[Chem. Pharm. Bull. 21(4) 742—751 (1973)]

UDC 547.892.04

Studies on Benzodiazepinooxazoles. III.[1] Reactions and Rearrangements of Benzo[6,7]-1,4-diazepino-[5,4-*b*]oxazole Derivatives

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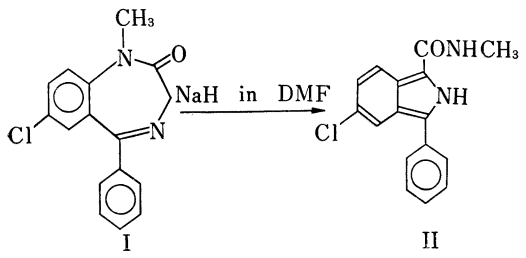
(Received July 8, 1972)

Treatment of 10-halogeno-2,3,5,6,7,11b-hexahydro-7-methyl-11b-phenylbenzo[6,7]-1,4-diazepino[5,4-*b*]oxazol-6-one (IIIa—d) with dimethyl formamide in the presence of sodium hydride gave exo-methylene compounds (Va—d). On the other hand, the compounds (IIIe—g) having halogen at *o*-position of the 11b-phenyl group gave no exo-methylene compounds, but isoindoles (XVIIIe—g) and acridanone derivatives (XIXe—g). A mechanistic assumption for the formation of these compounds from benzo[6,7]-1,4-diazepino[5,4-*b*]oxazole derivatives was given.

In the preceding paper,[3] we have reported the syntheses and pharmacology of benzo [6,7]-1,4-diazepino[5,4-*b*]oxazoles and their analogues. In the continuation and extention of our studies on the 1,4-benzodiazepinooxazole chemistry, we found the new reactions of benzo[6,7]-1,4-diazepino[5,4-*b*]oxazoles with dimethyl formamide (DMF) in the presence of sodium hydride.



I II

Chart 1

Fryer, *et al.*[4] have described the rearrangement of 10-chloro-2,3-dihydro-1-methyl 5-phenyl-2H-1,4-benzodiazepin-2-one (I) to an isoindole derivative (II) on treatment with sodium hydride in DMF as shown in Chart 1.

Furthermore, there have appeared several reports of the rearrangements and transformations of substituted 1,4-benzodiazepine 4-oxide to afford the derivatives of indole,[5] quinazoline[6–8] and quinoxaline.[9] These interesting reactions were applied to the benzodiazepinooxazoles in order to examine whether or not they differ from I or its 4-oxides in the chemical behaviors and novel reactions were found in the reaction with DMF-NaH.

Treatment of 10-chloro-2,3,5,6,7,11b-hexahydro-7-methyl-11b-phenylbenzo[6,7]-1,4-diazepino[5,4-*b*]oxazol-6-one (IIIa) with sodium hydride in DMF at 85—90° for 8 hr, and then with water gave two compounds, one of which was identified with 2-methylamino-5-

1) Part II: S. Sato, N. Sakurai, T. Miyadera, C. Tamura, and R. Tachikawa, *Chem. Pharm. Bull.* (Tokyo), **19**, 2501 (1971).
2) Location: *2–58, 1-chome, Hiromachi, Shinagawa-ku, Tokyo.*
3) T. Miyadera, A. Terada, M. Fukunaga, Y. Kawano, T. Kamioka, C. Tamura, H. Takagi, and R. Tachikawa, *J. Med. Chem.*, **14**, 520 (1971).
4) R.I. Fryer, J.V. Earley, and L.H. Sternbach, *J. Org. Chem.*, **34**, 649 (1969).
5) W. Metlesics, G. Silverman, and L.H. Sternbach, *J. Org. Chem.*, **29**, 1621 (1964).
6) S.C. Bell and S.J. Childress, *J. Org. Chem.*, **27**, 1691 (1962).
7) S.C. Bell, C. Gocheman, and S.J. Childress, *J. Org. Chem.*, **28**, 3010 (1963).
8) L.H. Sternbach, E. Reeder, A. Stempel, and A.I. Rachlin, *J. Org. Chem.*, **29**, 332 (1964).
9) S.C. Bell and S.J. Childress, *J. Org. Chem.*, **29**, 506 (1964).

chlorobenzophenone (IV) by comparison with an authentic sample. The structural assignment of another product (Va) was collaborated by its physical data and by comparison of some of the derivatives with authentic specimens. The elemental analysis ($C_{19}H_{17}O_2N_2Cl$) and mass spectrum (M^+=340) of Va indicated the incorporation of one carbon atom into the starting material (IIIa, $C_{18}H_{17}O_2N_2Cl$). The infrared (IR) spectrum showed an amide band at 1671 cm^{-1} and a new exo-methylene band at 915 cm^{-1}. The ultraviolet (UV) spectrum exhibited an absorption maximum at 242 nm (ε=19200). In the nuclear magnetic resonance (NMR) spectra of IIIa and Va as shown in Fig. 1, an AB type quartet at 3.03 (J=11 Hz) and 3.65 ppm (J=11 Hz) due to the methylene protons at 5-position were absent but a new AB type quartet for the exo-methylene protons appeared at 3.98 (J=1.2 Hz) and 4.45 ppm (J=1.2 Hz) in Va. From these results, the compound, Va was assigned to be 10-chloro-2,3,5,6,7,11b-hexahydro-5-methylene-7-methyl-11b-phenylbenzo[6,7]-1,4-diazepino[5,4-*b*]oxazol-6-one.

