize from ethanol and melt at 176—177°C. The identity with *XI* was established by the mixed melting point and by comparison with the synthetic product (obtained under *A*) by means of TLC.

2-(4-Chloroanilino)-1,2-bis(2-chlorophenyl)ethanone (*XII*)

A mixture of 2·81 g 2,2'-dichlorobenzoin[27] (m.p. 56—58°C), 1·28 g 4-chloroaniline and 2 drops hydrochloric acid was heated for 1·5 h to 140—150°C. After cooling the mixture was dissolved in ether, the solution dried and evaporated. The residue was dissolved in 4 ml boiling cyclohexane and the solution was treated with 12 ml hexane and cooled; 2·5 g (65%), m.p. 129—130°C UV spectrum: λ_{max} 251·5 nm (log ε 4·36), infl. 295 nm (3·44). IR spectrum: 742, 757, 810, 829 (4 and 2 adjacent Ar—H), 1500, 1590, 1600, 3040 (Ar), 1700 (ArCO), 3369 cm^{-1} (NH). ^{1}H-NMR spectrum: δ 7·00—7·50 (m, 8 H, Ar—H in the deoxybenzoin part), 7·09 (d, J = 8·5 Hz, 2 H, 3,5-H_2 in the chloroaniline fragment), 6·53 (d, J = 8·5 Hz, 2 H, 2,6-H_2 in the chloroaniline fragment), 6·30 (s, 1 H, ArCHCO), 5·55 (bs, 1 H, NH). For $C_{20}H_{14}Cl_3NO$ (390·7) calculated: 61·49% C, 3·62% H, 27·20% Cl, 3·59% N; found: 61·64% C, 3·58% H, 27·21% Cl, 3·50% N.

1,2-Bis(2-chlorophenyl)-1,2-bis(4-chlorophenylimino)ethane (*XIII*)

A mixture of 2·81 g 2,2'-dichlorobenzoin[27], 4·60 g 4-chloroaniline and 0·55 ml hydrochloric acid was heated for 2 h to 150—160°C. After cooling it was dissolved in benzene, the solution washed with dilute hydrochloric acid, 10% $NaHCO_3$ and water, dried with Na_2SO_4 and evaporated. The remaining oil (4·3 g) was chromatographed on a column of 100 g Al_2O_3. The homogeneous first fractions (3·20 g, 64%), obtained by elution with benzene, were dissolved in 10 ml boiling ethanol. The product crystallized on cooling; yellow crystals, m.p. 188—191°C. Analytical sample, m.p. 190—191°C (ethanol). UV spectrum: λ_{max} 232 nm (log ε 4·51), 360 nm (3·72). IR spectrum: 742, 830 (4 and 2 adjacent Ar—H), 1483, 1590, 3045 (Ar), 1627 cm^{-1} (Ar—C=N—Ar). For $C_{26}H_{16}Cl_4N_2$ (498·2) calculated: 62·69% C, 3·21% H, 28·47% Cl, 5·63% N; found: 63·22% C, 3·48% H, 28·12% Cl, 5·59% N.

1,2-Bis(2-chlorophenyl)-1-(4-chlorophenylimino)-2-(phenylimino)ethane (*XIV*)

A mixture of 3·90 g *XII*, 3·3 g aniline and 2 drops hydrochloric acid was heated for 6 h to 150 to 160°C in nitrogen atmosphere. After cooling it was dissolved in ether, the solution washed with dilute hydrochloric acid, 10% $NaHCO_3$ and water, dried with Na_2SO_4 and evaporated. The residue (4·3 g) was chromatographed on a column of 120 g Al_2O_3. Elution with benzene gave first 2·1 g (45%) homogeneous yellow crystal which were crystallized from hexane, m.p. 227 to 228°C. UV spectrum: λ_{max} 226 nm (log ε 4·51), 358 nm (3·68). IR spectrum: 682, 741, 832 (5, 4 and 2 adjacent Ar—H), 1478, 1482, 1589, 3030 (Ar), 1620 cm^{-1} (Ar—C=N—Ar). For $C_{26}H_{17}Cl_3N_2$ (463·8) calculated: 67·35% C, 3·69% H, 22·92% Cl, 6·04% N; found: 67·61% C, 3·74% H, 22·68% Cl, 6·02% N.

