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Chemistry of Salicylic Acid and Anthranilic Acid. II. Formation of 2-Alkyl-3-(2-carboxyphenyl)-4-quinazolone from 2-Alkyl-4-oxo-4*H*-3,1-benzoxazine by Dimeric Condensation[1]

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Treatment of 2-alkyl-4-oxo-4*H*-3,1-benzoxazines (Ia—d, f, i, l) with ethanol gave 2-alkyl-3-(2-carboxyphenyl)-4-quinazolones (VIIa—d, f, i, l) along with the liberation of ethyl alkanoate. This dimeric condensation may be explained in terms of the contribution of the C=N double bond of Ia—d, f, i, l.

It was also revealed that the intermediate of the formation of 4-quinazolone (XVIII) in the reaction of Ia with aniline, was the amidine (XVII), which was produced by the addition of aniline to the C=N double bond of Ia.

Keywords——2-alkyl-4-oxo-4*H*-3,1-benzoxazine; 2-alkyl-3-(2-carboxyphenyl)-4-quinazolone; dimeric condensation; formation of 4-quinazolone; effect of substituent;

4-Oxo-4*H*-3,1-benzoxazine (I) is known as "acylanthranil" probably because it is conveniently obtained from N-acylanthranilic acid by dehydration in acetic anhydride.[3] The carbonyl group of I at position 4 is susceptible to nucleophilic attack due to its structural resemblance to acid anhydride and treatment of I with ammonia or a primary amine affords the corresponding 4-quinazolone (II) and/or 2-acylaminobenzamide (III) as the major products (Chart 1). In this reaction we used 6-chloroanthranilic acid as a primary amine and found an unusual dimeric condensation of various 2-alkyl-4-oxo-4*H*-3,1-benzoxazines.[3]

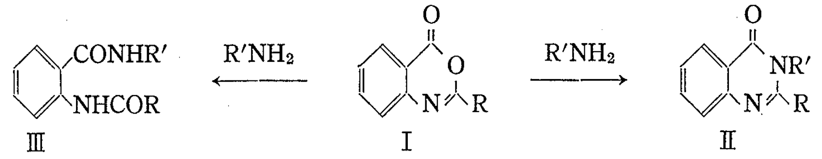

Chart 1

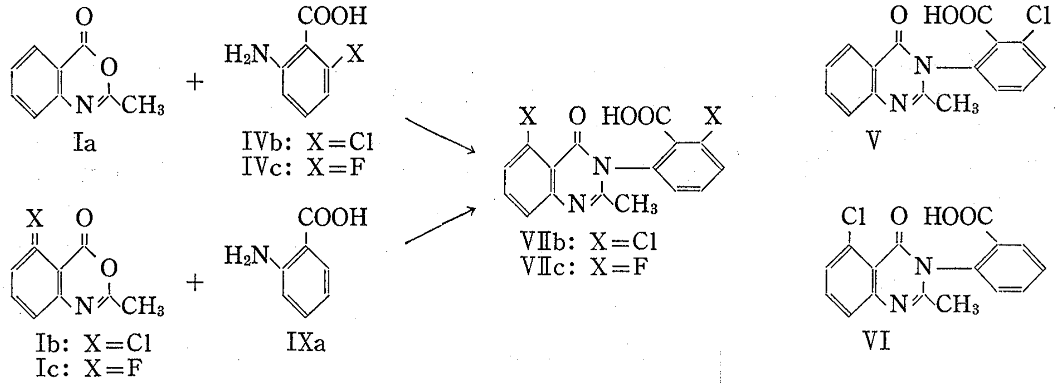

Chart 2

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[1] Presented at the 6th Congress of Heterocyclic Chemistry, November, 1973, Nagoya, Japan.

[2] Location: *Jusohonmachi, Yodogawa-ku, Osaka 532, Japan.*

[3] For example; *a*) W.L.F. Armarego, "The Chemistry of Heterocyclic Compounds, Fused Pyrimidines Part 1 Quinazolines," ed. by A. Weissberger, Interscience Publishers, Inc., New York, 1967, Chapter 4; *b*) R.C. Elderfield, W.H. Todd, and S. Gerber, "Heterocyclic Compounds," Vol. 6, ed. by R.C. Elderfield, John Wiley and Sons, Inc., New York, 1957, p. 353.