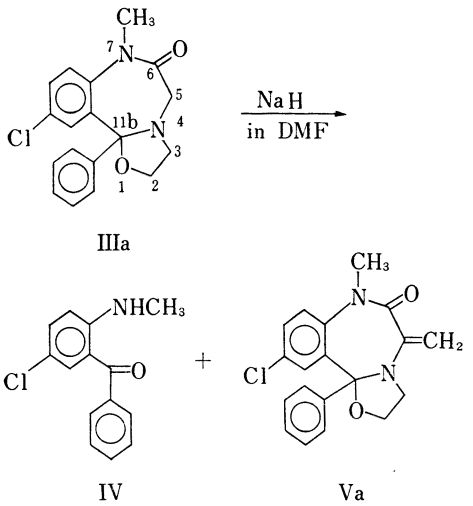


Chart 2

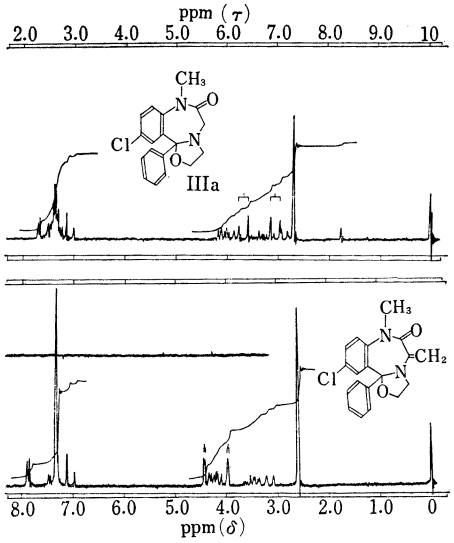


Fig. 1. The NMR Spectra of IIIa and Va

The yield of exo-methylene compound (Va) was only 41% when equimolar amounts of IIIa and sodium hydride were used in this reaction. However, the yield increased to 81% when two mole equivalent of sodium hydride was employed. This fact suggested that two mole equivalent of sodium hydride was required in this reaction. Furthermore, the compound, Va was unambigously identified by converting it to the known compounds. The acid hydrolysis of Va with conc. sulfuric acid in acetic acid under drastic conditions gave 2-methylamino-5-chlorobenzophenone (IV) which was identical with an authentic sample. On the other hand, treatment of Va with 2% ethanolic hydrochloric acid under mild conditions afforded colorless crystals (VI) of mp 108—109° in 47% yield. The structural assignment of VI was based on the elemental analysis ($C_{17}H_{14}O_3NCl$) and MS (M^+=286). The depicted structure, 2-(N-methyl-N-pyruvoylamino)-5-chlorobenzophenone, was presented from the following spectral data. The IR spectrum showed the existence of a pyruvoyl group (1716 cm^{-1} for C=O and 1676 cm^{-1} for N-C=O) and an aryl ketone group (1655 cm^{-1}). The UV absorption maximum appeared at 252.1 nm (ε=17300). The NMR spectrum in deuteriochloroform revealed a singlet at 2.30 ppm (3H) due to the methyl group, a singlet at 3.18 ppm (3H) assignable to the N-methyl group and an aromatic multiplet centered at 7.58 ppm (8H).

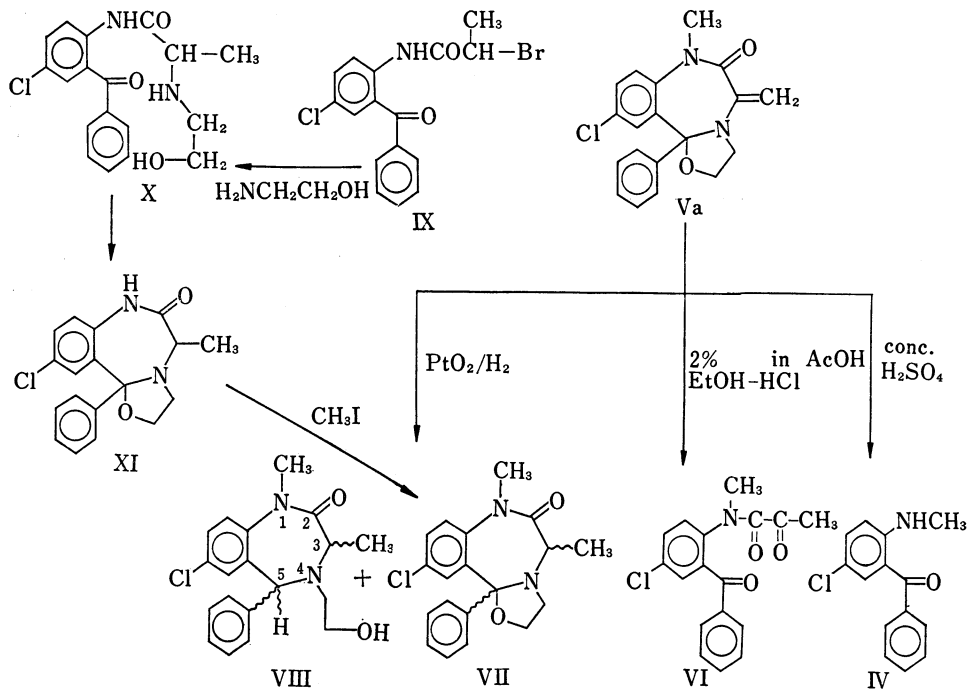


Chart 3

A possible mechanism for the formation of VI from Va involves a hydrolysis of the enamine moiety. This would lead to the intermediate (XII) which is decomposed to the azomethine (XIII) and subsequently hydrolyzed to the product (VI).

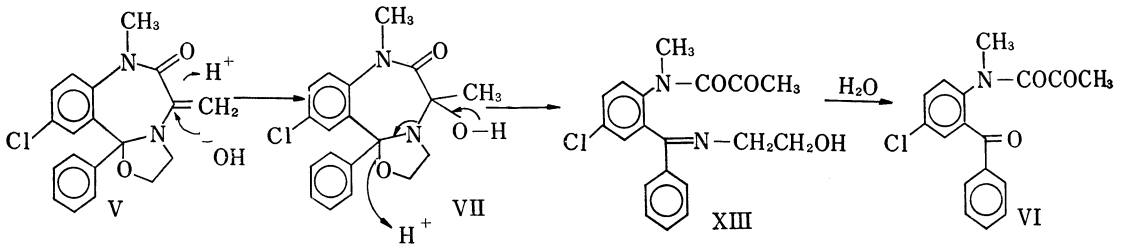


Chart 4

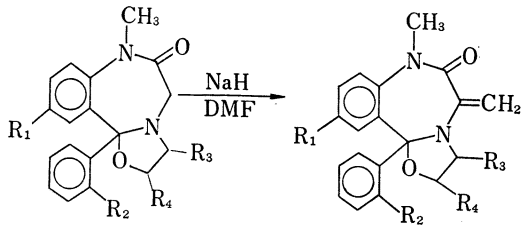
The structure of Va was further confirmed by converting it to the known compound, 10-chloro-2,3,5,6,7,11b-hexahydro-5,7-dimethyl-11b-phenylbenzo[6,7]-1,4-diazepino[5,4-*b*]oxazol-6-one (VII).[3] Catalytic hydrogenation of Va with platinum oxide in ethanol gave two reduction products, VII and VIII, in 45% and 15% yield, respectively. The structure of the first product (VII) was determined by comparison with an authentic sample prepared from 2-(2-bromopropionamido)-5-chlorobenzophenone (IX) and ethanolamine, followed by methylation, according to the procedure established by us.[3] There should be two configurational isomers, *trans*- and *cis*-form, since VII has two asymmetric centers at 5- and 11b-positions. The NMR spectrum of VII obtained from Va was superimposable on that of the product from IX showing that VII is one fo the two possible isomers.