1,2-Bis(2-chlorophenyl)-1,2-bis(phenylimino)ethane (*XV*)

A mixture of 2·12 g 2,2'-dichlorobenzoin[27], 3·36 g aniline and 0·55 ml hydrochloric acid was heated for 2 h to 185—200°C under nitrogen and then processed similarly like in the preparation

of *XIII*. Chromatography and crystallization of the homogeneous fraction from ethanol gave 1·4 g pure *XV*, yellow needles of m.p. 217—218°C. Mass spectrum, *m/e* (%): 428 (M^+ corresponding to $C_{26}H_{18}Cl_2N_2$, 12), 216 (25), 214 (75), 77 (100). UV spectrum: λ_{max} 354 nm (log ε 3·60). IR spectrum: 701, 739, 760, 777 (5 and 4 adjacent Ar—H), 1489, 1596, 3070 (Ar), 1639 cm^{-1} (Ar—C=N—Ar). The literature[34] reported a m.p. of 216—217°C for compound *XV* obtained differently.

1,2-Bis(2-chlorophenyl)ethanol (*XVI*)

A solution of 6·4 g 2,2'-dichlorodeoxybenzoin[27] in 100 ml ethanol was stirred, treated over 10 min with 1·2 g $NaBH_4$ and refluxed for 1·5 h. It was then evaporated under reduced pressure, the residue was decomposed with 20 ml water and extracted with chloroform. The extract was washed with dilute NaCl, dried with Na_2SO_4 and evaporated; 5·9 g (92%), m.p. 76—78°C. Analytical sample, m.p. 81—82°C (needles from chloroform–hexane). IR spectrum: 750, 760 (4 adjacent Ar—H), 1031, 1050, 1060 (Ar—CHOH), 1476, 1573, 1593, 3040 (Ar), 3240, 3315 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 7·00—7·80 (m, 8 H, Ar—H), 5·41 (m, after D_2O dd, J = 8·0; 4·0 H, 1 H, Ar—CH—O), 3·29 and 3·00 (2 dd, J = 14·0; 4·0 Hz and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 2·12 (d, J = 4·0 Hz, disappears after D_2O, 1 H, OH). For $C_{14}H_{12}Cl_2O$ (267·2) calculated: 62·98% C, 4·53% H, 26·55% Cl; found: 62·45% C, 4·63% H, 26·25% Cl. The literature[35] reported for *XVI*, obtained by a different method, the m.p. of 82—84°C (no analytical data, erroneous values in the IR spectrum).

2-Chloroacridine-9 carboxamide (*XXIII*)

A mixture of 3·0 g *XX*, 4·0 g KOH and 6 ml ethanol was refluxed for 2 h at a bath temperature of 130—140°C. It was diluted with 80 ml water and the precipitated solid was filtered and washed with water; 1·7 g *XXIII* contaminated with about 25% of the N-oxide *XXI*, m.p. 225—227°C. Repeated crystallization from a mixture of ethanol and ether gave a product melting at 245 to 246°C which is still a mixture of *XXIII* and *XXI*. Mass spectrum, *m/e*: 272 (M^+ corresponding to $C_{14}H_9ClN_2O_2$, *XXI*), 256 (base peak corresponding to $C_{14}H_9ClN_2O$, *XXIII*). UV spectrum: λ_{max} 254 nm (log ε 5·01), 347 nm (3·88), 362 nm (3·85). IR spectrum: 763, 776, 827, 862 (4 and 2 adjacent and solitary Ar—H), 1305 (Ar—N—O), 1518, 1549 (Ar), 1672 ($ArCONH_2$), 3120, 3290 cm^{-1} (NH_2). Polarography in 0·5M-HCl displays a reduction wave with $E_{1/2}$ = —0·30 V (against a saturated calomel electrode. For $C_{14}H_9ClN_2O$ (256·7) calculated: 65·51% C, 3·53% H, 13·81% Cl, 10·92% N; found: 64·74% C, 3·56% H, 13·70% Cl, 10·97% N.