The reaction of 3-methyl-4-oxo-4*H*-3,1-benzoxazine (Ia) with 6-chloroanthranilic acid (IVb) in boiling ethanol gave a crystalline product which was different from 3-(2-carboxy-3-chlorophenyl)-2-methyl-4-quinazolone (V), the expected product from the widely accepted reaction given in Chart 1. The elemental analysis and mass (MS) spectrum of the product led to the molecular formula of $C_{16}H_{10}Cl_2N_2O_3$ and the structure VIIb was proposed as the most probable one. For the synthesis of VIIb, a method similar to the one used by Ecsery[4] was used. As shown in Chart 3, he reacted anthranilic acid with acetoiminoester hydrochloride to obtain VIIIa then converted VIIIa to VIIa by treatment with hydrogen chloride in acetic acid. In our case, however, a similar reaction of 6-chloroanthranilic acid with acetoiminoester hydrochloride afforded VIIb directly without any intermediate. The infrared (IR), nuclear magnetic resonance (NMR) and MS spectra of 4-quinazolone (VIIb), thus obtained agreed with those of the reaction product of Ia and IVb. The reaction of IVa and Ib also gave VIIb and no product having the structure VI was isolated from the mother liquor. These observations strongly suggest that Ia, Ib, IVa and IVb are in equilibrium with each other in ethanol as shown in Chart 4.

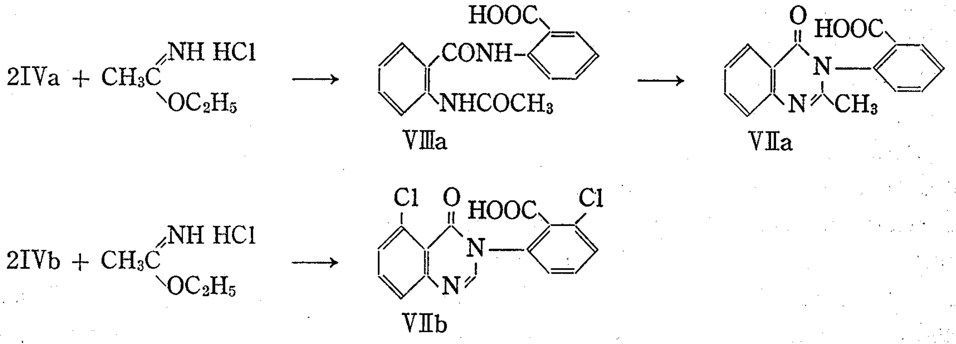

Chart 3

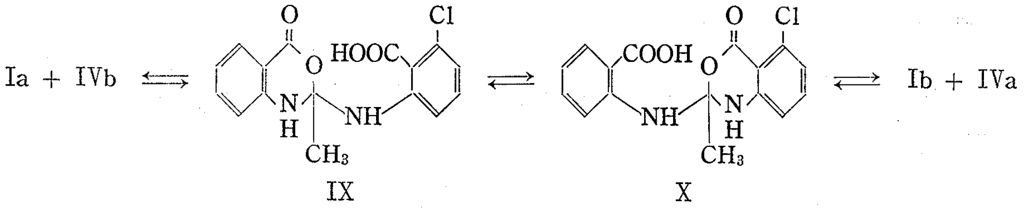

Chart 4

The equilibrium is assumed to be established through nucleophilic attack of the amino group in IVa or IVb to position 2 in benzoxazine (Ia or Ib) and recyclization of the dihydro-oxazine ring followed by dissociation to anthranilic acid and benzoxazine analogues. Compound VIIb was formed either from the reaction of Ib and IVb or dimeric condensation of Ib. To check the reaction mechanism, Ib was heated alone in ethanol and, as expected, VIIb was isolated in good yield. From the reaction mixture, a considerable amount of ethyl acetate was detected. It seems that on dimeric condensation of Ib, the methyl group at position 2 in half of the molecules was eliminated, by the reaction with the ethanol, as ethyl acetate. In the reaction of Ia with IVb or Ib with IVa described above, about an equimolecular amount of ethyl acetate, along with VIIb, was also detected from the reaction mixture by gas chromatography. This suggests that even the reaction of Ia with IVb will proceed mainly through formation of Ib as the first stage, followed by its dimeric condensation. The equilibrium between Ia+IVb and Ib+IVa seems to occur instantaneously since the reaction of benzoxazine with amine is rapid. For example, on adding aniline to a solution of Ia,