The second product (VIII) with the empirical formula, $C_{19}H_{20}O_2N_2Cl$, showed a hydroxyl band at 3480 cm^{-1} and an amide band at 1663 cm^{-1} in the IR spectrum. The NMR spectrum

exhibited a doublet at 1.34 (3H, J=6.0 Hz) due to the methyl protons, a broad singlet at 2.33 (1H) for hydroxyl proton, a singlet at 2.62 (3H) assigned to the N-methyl protons, a quartet at 3.03 (1H, J=6.0 Hz) assignable to the methine proton, an A_2B_2 pattern (2.72—2.90; 2H, multiplet and 3.63—3.83; 2H, multiplet) due to -N-CH_2-CH_2-O-, a singlet at 4.90 (1H) assigned to the methine proton and aromatic multiplet centered at 7.27 ppm (8H). From these results, the structure of VIII was assigned to be 7-chloro-1,3,4,5-tetrahydro-4-(2-hydroxyethyl)-5-phenyl-2H-1,4-benzodiazepin-2-one. At present, the stereochemistry of VII and VIII are not elucidated.

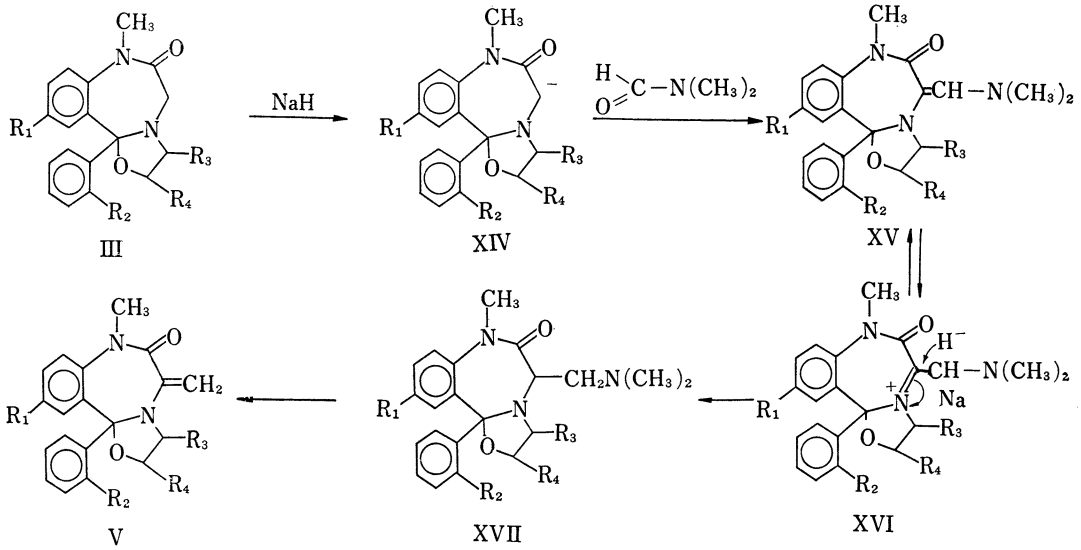
The reaction of various substituted benzo[6,7]-1,4-diazepino[5,4-*b*]oxazole derivatives (IIIa—d) with sodium hydride in DMF gave the corresponding exo-methylene compounds (Va—d) and the results are summarized in Table I.

Table I.



III V

	R_1	R_2	R_3	R_4	NaH (mole)	Yield (%)	mp (°C)
a	Cl	H	H	H	1	41	210—212
a′	Cl	H	H	H	2	81	210—212
b	Br	H	H	H	1	40.5	208—210
b′	Br	H	H	H	2	67	208—210
c	Cl	H	CH_3	H	1	18.3	180—182
c′	Cl	H	CH_3	H	2	41	180—182
d	Cl	H	H	CH_3	1	21	122—126



III XIV XV

V XVII XVI

Chart 5

A plausible mechanism for the formation of the exo-methylene compound (V) is presented in Chart 5. The initially formed carbanion (XIV) might react with DMF to afford the intermediate (XV) by an aldol type condensation. Its immonium form (XVI) would be reduced by hydride ion leading to XVII which would then undergo the deamination to give the product, V. The reaction mechanism can be supported by the fact that two moles of sodium hydride is required. Usually β-amino ketones such as XVII are easily deaminated under basic conditions.

Contrary to our expectation, the compound (IIIe) having halogen at R_2 gave no exo-methylene compound (XX) but some interesting results were observed.

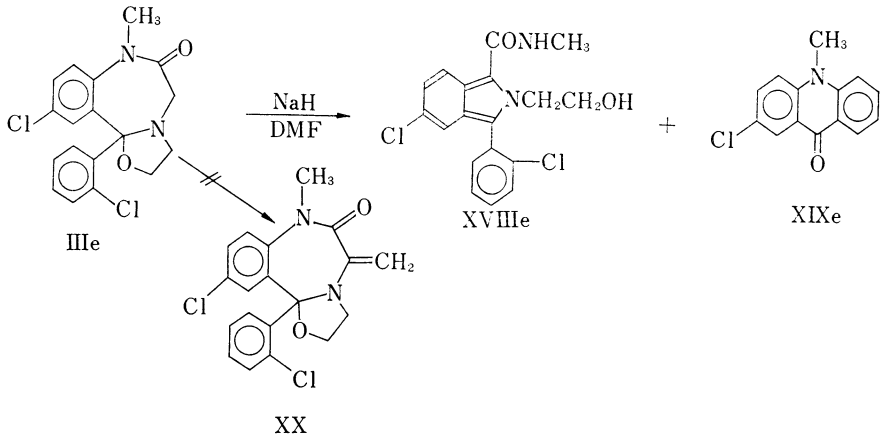


Chart 6

Reaction of 10-chloro-2,3,5,6,7,11b-hexahydro-7-methyl-11b-(*o*-chlorophenyl)benzo[6,7]-1,4-diazepino[5,4-*b*]oxazol-6-one (IIIe) with sodium hydride in DMF at 85—90° for 8 hr gave two compounds, an isoindole (XVIIIe) and an acridanone derivative (XIXe) in 7.5 and 4.5% yield, respectively. The IR spectrum of XVIIIe showed a hydroxyl band at 3310 cm^{-1} and secondary amide bands at 1643 and 1560 cm^{-1}. The NMR spectrum revealed a doublet at 3.09 ppm (3H) due to the methyl protons which changed to a singlet on addition