The alkaline filtrate after the preceding product was acidified with dilute hydrochloric acid and the yellow solid was filtered. It was purified by dissolving in 5% Na_2CO_3 and reprecipitation by dilute hydrochloric acid. It was then filtered, washed with water, ethanol and ether, and dried *in vacuo*, m.p. above 300°C. It is considered to be 2-chloro-10-hydroxyacridine 10-oxide (*XXII*) in equilibrium with the tautomeric 2-chloro-10-hydroxy-9-acridanone (*XXV*) (*cf.*[60,61]). Mass spectrum, *m/e*: 245 (M^+ corresponding to $C_{13}H_8ClNO_2$). UV spectrum: λ_{max} 253 nm (log ε 4·58), 260 nm (4·56), infl. 258 nm (4·49), infl. 275 nm (4·38), 304 nm (3·69), 317·5 nm (3·67), 404 nm (3·82), 422 nm (3·81). IR spectrum (Nujol): 752, 820, 903 (4 and 2 adjacent and solitary Ar—H), 1489, 1506, 1555, 1590, 3055, 3100 (Ar), 1617 (Ar_2C—O..HO), 2710 cm^{-1} (OH..O=C); in dioxane: 1593, 1602 (Ar), 1613 (Ar_2C=O..HO), 1642 (C=N), 3200 cm^{-1} (OH). Polarographic reduction in 0·5M-HCl (in 50% ethanol) displays two waves with $E_{1/2}$ —0·65 and —0·82 V (3 : 1). For $C_{13}H_8ClNO_2$ (245·7) calculated: 63·56% C, 3·28% H, 14·43% Cl, 5·70% N; found: 63·01% C, 3·46% H, 14·58% Cl, 5·72% N.

9-(Aminomethyl)-2-chloroacridan (*XXVI*)

A solution of 22·0 g *XX* in 1 100 ml benzene was reduced by treatment with a solution of 12 g $LiAlH_4$ in 180 ml ether, the mixture was refluxed for 5 h, cooled and decomposed with 50 ml 20% NaOH. After standing for 30 min the solid was filtered off, the filtrate was shaken with 300 ml 1 : 9 dilute hydrochloric acid. The aqueous layer was filtered with charcoal, the filtrate was made alkaline with 20% NaOH and the product extracted with benzene. The extract was dried and evaporated; 10·7 g (51%) crude base *XXVI*. Crystallization from benzene–hexane gave a product melting at 154—155°C. ^{1}H-NMR spectrum (CD_3SOCD_3): δ 8·80 (s, 1 H, NH), 6·60—7·20 (m, 7 H, Ar—H), 3·71 (t, J = 6·0 Hz, 1 H, Ar_2CH), 2·49 (d, J = 6·0 Hz, 2 H, CH_2N). 1·15 (bs, 2 H, NH_2). For $C_{14}H_{13}ClN_2$ (244·5) calculated: 68·71% C, 5·32% H, 14·52% Cl, 11·45% N; found: 68·98% C, 5·38% H, 14·76% Cl, 11·32% N.

Hydrochloride, m.p. 179—180°C (ethanol–ether). For $C_{14}H_{16}Cl_2N_2$ (281·2) calculated: 59·80% C, 5·02% H, 25·22% Cl, 9·96% N; found: 59·55% C, 5·10% H, 25·28% Cl, 9·95% N.

The organic layer was washed with water, dried and evaporated; 7·3 g (40%) crude 2-chloroacridan (*XXVI*) which was purified by crystallization from hexane, m.p. 132—133°C. Mass spectrum, *m/e* (%): 215·0487 (M^+ corresponding to $C_{13}H_{10}ClN$, 100), 179 (28), 151 (14), 76 (14). UV spectrum: λ_{max} 251 nm (log ε 4·54), 290 nm (4·10). IR spectrum: 756, 820, 884 (4 and 2 adjacent and solitary Ar—H), 1 489, 3 020, 3 045, 3 060 (Ar), 1 582, 1 600, 1 609 (Ar, R—NH_2), 3 382 cm^{-1} (NH). ^{1}H-NMR spectrum: δ 6·70—7·20 (m, 5 H, 1,3,6,7,8-H_5), 6·50 (m, 2 H, 4,5-H_2), 5·80 (bs, 1 H, NH), 3·90 (s, 2 H, $ArCH_2Ar$). For $C_{13}H_{10}ClN$ (215·5) calculated: 72·39% C, 4·64% H, 16·47% Cl, 6·50% N; found: 72·18% C, 4·53% H, 16·58% Cl, 6·41% N.