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4) Z. Ecsery and I. Rosa, *Chem. Ber.*, **97**, 302 (1964).

an adduct shown later to be XVII separated out within a few minutes. Recyclization of the dihydrobenzoxazine ring between IX and X may proceed in the direction of X. This shift of the equilibrium may be attributed to the steric force brought about by the *ortho* substituents, Cl and COOH, to minimize the steric interaction. The effect of the *ortho* Cl atom on the ring formation is also demonstrated by the following example. As shown in "Organic Synthesis,"[5] anthranilic acid is converted to 2-hydrazinobenzoic acid in good yield through diazotization with sodium nitrate and successive reduction with sulfur dioxide. However, our experiment showed that under the same reaction conditions, 6-chloroanthranilic acid gave 4-chloro-3-indazolone (XII) and no hydrazinobenzoic acid was recovered from the reaction mixture (Chart 5). An alternative explanation is that the carboxy group having an *ortho* Cl substituent is electronically more negative than that without Cl substituent and consequently is more vulnerable to dihydrobenzoxazine formation. The low yield of 5-fluorobenzoxazine (Ic) on mixing Ia and 6-fluoroanthranilic acid (IVc), which seems to exhibit no *ortho* interaction but has a more electronegative substituent than IVb, may also support the idea of effective contribution of the steric force from *ortho* Cl atom to the formation of Ib from IVb and Ia.

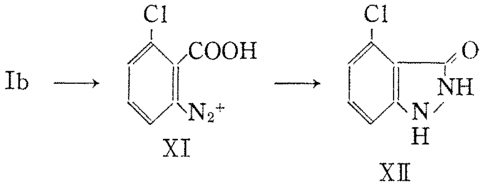
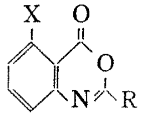


Chart 5

Table I. Dimeric Condensations of 4-Oxo-4*H*-3,1-benzoxazines



Ia—m

Comp. No.	Substituent		Solvent	Yield (%) of VII	Yield (%) of VIII
	R	X			
Ia	CH_3	H	MeOH	58	18
Ib	CH_3	Cl	EtOH	70	0
Ic	CH_3	F	EtOH	60	—
Id	C_2H_5	H	MeOH	37	35
Ie	C_2H_5	Cl	EtOH	65	0
If	iso-C_3H_7	H	MeOH	—	—
Ig	iso-C_3H_7	Cl	EtOH	46	0
Ih	*tert*-C_4H_9	H	MeOH	0	0
Ii	*tert*-C_4H_9	Cl	MeOH	0	0
Ij	*n*-C_7H_{15}	Cl	EtOH	64	0
Ik	Phenyl	Cl	EtOH	0	0
Il	PhCH=CH	Cl	EtOH	0	0
Im	$PhCH_2$	Cl	EtOH	34	0

The yield of 4-quinazolone by dimeric condensation of benzoxazine is fairly influenced by the solvent used or the kind of substituents at position 2 or 5. In the case of Ib, though the reaction proceeded smoothly in methanol or ethanol, it was retarded in isopropanol and even more strongly in *t*-butanol. In aprotic solvents, such as benzene or pyridine, the dimeric condensation did not occur. This can be reasonably understood from the observation

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5) E.M.F. Stephenson, "Organic Synthesis," Coll. Vol. III, ed. by A.H. Blatt, John Wiley and Sons, Inc., New York, 1955, p. 475.

mentioned above that the solvent molecule takes part in the reaction to give, for example, ethyl acetate. Acetic acid was also found to be unsuitable as a solvent.

Table I summarizes the effect of the substituents at position 2 and 5. When position 5 was unsubstituted, open-ring diamides (VIIIa and VIIId) were produced along with 4-quinazolones (VIIa and VIId), whereas a Cl atom at this position directed the reaction exclusively to 4-quinazolones (VIIb, VIIe, VIIg, VIIj, and VIIm). In the case when the substituent at position 2 was a straight chain alkyl group, the yield of 4-quinazolone was relatively high (VIIa—e, VIIj). An isopropyl or benzyl group at this position considerably reduced the yield (VIIg, VIIm) and, if position 5 was free of substituent, the formation of 4-quinazolone (VIIf) was only detected weakly on thin-layer chromatogram. A more bulky substituent, *e.g.* *t*-butyl, phenyl, or styryl group, inhibited the formation of 4-quinazolone completely even when a Cl atom was at position 5. Such a remarkable influence of the 2-substituent suggests that position 2 plays an important part in the reaction. From this evidence, we proposed the reaction mechanism shown in Chart 6.