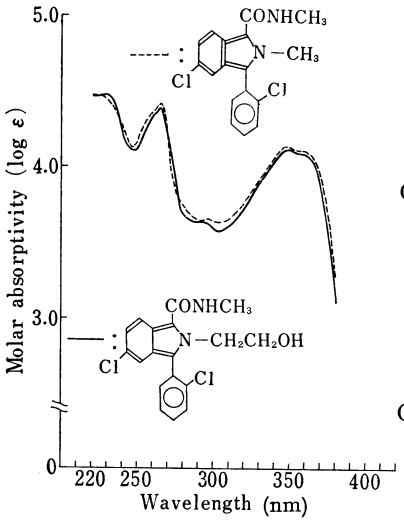


Fig. 2

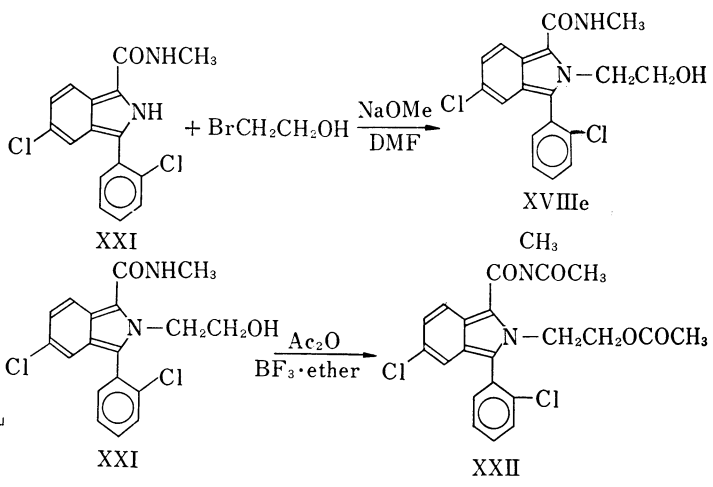


Chart 7

of deuterium oxide. These observations indicated the existence of -$CONHCH_3$ moiety. The UV spectra of XVIIIe and the 2-methyl derivative are shown in Fig. 2. The absorption of XVIIIe closely resembles that of the 2-methyl derivative which was synthesized according to Fryer's method.[10] Thus, XVIIIe was concluded to be 5-chloro-N-methyl-2-(2-hydroxyethyl)-3-(*o*-chlorophenyl)-1-isoindolecarboxamide. The structure of XVIIIe was unambigously confirmed by comparison with an authentic sample prepared from ethylenebromohydrin and isoindole compound (XXI).[10] Reaction of XVIIIe with acetic anhydride in the presence of trifluoroborate gave N,O-diacetyl compound (XXII).

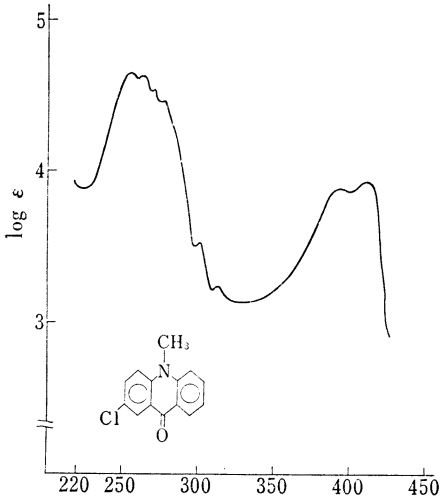
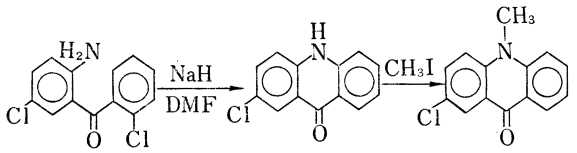


Fig. 3

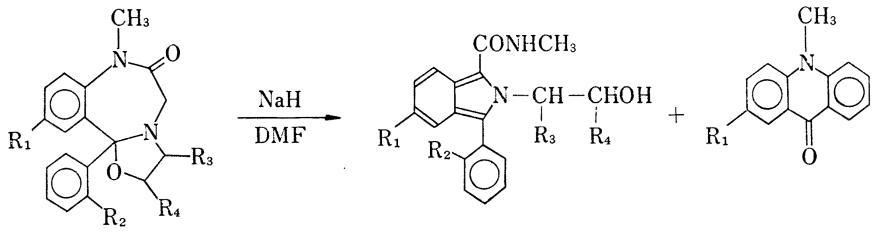


XXIII XXIV XIXe

Chart 8

The second product, 2-chloro-10-methylacridin-9-one (XIXe), showed a diaryl ketone band at 1650 cm^{-1} in the IR spectrum and revealed a singlet at 3.73 ppm due to the methyl protons in the NMR spectrum. The UV spectrum showed a typical acridanone absorption pattern as shown in Fig. 3. Sternbach and his co-workers have reported the synthesis of acridanone derivative by the reaction of fluorine substituted aminobenzophenone with sodium carbonate in DMF.[11] Considering their results and the reaction mechanism for the formation of XIXe, the chlorine substituted aminobenzophenone (XXIII) was allowed to react with sodium hydride in DMF, followed by methylation to give the acridanone derivative (XIXe) as was expected.

Table II.



III XVIII XIX

	R_1	R_2	R_3	R_4	XVIII Yield (%)	XVIII mp	XIX Yield (%)	XIX mp
e	Cl	Cl	H	H	7.5	186—189	4.5	176
f	Br	Cl	H	H	5.0	187—190	4.0	198—200
g	Cl	Cl	H	CH_3	2.5	182—183	5.0	176

10) R.I. Fryer, J.V. Earley, and L.H. Sternbach, *J. Org. Chem.*, **34**, 649 (1969).
11) R.I. Fryer, J.V. Earley, and L.H. Sternbach, *J. Chem. Soc.*, **1963**, 4979.

Similarly, the reactions of the compounds having chlorine at R_2 with sodium hydride in DMF under the same conditions gave the corresponding isoindole and acridanone derivatives as summarized in Table II.

A mechanistic assumption for the formation of XVIII is depicted in Chart 9. When R_2 is chlorine, carbanion (XXVI) might be formed from zwitter ion (XXV). In this case, the ionic contribution should be greater than that of the oxazolidine structure (III) in a solution because of the mesomeric effect of chlorine. This effect should stabilize the azomethine bond. But we have no direct evidence for the existence of this zwitter ion structure. The carbanion (XXVI) thus formed could undergo the ring contraction to give the tricycric intermediate (XXVII). This intermediate could then further undergo the ring contraction, followed by bond isomerization to afford the product, XVIII. On the other hand, as mentioned above, the exo-methylene compound (V) which was obtained from the compounds in which R_2 is hydrogen would be formed from oxazolidine carbanion (XIV). In this case, the oxazolidine contribution would be more favorable than in the chlorine substituted compounds. There is no conjugation between the carbanion and phenyl ring, so ring contraction may not occur.