Reaction of 4-Chloronitrobenzene with (2-Fluorophenyl)acetonitrile

A solution of 35·6 g 4-chloronitrobenzene and 31·8 g (2-fluorophenyl)acetonitrile[21] in 100 ml benzene was added over 2 h to a stirred solution of 142 g 79% KOH in 280 ml methanol at 25°C. The mixture was stirred for 2 h at room temperature and poured into a solution of 135 g NH_4Cl in 900 ml water. The solid was filtered off, washed with 50 ml benzene and dried; 17 g crude *XX*, m.p. 197—199°C. The filtrate was extracted with benzene, the extract washed with NaCl solution, dried and evaporated. The residue was dissolved in 150 ml ether and the solution treated with hexane; a further crop of 16 g *XX* was obtained and combined with the first product. Crystallization from benzene gave the pure compound melting at 201—202°C, identified by analysis and comparison with the product described above.

The mother liquors were evaporated and the residue (21 g) was chromatographed on a column of 600 g Al_2O_3. Elution with hexane gave first 0·2 g (2-fluorophenyl)acetonitrile (n_D^{24} 1·5015 corresponds to the value of the authentic substance) and then 5·5 g 4-chloronitrobenzene, m.p. 82—83°C (hexane). Elution with benzene gave first 4·5 g oil which after distillation solidified to needles, compound *F*. Continued elution with benzene gave 1·2 g of the hexane–soluble compound *G* and 2·4 g hexane-insoluble compound H. The most polar product (elution with benzene-ethanol and finally chloroform) is again *XX*, the yield of which rose to 39·8 g (73%).

Compound *F*, 4-nitroanisole, yield approximately 8%, b.p. 148—150°C/1·3 kPa, m.p. 51—53°C (hexane), analysis corresponds to $C_7H_7NO_3$. The literature[41] reports the m.p. of 54°C. In mixture with a commercial product, our substance melts without depression.

Compound *G*, 2-fluoro-4′-nitrobenzophenone (*XVIII*), yield approximately 2%, m.p. 115°C (ethanol). Mass spectrum, *m/e*: 245 (M^+ corresponding to $C_{13}H_8FNO_3$), 150, 123 (base peak), 104, 95. UV spectrum: λ_{max} 264 nm (log ε 4·29). IR spectrum: 739, 759, 855 (4 and 2 adjacent Ar—H), 1 350, 1 516 (Ar—NO_2), 1 603, 1 610, 3 030, 3 062, 3 090 (Ar), 1 667 cm^{-1} (ArCOAr).

^{1}H-NMR spectrum: δ 8·38 (d, J = 8·0 Hz, 2 H, Ar—H adjacent to NO_2), 8·00 (d, $^5J_{H-F}$ = 1·0 Hz, J_{H-H} = 8·0 Hz, 2 H, 2,6-H_2 of nitrophenyl), 7·00—7·80 (m, 4 H, Ar—H of fluorophenyl). For $C_{13}H_8FNO_3$ (245·2) calculated: 63·68% C, 3·28% H, 7·75% F, 5·71% N; found: 63·82% C, 3·31% H, 7·44% F, 5·70% N.

Compound *H*, 2-chloroacridine-9-carbonitrile (*XXIV*), yield approximately 4%, crystals melting at 204—205°C (ethanol–benzene–hexane). In a mixture with *XX* (m.p. 203—204°C) the m.p. shows a deep depression (177—180°C). Mass spectrum, *m/e*: 238 (M^+ corresponding to $C_{14}H_7ClN_2$), 203 (M — Cl). UV spectrum: λ_{max} 217 nm (log ε 4·40), 258·5 nm (5·17), infl. 252·5 nm (4·80), 280 nm (3·70), infl. 355 nm (3·91), 375 nm (4·07), 403 nm (3·70). IR spectrum: 760, 835, 869 (4 and 2 adjacent and solitary Ar—H), 1515, 1552, 3035, 3055 (Ar), 1608, 1627 (C=N), 2220 cm^{-1} (Ar—CN). For $C_{14}H_7ClN_2$ (238·7) calculated: 70·45% C, 2·96% H, 14·85% Cl, 11·74% N; found: 70·67% C, 2·95% H, 15·20% Cl, 11·72% N. A sample of compound *H* (195 mg) was oxidized with 0·5 ml 30% H_2O_2 in 4 ml acetic acid by refluxing for 8 h. After cooling the mixture was diluted with 10 ml water, neutralized with K_2CO_3 and the product isolated by extraction with chloroform. Evaporation of the extract and crystallization of the residue from a mixture of benzene and ethanol gave 135 mg yellow needles, m.p. 203—204°C, melting in admixture with authentic *XX* without depression.