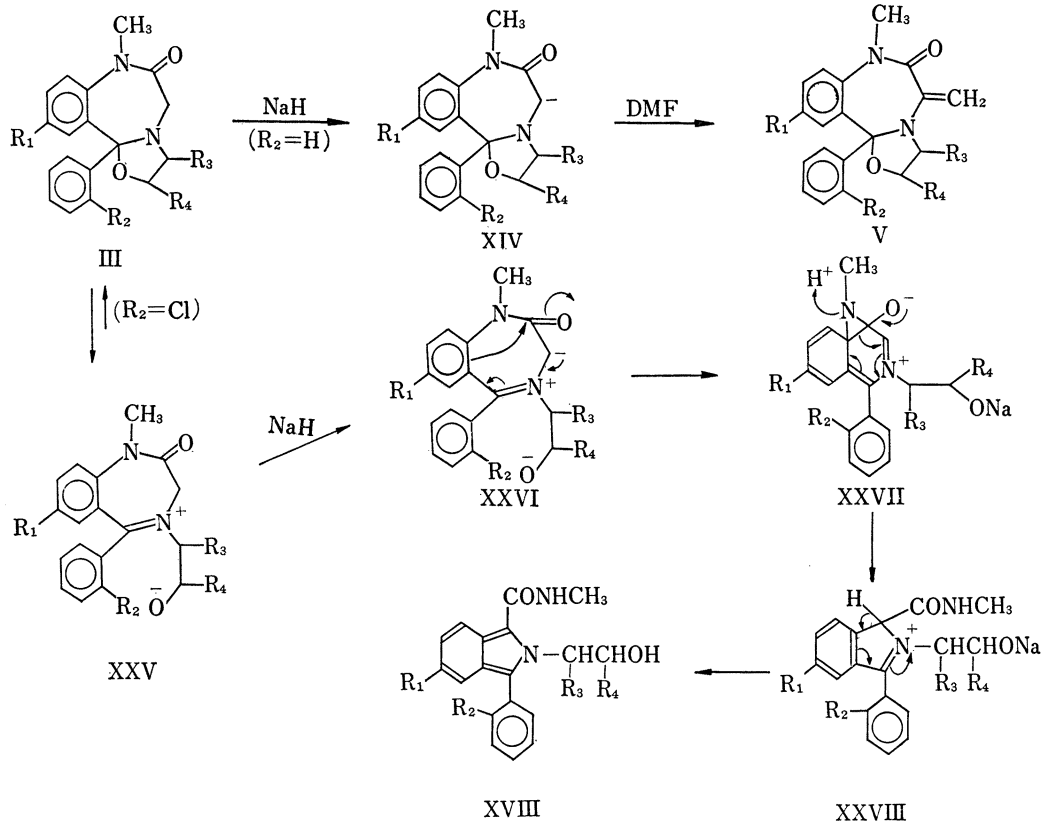


Chart 9

On the other hand, the formation of XIX possibly involves the attack of the oxygen anion to the amide carbonyl group in the compound (XXV) leading to the intermediate. When R_2 is chlorine, the addition-elimination reaction may take place to give the acridanone derivative (XIX) *via* the intermediate XXXI.

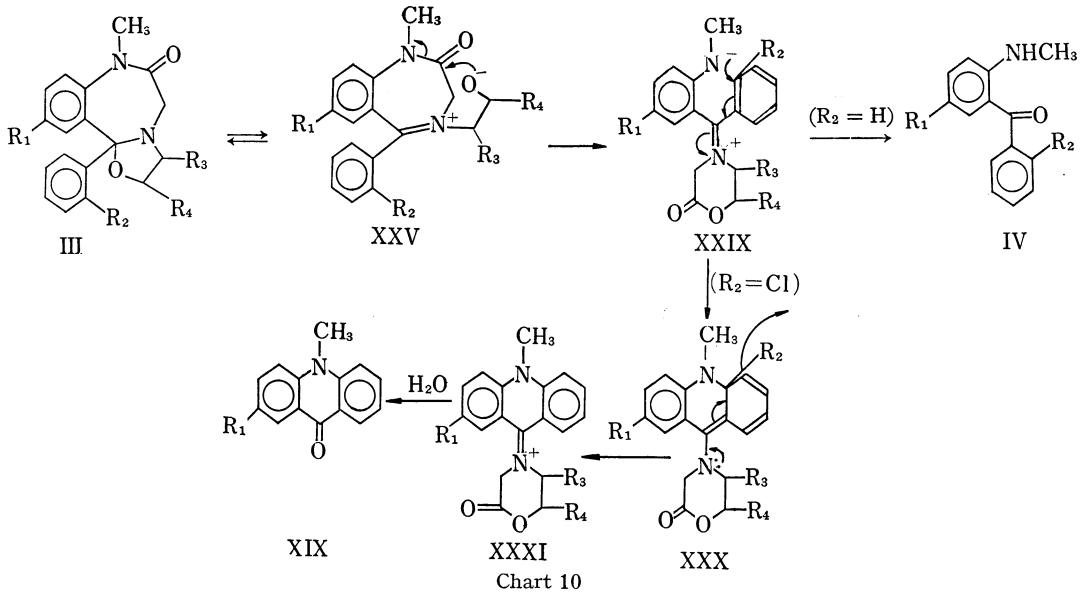


Chart 10

Experimental[12]

General Procedure for the Preparation of 10-Halogeno-2,3,5,6,7,11b-hexahydro-5-methylene-7-methyl-11b-phenylbenzo[6,7]-1,4-diazepino[5,4-*b*]-oxazol-6-one (Va—d)——To a solution of 10-halogeno-2,3,5,6,7,-11b-hexahydro-7-methyl-11b-phenylbenzo[6,7]-1,4-diazepino[5,4-*b*]-oxazol-6-one (IIIa—d, 10 mmole) in 24—40 ml of dry DMF was added NaH (50% mineral oil dispersion, 10 or 20 mmole) at 0° and the reaction mixture was warmed at 85—90° for 8 hr under N_2 atmosphere. After cooling, the reaction mixture was poured into ice–water. The resulting precipitate was collected by filtration and recrystallized from EtOH to afford Va—d. The aqueous layer was extracted with AcOEt, washed with H_2O and dried over Na_2SO_4. The solvent was evaporated and the residue was chromatographed on silica gel. Elution with C_6H_6: AcOEt (10: 1) gave 5-halogeno-2-(N-methylamino)benzophenone.

10-Chloro-2,3,5,6,7,11b-hexahydro-5-methylene-7-methyl-11b-phenylbenzo[6,7]-1,4-diazepino[5,4-*b*]-oxazol-6-one (Va)——The reaction of 10-chloro-2,3,5,6,7,11b-hexahydro-7-methyl-11b-phenylbenzo[6,7]-1,4-diazepino[5,4-*b*]oxazol-6-one (IIIa) (3.33 g) and NaH (0.48 g) in DMF (25 ml) gave Va (1.41 g) as pale yellow needles, mp 210—212°. *Anal.* Calcd. for $C_{19}H_{17}O_2N_2Cl$: C, 66.90; H, 5.03; N, 8.22; Cl, 10.40. Found: C, 67.19; H, 4.96; N, 7.97; Cl, 10.31. Treatment of IIIa (3.33 g) with DMF (25 ml) in the presence of NaH (0.96 g) afforded Va (2.8 g).

10-Bromo-2,3,5,6,7,11b-hexahydro-5-methylene-7-methyl-11b-phenylbenzo[6,7]-1,4-diazepino[5,4-*b*]-oxazol-6-one (Vb)——The reaction of 10-bromo-2,3,5,6,7,11b-hexahydro-7-methyl-11b-phenylbenzo[6,7]-1,4-diazepino[5,4-*b*]-oxazol-6-one (IIIb) (3.73 g) and NaH (0.48 g) in 40 ml of DMF afforded Vb (1.54 g) as pale yellow needles, mp 208—210°. IR ν_{max}^{Nujol} cm^{-1}: 1660, 917. UV λ_{max}^{EtOH} nm (ε): 244.3 (40900). NMR (δ in $CDCl_3$): 2.59 (3H, singlet, N–CH_3), 3.37 (center, 2H, multiplet, –N–CH_2–) 3.98, 4.44 (2H, AB type quartet, J=1.2 Hz, >C=CH_2) 4.22 (2H, multiplet, –CH_2–O–), 7.3 (center, 8H, multiplet, aromatic protons). *Anal.* Calcd. for $C_{19}H_{17}O_2N_2Br$: C, 59.23; H, 4.45; N, 7.27; Br, 20.74. Found: C, 59.45; H, 4.23; N, 7.14; Br, 20.71.

Treatment of IIIb (3.73 g) with DMF (40 ml) in the presence of NaH (0.96 g) gave Vb (2.54 g).

10-Chloro-2,3,5,6,7,11b-hexahydro-2,7-dimethyl-5-methylene-11b-phenylbenzo[6,7]-1,4-diazepino[5,4-*b*]-oxazol-6-one (Vc)——The reaction of 10-chloro-2,3,5,6,7,11b-hexahydro-2,7-dimethyl-11b-phenylbenzo[6,7]-1,4-diazepino[5,4-*b*]-oxazol-6-one (IIIc) (3.43 g) and NaH (0.48 g) in 30 ml of DMF gave Vc (0.74 g) as colorless prisms, mp 122—126°. IR ν_{max}^{Nujol} cm^{-1}: 1665, 910. UV λ_{max}^{EtOH} mμ (ε): 247 (18900). NMR (δ in $CDCl_3$): 1.42 (3H, doublet, J=5.8 Hz, C–CH_3) 2.63 (3H, singlet, N–CH_3) 3.41 (2H, multiplet, CH_2), 3.99, 4.46 (2H AB type quartet, J=1.2 Hz, >C=CH_2), 4.20 (1H, multiplet, –CH–O–), 7.32 (center, 8H, multiplet aromatic protons). *Anal.* Calcd. for $C_{20}H_{19}O_2N_2Cl$: C, 67.77; H, 5.40; N, 7.90; Cl, 9.99. Found: C, 67.96; H, 5.23; N, 7.68; Cl, 10.12.

Treatment of IIIc (3.43 g) with DMF (30 ml) in the presence of NaH (0.48 g) gave Vc (1.66 g).

10-Chloro-2,3,5,6,7,11b-hexahydro-3,7-dimethyl-5-methylene-11b-phenylbenzo[6,7]-1,4-diazepino[5,4-*b*]-

12) All melting points are uncorrected. NMR spectra were recorded on a Varian A-60 spectrometer.

oxazol-6-one (Vd)——The reaction of 10-chloro-2,3,5,6,7,11b-hexahydro-3,7-dimethyl-11b-phenylbenzo[6,7]-1,4-diazepino[5,4-*b*]-oxazol-6-one (IIId) (3.43 g) and NaH (0.48 g) in 30 ml of DMF afforded colorless prisms of Vd (0.65 g), mp 180—182°. IR ν_{max}^{Nujol} cm^{-1}: 1650, 906. UV λ_{max}^{EtOH} nm (ε): 243 (18300). NMR (δ in $CDCl_3$): 1.38 (3H. doublet, J=5.5 Hz, $-CH_3$), 2.56 (3H, singlet, N–CH_3) 3.79 (1H, multiplet, –CH–), 4.00 4.44 (2H, AB type quartet, J=1.2 Hz, $>C=CH_2$), 4.35 (2H, multiplet, $-CH_2-$) 7.32 (center, 8H, multiplet, aromatic protons). *Anal.* Calcd. for $C_{20}H_{19}O_2N_2Cl$: C, 67.77; H, 5.40; N, 7.90; Cl, 9.99. Found: C, 67.89; H, 5.26; N, 7.71; Cl, 10.06.

Reaction of 10-chloro-2,3,5,6,7,11b-hexahydro-5-methylene-7-methyl-11b-phenylbenzo[6,7]-1,4-diazepino[5,4-*b*]-oxazol-6-one (Va) with H_2SO_4——A mixture of Va (318 mg), H_2SO_4 (2.0 g), AcOH (7 ml), and H_2O (5 ml) was heated under reflux for 15 hr. The reaction mixture was neutralized with K_2CO_3 and extracted with ether. The combined extracts were washed with H_2O, dried over Na_2SO_4, and the solvent evaporated under reduced pressure to give a yellow solid. Recrystallization from EtOH gave 5-chloro-2-(N-methylamino)benzophenone (IV) (110 mg), mp 94—95.5°, as yellow needles. *Anal.* Calcd. for $C_{14}H_{12}ONCl$: C, 68.43; H, 4.93; N, 5.70; Cl, 14.43. Found: C, 68.30; H, 4.97; N, 5.39; Cl, 14.51.

Reaction of 10-Chloro-2,3,5,6,7,11b-hexahydro-5-methylene-7-methyl-11b-phenylbenzo[6,7]-1,4-diazepino[5,4-*b*]-oxazol-6-one (Va) with HCl——A solution of Va (207 mg) in 20 ml of 2% HCl–EtOH was stood for 2 days at room temperature and then EtOH evaporated under reduced pressure. The residue was extracted with $CHCl_3$, washed with H_2O and dried over Na_2SO_4. Evaporation under reduced pressure gave a yellow solid. Recrystallization from *n*-hexane afforded 5-chloro-2-(N-methyl-N-pyruvoylamino)-benzophenone (VI) (90 mg), mp 108—109°. IR ν_{max}^{Nujol} cm^{-1}: 1716, 1665, 1655. UV λ_{max}^{EtOH} nm (ε): 252.1 (17300). NMR (δ in $CDCl_3$): 2.30 (3H, singlet, $COCH_3$), 3.18 (3H, singlet, N–CH_3), 7.58 (center, 8H, multiplet, aromatic protons). *Anal.* Calcd. for $C_{17}H_{14}O_3NCl$: C, 64.67; H, 4.47; N, 4.44; Cl, 11.23. Found: C, 64.95; H, 4.58; N, 4.13; Cl, 11.35.