5,2′-Dichloro-2-(phthalimidoacetamido)benzophenone (*VI*)

A mixture of 66·5 g *V*, 55·5 g phthalimidoacetyl chloride[43-45] and 330 ml chloroform was refluxed for 6 h. A part of chloroform (220 ml) was distilled off, the residue was diluted with 460 ml ethanol and the solution was allowed to stand overnight to crystallize; 106 g (94%) *VI* melting at 94—97°C and after resolidification again at 164—166°C. Recrystallization from ethanol does not change this melting point. UV spectrum: λ_{max} 237·5 nm (log ε 4·62), 264·5 nm (4·18), infl. 271·5 nm (4·23), 346 nm (3·75). IR spectrum: 760, 784, 850 (4 and 2 adjacent and solitary Ar—H), 1516, 1712 (CONH), 1581, 1602 (Ar), 1645 (ArCOAr), 1722, 1776 (ArCONCOAr), 3195, 3220 cm^{-1} (NH). ^{1}H-NMR spectrum: δ 11·72 (bs, 1 H, NH), 8·69 (d, J = 8·5 Hz, 1 H, Ar—H adjacent to NH), 7·60—8·00 (m, 4 H, Ar—H of phthalimide), 7·00—7·60 (m, 6 H, remaining Ar—H), 4·59 (s, 2 H, $COCH_2N$). For $C_{23}H_{14}Cl_2N_2O_4$ (453·3) calculated: 60·94% C, 3·11% H, 15·65% Cl, 6·18% N; found: 60·64% C, 3·44% H, 15·70% Cl, 6·01% N.

7-Chloro-5-(2-chlorophenyl)-1,3-dihydro-1,4-benzodiazepin-2-one (*II*)

A mixture of 25 g *VI*, 400 ml methanol and 19·7 ml 18% aqueous N_2H_4 was stirred for 3 h at 60°C and allowed to stand overnight at room temperature. The separated phthalylhydrazine was filtered off and methanol distilled off from the filtrate. The residue was diluted with 90 ml water, treated with 8 ml NH_4OH and the mixture stirred for 30 min. The solid product was filtered, suspended in a mixture of 75 ml water and 8 ml NH_4OH and stirred again for 30 min. It was then filtered, washed with dilute NH_4OH and water and dried *in vacuo*; 16·5 g (98%), m.p. 196—199°C. Analytical sample, m.p. 199—201°C (ethanol–methanol–hexane). UV spectrum: λ_{max} 230 nm (log ε 4·47), infl. 251 nm (4·12), 319 nm (3·32). IR spectrum: 736, 753, 840, 888 (4 and 2 adjacent and solitary Ar—H), 1488, 1573, 1593, 3055, 3082 (Ar), 1629 (C=N), 1678 (ArNHCO), 3103, 3200 cm^{-1} (NH). ^{1}H-NMR spectrum: δ 10·18 (bs, 1 H, NH), 7·20—7·60 (m, 5 H, 8-H and Ar—H of chlorophenyl), 7·08 (d, J = 8·5 Hz, 1 H, 9-H), 7·00 (mcs, J = 2·0 Hz, 1 H, 6-H), 4·38 (s, 2 H, $COCH_2N$=). The literature[2] reported for *II*, prepared by three different methods, the same melting point.

N-(Benzamidoacetyl)-N-methylaniline (*XXVIII*)

A solution of 18 g hippuric acid in 400 ml benzene was treated with 16 ml N-methylaniline and then slowly with 7·5 ml PCl_3. The mixture was refluxed for 2 h, evaporated *in vacuo*, the residue was mixed with 300 ml 10% Na_2CO_3 and extracted with benzene. The extract was washed with 1 : 2 dilute hydrochloric acid, with water, dried with K_2CO_3 and evaporated. The residue was crystallized from a mixture of benzene and light petroleum, 15·4 g (57%), m.p. 87—89°C. UV spectrum: λ_{max} 228 nm (log ε 4·21). IR spectrum: 690, 700, 770, 787 (C_6H_5), 1 295 (C—N), 1 400 (C—H in CH_2CO), 1 550 (CONH), 1 600 (Ar), 1 645 (ArCONH and CON), 3 310 cm^{-1} (NH) ^{1}H-NMR spectrum (ZKR-60): δ 7·90 (m, 2 H, Ar—H adjacent to CO), 7·10—7·70 (m, 8 H, remaining Ar—H), 3·91 (d, 2 H, $COCH_2N$), 3·32 (s, 3 H, NCH_3). For $C_{16}H_{16}N_2O_2$ (268·3) calculated: 71·62% C, 6·01% H, 10·44% N; found: 71·58% C, 6·08% H, 10·42% N.