10-Chloro-2,3,5,6,7,11b-hexahydro-5,7-dimethyl-11b-phenylbenzo[6,7]-1,4-diazepino[5,4-*b*]-oxazol-6-one (VII) and 7-Chloro-1,2,3,5-tetrahydro-1,3-dimethyl-4-(2-hydroxyethyl)-5-phenylbenzodiazepin-2-one(VIII)——A suspension of platinum oxide (71 mg) in EtOH (5 ml) was stirred under H_2 atmosphere until no more hydrogen was absorbed. Then 10-chloro-2,3,5,6,7,11b-hexahydro-5-methylene-7-methyl-11b-phenylbenzo-[6,7]-1,4-diazepino[5,4-*b*]-oxazol-6-one (Va) (679 mg) in EtOH (5 ml) was added and the mixture stirred under H_2 atmosphere. After one mole of H_2 was absorbed, the catalyst was filtered off and washed with EtOH. The combined filtrate was evaporated under reduced pressure. The oily residue was chromatographed on silica gel (30 g) and eluted with $CHCl_3$ to give the following products: VII (310 mg), mp 193—195°. IR ν_{max}^{Nujol} cm^{-1}: 1674. UV λ_{max}^{EtOH} nm (ε): 244.2 (13100). NMR (δ in $CDCl_3$): 1.39 (3H, doublet, J= 6.5 Hz, C–CH_3), 2.44 (3H, singlet, N–CH_3), 2.93 (1H, quartet, J=6.5 Hz, –CO–CH–N–), 3.32—3.59 (2H, multiplet, –N–CH_2–), 3.93—4.20 (2H, multiplet, $-CH_2-O-$), 7.28 (center, multiplet, aromatic protons). *Anal.* Calcd. for $C_{19}H_{19}O_2N_2Cl$: C, 66.56; H, 5.59; N, 8.17; Cl, 10.34. Found: C, 66.85; H, 5.58; N, 7.89; Cl, 10.39. VIII (105 mg), mp 186—189.5°. IR ν_{max}^{EtOH} cm^{-1}: 3465, 1660, UV λ_{max}^{EtOH} nm (ε): 241.6 (12200). NMR (δ in $CDCl_3$): 1.34 (3H, doublet, J=6 Hz, C–CH_3), 2.33 (1H, broad singlet, OH), 2.62 (3H, singlet, N–CH_3) 2.72—2.91 (2H, multiplet, –N–CH_2), 3.03 (1H, quartet, J=6 Hz, CO–CH–N–), 3.63—3.82 (2H, multiplet, $-CH_2-O-$), 4.90 (1H, singlet, –CH–N), 7.27 (8H, multiplet, aromatic protons). *Anal.* Calcd. for $C_{19}H_{21}O_2N_2Cl$: C, 66.17; H, 6.13; N, 8.12; Cl, 10.28. Found: C, 66.38; H, 6.31; N, 8.02; Cl, 9.99.

5-Chloro-N-methyl-2-(2-hydroxyethyl)-3-(*o*-chlorophenyl)-1-isoindolecarboxamide (XVIIIe) and 2-Chloro-10-methylacridin-9-one (XIXe)——A mixture of 10-chloro-2,3,5,6,7,11b-hexahydro-7-methyl-11b-(*o*-chlorophenyl)-benzo[6,7]-1,4-diazepino[5,4-*b*]-oxazol-6-one (IIIe) (16.3 g), NaH (50% mineral oil dispersion, 2.6 g) and 135 ml of DMF was warmed at 85—90° for 8 hr under N_2 atmosphere. After cooling, the reaction mixture was poured into ice–water and extracted with CH_2Cl_2. The combined extracts were washed with H_2O and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give 16.0 g of brown liquid which was chromatographed on Al_2O_3 (Merck, grade II, 350 g). Elution with C_6H_6–EtOH (40: 1) afforded 0.48 g of XIXe, mp 176°. IR ν_{max}^{Nujol} cm^{-1}: 1650. UV λ_{max}^{EtOH} nm (ε): 253.1 (46360), 260.5 (45700), 268.5 (32463), 275.5 (27300), 299 (3300), 310.5 (1800), 391.5 (8200), 411 (9200). NMR (δ in $CDCl_3$): 3.73 (3H, singlet, CH_3). *Anal.* Calcd. for $C_{14}H_{10}ONCl$: C, 68.99; H, 4.14; N, 5.75; Cl, 14.55. Found: C, 68.76; H, 4.30; N, 5.83; Cl, 14.54. After elution of XIXe, XVIIIe (1.24 g) of mp 186—189° was eluted with C_6H_6-EtOH (4: 1). IR ν_{max}^{Nujol} cm^{-1}: 3325, 1643. 1625. UV λ_{max}^{EtOH} nm (ε): 264.6 (23800), 343.5 (12300), 360 (shoulder). NMR (δ in $CDCl_3$): 3.09 (3H, doublet, J=7.5 Hz, –N–CH_3).

5-Bromo-N-methyl-2-(2-hydroxyethyl)-3-(*o*-chlorophenyl)-1-isoindolecarboxamide (XVIIIf) and 2-Bromo-10-methylacridin-9-one (XIXf)——A mixture of 10-bromo-2,3,5,6,7,11b-hexahydro-7-methyl-11b-(*o*-chlorophenyl)-benzo[6,7]-1,4-diazepino[5,4-*b*]oxazol-6-one (IIIf) (4.07 g), NaH (50% mineral oil dispersion, 0.58 g) and 30 ml of DMF was warmed at 85—90° for 8 hr under N_2 atmosphere. After cooling, the reaction mixture was poured into ice–water and extracted with CH_2Cl_2. The combined extracts were washed with H_2O and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give 3.5 g of brown liquid which was chromatographed on Al_2O_3 (Merck, grade II, 100 g). Elution with C_6H_6–EtOH (40: 1) afforded 0.112 g of XIXf, mp 198—200°. IR ν_{max}^{Nujol} cm^{-1}: 1636. UV λ_{max}^{EtOH} mμ (ε): 254 (44000), 261.5 (43700), 269.5 (shoulder), 278.5 (29300), 299.5 (3800), 311 (2200), 392 (8600), 411 (7700). NMR (δ in $CDCl_3$): 3.74 (3H, singlet, CH_3). *Anal.* Calcd. for $C_{14}H_{10}ONBr$: C, 58.33; H, 3.47; N, 4.86; Br, 27.77. Found: C, 58.12;

H, 3.36; N, 4.95; Br, 27.71. After elution of XIXf, XVIIIf (0.21 g) of mp 187—190° was eluted by C_6H_6–EtOH (4: 1). IR ν_{max}^{Nujol} cm^{-1}: 3350, 1640, 1630. UV λ_{max}^{EtOH} $m\mu$ (ε): 265 (25200), 344.3 (1200), 361 (shoulder). NMR (δ in $CDCl_3$): 3.08 (3H, doublet, $J=8.0$ Hz, –NH–CH_3).