4-Chloro-N-(benzamidoacetyl)-N-methylaniline (*XXIX*)

A mixture of 24 g 4-chloro-N-methylaniline[50], 28·4 g hippuric acid, 530 ml benzene and 10·5 ml PCl_3 was refluxed for 2 h and processed similarly like in the preceding experiment. Crystallization of the crude product from a mixture of benzene and light petroleum gave 35·5 g (70%) product melting at 116—118°C. Analytical sample, m.p. 118—120°C (benzene–light petroleum). IR spectrum (KBr): 696, 726 (C_6H_5), 841 (2 adjacent Ar—H), 1 288, 1 301 (C—N), 1 403 (C—H in CH_2CO), 1 489, 1 601 (Ar), 1 535, 1 546, 1 641 (CONH and CON), 3 320 cm^{-1} (NH). ^{1}H-NMR spectrum (ZKR 60): δ 7·88 (m, 2 H, Ar—H adjacent to CO), 7·50 (d, J = 9·0 Hz, 2 H, Ar—H adjacent to Cl), 7·23 (d, J = 9·0 Hz, 2 H, Ar—H adjacent to NCO), 7·40—7·60 (m, 3 H, remaining Ar—H), 3·92 (d, 2 H, $COCH_2N$), 3·30 (s, 3 H, NCH_3). For $C_{16}H_{15}ClN_2O_2$ (302·8) calculated: 63·47% C, 4·99% H, 11·71% Cl, 9·26% N; found: 63·29% C, 5·10% H, 11·89% Cl, 9·39% N.

N-Phenylanthranilic Acid (*XXX*)

A mixture of 63 g 2-iodobenzoic acid[52], 15·7 g KOH, 130 ml water, 33 g aniline and 3 g "molecular" copper was stirred and refluxed for 9 h. A solution of 15·7 g KOH in 100 ml water was added and the mixture was filtered. Acidification of the filtrate with hydrochloric acid gave 52·6 g (97%) crude *XXX*, m.p. 179—184°C. Crystallization from a mixture of benzene and light petroleum gave a product melting at 183—184°C. The literature[51] reported for *XXX* obtained differently, the m.p. of 182—183°C.

N-(Aminocarbonylmethyl)-N-phenylanthranilic Acid (*XXXIII*)

A solution of 8·0 g *XXXII* (ref.[53]) in 25 ml ethanol was treated with a solution of 5·0 g KOH in 25 ml water and the mixture was refluxed for 2 h. Ethanol was evaporated *in vacuo*, the residue diluted with water and the solution acidified with hydrochloric acid. The precipitated product was filtered, washed with water and dried *in vacuo*: 5·0 g (58%), m.p. 190—196°C. Analytical sample, m.p. 201—203°C (aqueous methanol). UV spectrum: λ_{max} 218 nm (log ε 4·12), 237 nm (4·13), 291 nm (3·95). IR spectrum: 690, 719, 750, 771 (5 and 4 adjacent Ar—H), 1 231, 1 251, 1 276 (COOH), 1 500, 1 550, 1 583, 1 598 (Ar), 1 637 ($CONH_2$), 1 697 ($CONH_2$ and ArCOOH) 3 235, 3 420 cm^{-1} (NH_2). For $C_{15}H_{14}N_2O_3$ (270·3) calculated: 66·65% C, 5·22% H, 10·37% N; found: 66·63% C, 5·34% N, 10·30% N.