5-Chloro-N-methyl-2-(2-hydroxypropyl)-3-(*o*-chlorophenyl)-1-isoindolecarboxamide (XVIIIg) and 2-Chloro-10-methylacridin-9-one (XIXg)——A mixture of 10-chloro-2,3,5,6,7,11b-hexahydro-2,7-dimethyl-11b-(*o*-chlorophenyl)benzo[6,7)-1,4-diazepino[5,4-*b*]oxazol-6-one (IIIb) (3.77 g), NaH (50% mineral oil dispersion, 0.58 g) and 30 ml of DMF was warmed at 95—96° for 8 hr under N_2 atmosphere. After cooling, the reaction mixture was poured into ice–water and extracted with CH_2Cl_2. The combined extracts were washed with H_2O and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give 3.3 g of brown liquid which was chromatographed on Al_2O_3 (Merck, grade II, 100 g). Elution with C_6H_6–EtOH (40: 1) afforded 0.121 g of XIXg, mp 198—200°. The IR spectrum of XIXg was superimposable on that of XIXe. After elution of XIXg, XVIIIg (0.095 g) of mp 182—183° was eluted with C_6H_6–EtOH (4: 1). IR ν_{max}^{EtOH} cm^{-1}: 3335, 1645, 1628. UV λ_{max}^{EtOH} $m\mu$ (ε). 228 (29300), 264 (23700), 347 (12500), 358.5 (12300). NMR (δ in $CDCl_3$): 3.08 (3H, doublet, $J=7.5$ Hz, –NH–CH_3).

5-Chloro-N-methyl-2-(2-hydroxyethyl)-3-(*o*-chlorophenyl)-1-isoindolecarboxamide (XVIIIe) from 5-Chloro-N-methyl-3-(*o*-chlorophenyl)-1-isoindolecarboxamide (XXI)——To a mixture of NaOMe in MeOH, prepared from Na (0.9 g) and 6 ml of MeOH, was added a solution of 5-chloro-N-methyl-3-(*o*-chlorophenyl)-1-isoindolecarboxamide (4.5 g) in 15 ml of DMF. After stirring for 30 min., a solution was cooled in an ice bath and dropwise ethylenebromohydrin (4.15 g) added. After standing 10 days, a mixture was warmed at 50° for 16 hr. and then poured into ice–water, extracted with CH_2Cl_2, washed with H_2O, dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The oily residue was chromatographed on Al_2O_3 (Merck, grade II, 100 g) and eluted with $CHCl_3$ to give 0.18 g of XVIIIe, mp 186—189°. The IR spectrum was superimposable on that of the compound obtained from IIIe.

5-Chloro-N-acetyl-N-methyl-2-(2-acetoxyethyl)-3-(*o*-chlorophenyl)-1-isoindolecarboxamide (XXII)——A solution of 5-chloro-N-methyl-2-(2-hydroxyethyl)-3-(*o*-chlorophenyl)-1-isoindolecarboxamide (XVIIe) (0.297 g) in 2.4 ml of acetic anhydride was treated with 2 drops of boron trifluoride etherate and warmed to 60° for 6 hr with stirring. After cooling, NH_4OH was added to the reaction mixture carefully and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with saturated brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give a solid. Recrystallization from *n*-heptane gave XXII (0.19 g) as pale yellow prisms mp 123—124.5.° IR ν_{max}^{Nujol} cm^{-1}: 1763, 1695, 1638. NMR (δ in $CDCl_3$): 1.88 (3H, singlet, –N–$COCH_3$), 2.19 (3H, singlet, –O–$COCH_3$), 3.33 (3H, singlet, –N–CH_3), 4.32 (2H, multiplet, –N–CH_2O), 4.75 (2H, multiplet, –CH_2–O–), 7.45 (center, 7H, multiplet, aromatic protons). *Anal.* Calcd. for $C_{22}H_{20}O_4N_2Cl_2$: C, 59.07; H, 4.50; N, 6.26; Cl, 15.85. Found: C, 59.01; H, 4.21; N, 6.21; Cl, 15.83.

2-Chloroacridin-9-one (XXIV)——A mixture of 2-amino-2′,5-dichlorobenzophenone (2.66 g), NaH (50% oily mixture, 0.5 g) and 15 ml of DMF was warmed at 85—90° for 6 hr. After cooling, the reaction mixture was poured into ice–water. The resulting precipitate was collected by filtration and washed with EtOH to give XXIV (1.12 g), mp 250°. *Anal.* Calcd. for $C_{13}H_8ONCl$: C, 67.98; H, 3.51; N, 6.09; Cl, 15.44. Found: C, 67.70; H, 3.53; N, 6.03; Cl, 15.62.

2-Chloro-10-methylacridin-9-one (XIXe) from XXIV——A mixture of NaOMe in MeOH, prepared from Na (0.17 g) and 5 ml of abs. MeOH, and 2-chloroacridin-9-one (XXIV) (1.12 g) was stirred for 1 hr and then MeOH was evaporated under reduced pressure below 40°. To the residual oil was added 20 ml of DMF and the mixture was stirred for 2 hr at room temperature. The resulting MeOH was again evaporated under reduced pressure at a low temperature and then CH_3I (2.83 g) was added to the above mixture with stirring under ice–water cooling. After standing overnight, the solvent was removed under reduced pressure to give a solid. Recrystallization from EtOH gave XIXe (0.753 g) as pale-yellow prisms, mp 176°, *Anal.* Calcd. for $C_{14}H_{10}ONCl$: C, 68.99; H, 4.14; N, 5.75; Cl, 14.55. Found: C, 68.52; H, 4.05; N, 5.53; Cl, 14.72.

Acknowledgement We wish to express our gratitude to Dr. G. Sunagawa, Director of this Laboratories, and to Dr. K. Tanabe, Assistant Director, for their encouragement and discussion. We are also indebted to Miss M. Takemasa for her technical assistance.