2,4,5-Trichlorophenyl N-Phenylanthranilate (*XXXI*)

A solution of 0·40 g *XXX* and 0·37 g 2,4,5-trichlorophenol in 15 ml dichloromethane was treated with a solution of 0·39 g dicyclohexylcarbodiimide in 15 ml dichloromethane and the mixture was stirred for 1 h at room temperature. After standing overnight the separated dicyclohexylurea was filtered off, the filtrate was evaporated *in vacuo* and the residue crystallized from aqueous ethanol; 0·45 g (61%), m.p. 89—90°C. UV spectrum: λ_{max} 212 nm (log ε 4·52), 222 nm (4·59), 240 nm (4·24), 286 nm (4·14), 410 nm (3·98). IR spectrum: 699, 759, 871 (5 and 4 adjacent and solitary Ar—H), 1220 (Ar—O—C), 1483, 1502, 1533, 1579, 1601 (Ar), 1709 (ArCOOAr), 3290, 3339 cm^{-1} (NH). For $C_{19}H_{12}Cl_3NO_2$ (392·7) calculated: 58·11% C, 3·08% H, 3·57% N; found: 58·30% C, 3·38% H, 3·95% N.

9-Oxoacridan-10-acetamide (*XXXVI*)

A) *XXXII* (ref.[53]) (2·0 g) was heated for 1 h to 150°C. The melt, primarily formed, solidified and was crystallized from a mixture of acetic acid and light petroleum; 1·8 g (90%), m.p. 330 to 335°C. Analytical sample, m.p. 337—339°C (acetic acid). IR spectrum: 748 (4 adjacent Ar—H), 1495, 1530, 1590 (Ar), 1634, 1671 (ArCOAr and $CONH_2$), 3197, 3223, 3260, 3386, 3483 cm^{-1} ($CONH_2$). For $C_{15}H_{12}N_2O_2$ (252·3) calculated: 71·41% C, 4·80% H, 11·11% N; found: 70·99% C 5·08% H, 10·90% N.

B) A mixture of 1·5 g *XXXIII* and 5 ml acetic anhydride was refluxed for 2 h. After cooling the separated product was filtered, washed with acetic acid, 10% $NaHCO_3$ and water, and dried *in vacuo*; 1·1 g (79%), m.p. 330—332°C. Recrystallization from acetic acid gave the pure product with m.p. 337—339°C, identical with *XXXVI*, obtained under *A*.

9-Oxoacridan-10-acetic Acid (*XXXVII*)

A mixture of 1·4 g *XXXVI*, 2 g KOH and 3 ml 1-butanol was refluxed for 5 h (bath of 150°C). It was diluted with water and 1-butanol was removed by steam-distillation. The residue was diluted with water, filtered and the filtrate acificied with hydrochlorid acid. The precipitated solid was filtered, washed with water and dried *in vacuo*; 1·2 g (86%), m.p. 268—274°C. Analytical sample, m.p. 280—282°C with decomposition (acetic acid). UV spectrum: λ_{max} 255·5 nm (log ε 4·70), infl. 293 nm (3·40), infl. 386 nm (3·89), 398 nm (3·93). IR spectrum: 750 (4 adjacent Ar—H), 910, 1182, 1220 (COOH), 1500, 1568, 1593 (Ar), 1610 (ArCOAr), 1728 cm^{-1} (COOH). ^{1}H-NMR spectrum (ZKR 60, CD_3SOCD_3): δ 8·40 (mcd, J = 8·0; 1·5 Hz, 2 H, Ar—H adjacent to CO), 7·20—8·00 (m, 6 H, remaining Ar—H), 5·33 (s, 2 H, NCH_2CO). The product was found identical with the compound, obtained by cyclization of *XXXIV* with sulfuric acid according to the described procedure[54], for which the melting point was not given. We found now the m.p. of 280—282°C (acetic acid). A more recent literature report[55] gives a higher melting point (294—296°C) for *XXXVII* obtained by a different method.

Methyl 9-Oxoacridan-10-acetate (*XXXVIII*)

XXXVII (2·0 g, obtained from *XXXII via XXXVI*) was esterified by refluxing (5 h) with 100 ml methanol and 20 ml H_2SO_4; 1·5 g (71%), m.p. 208—210°C (methanol). UV spectrum: λ_{max} 252·5 nm (log ε 4·71), 379 nm (3·91), 393 nm (3·98). IR spectrum: 750 (4 adjacent Ar—H), 1225 (CO), 1488, 1600 (Ar), 1640 (ArCOAr), 1730 cm^{-1} (RCOOR). ^{1}H-NMR spectrum (ZKR 60): δ 8·52 (dd, 2 H, Ar—H adjacent to CO), 7·05—7·90 (m, 6 H, remaining Ar—H), 4·99 (s, 2 H, NCH_2CO), 3·75 (s, 3 H, OCH_3). For $C_{16}H_{13}NO_3$ (267·3) calculated: 71·90% C, 4·90% H,

5·24% N; found: 72·15% C, 4·88% H, 5·37% N. The same compound (m.p. 208—210°C) was obtained by esterification of the acid *XXXVII*, prepared by cyclization of *XXXIV* (ref.[54]), for which, however, the literature[54] reported the m.p. of 178—179°C. A completely different way led more recently to *XXXVIII* for which the authors[56] reported the m.p. of 207—209°C.

N-(3-Dimethylaminopropyl)-9-oxoacridan-10-acetamide (*XXXIX*)

XXXVI (2·0 g) in 40 ml dimethylformamide was added dropwise to a suspension of 0·24 g NaH in 40 ml dimethylformamide, the mixture was stirred for 1 h at room temperature and then treated dropwise with a solution of 1·1 g 3-dimethylaminopropyl chloride in 30 ml dimethylformamide, The mixture was stirred and heated to 90°C for 3 h. Dimethylformamide was evaporated *in vacuo*, the residue was dissolved in benzene and the basic product was extracted with dilute hydrochloric acid. The separated aqueous solution was made alkaline with 10% NaOH and the base isolated by extraction with chloroform; yellowish crystals melting at 211—213°C (benzene). UV spectrum: λ_{max} 255 nm (log ε 4·83), infl. 264 nm (4·50), 290 nm (3·43), 386 nm (3·93), 399 nm (3·96). IR spectrum: 755 (4 adjacent Ar—H), 1 209 (CO), 1 496, 1 600 (Ar), 1 565 (CONH), 1 635, 1 646, 1 651, (ArCOAr, CONHR), 3 095, 3 287 cm^{-1} (CONHR). For $C_{20}H_{23}N_3O_2$ (337·4) calculated: 71·19% C, 6·87% H, 12·45% N; found: 70·87% C, 7·08% H, 12·50% N.

Hydrochloride, yellow crystals melting at 258—260°C (methanol). For $C_{20}H_{24}ClN_3O_2$ (373·9) calculated: 64·25% C, 6·47% H, 9·49% Cl, 11·24% N; found: 63·64% C, 6·79% H, 9·30% Cl, 11·12% N.

Methyl 3-(Diphenylaminocarbonyl)propionate (*XL*)

A solution of 17 g diphenylamine and 8·0 g pyridine in 250 ml benzene was treated with 15 g methyl 3-(chlorocarbonyl)propionate[58] and the mixture was stirred for 5 h at room temperature. The separated solid was then filtered off, the filtrate was washed with 5% $NaHCO_3$ and water, dried with Na_2SO_4 and evaporated; the residue was crystallized from a mixture of benzene and light petroleum; 18·9 g (67%), m.p. 86—93°C. Analytical sample, m.p. 93°C (benzene–light petroleum). For $C_{17}H_{17}NO_3$ (280·3) calculated: 72·06% C, 6·05% H, 4·94% N; found: 72·26% C, 6·18% H, 4·98% N.

3-(Diphenylaminocarbonyl)propionic Acid (*XLI*)

A solution of 22·8 g *XL* in 150 ml ethanol was treated with a solution of 5·4 g KOH in 30 ml water and the mixture was refluxed for 2 h. Ethanol was evaporated under reduced pressure, the residue was diluted with water, the solution washed with ether, filtered and acidified with hydrochloric acid; 20·0 g (92%), m.p. 118—120°C. Analytical sample, m.p. 119—120°C (aqueous methanol). UV spectrum: λ_{max} 234 nm (log ε 4·03). IR spectrum: 702, 767 (C_6H_5), 928, 1 256, 1 712, 1 721, 3 200 (COOH), 1 590 (Ar), 1 667 cm^{-1} ($CONAr_2$). For $C_{16}H_{15}NO_3$ (269·3) calculated: 71·36% C, 5·61% H, 5·20% N; found: 71·35% C, 5·68% H, 5·12% N. The literature[59] reported for *XLI*, prepared differently, the m.p. of 116·5°C.

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