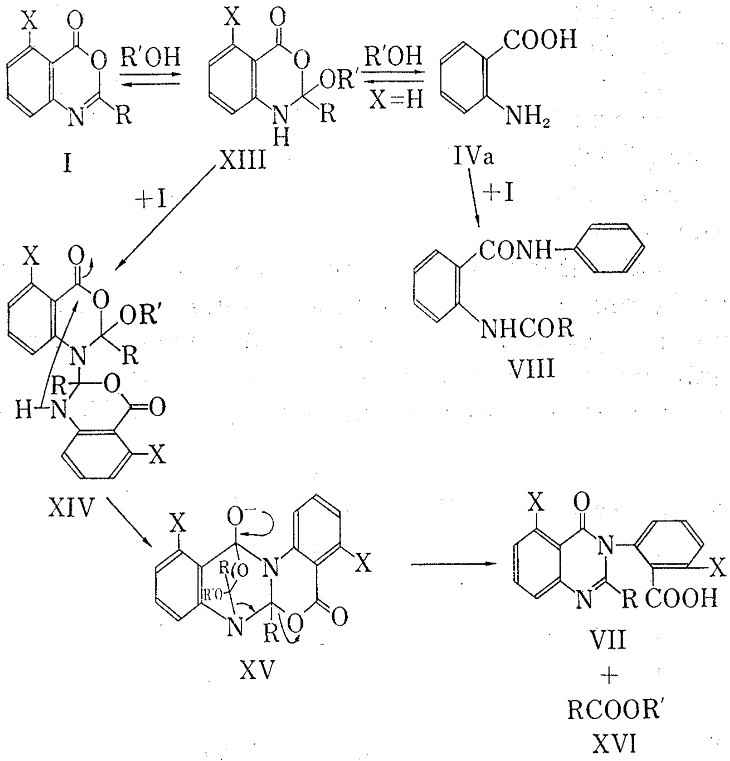

Chart 6

The route of the formation of 4-quinazolone (VII) from benzoxazine (I) consists of the nucleophilic attack by the solvent molecule to form an intermediate (XIII), with subsequent addition of the NH group of XIII to the C=N bond of another benzoxazine molecule affording a dimeric intermediate (XIV), which is transformed to 4-quinazolone (VII) along with elimination of a carboxylic ester (RCOOR′, XVI) by intramolecular rearrangement *via* an intermediate (XV). The fact that the treatment of diamide (VIII) under the condition of dimeric condensation did not give VII in any detectable amount or *vice versa*, may support this proposed mechanism.

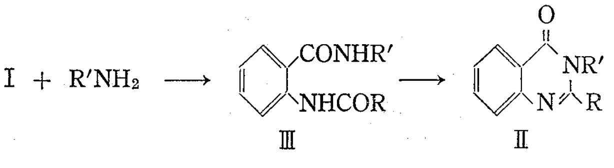

Chart 7

The route of the formation of diamide (VIII) remained ambiguous because none of the elimination product derived from the substituent at position 2 has been identified. But the mechanism given in Chart 6, in which the intermediate (XIII) is decomposed with ethanol to IVa6) and the reaction of IVa with benzoxazine (I) affords VIII, is a probable one. Retar-

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6) *a*) R.M. Roberts, *J. Am. Chem. Soc.*, **71**, 3849 (1949); *b*) R.M. Roberts, *ibid.*, **72**, 3603 (1950); *c*) R.M. Roberts and R.H. De Wolfe, *ibid.*, **73**, 2277 (1951); *d*) R.M. Roberts and R.H. De Wolfe, *ibid.*, **76**, 2411 (1954).

dation of both VII and VIII by a bulky substituent at position 2 may be explained by this mechanism without any contradiction.

The reason that 2-phenyl- or 2-styryl-benzoxazine (Ik or Il) did not afford 4-quinazolones, might be that a phenyl or styryl group at position 2 makes the C=N bond less polarized preventing the nucleophilic attack of the solvent molecule.

These considerations show that benzoxazine with an alkyl substituent at position 2 is susceptible to nucleophilic attack at position 2 rather than at position 4. From this standpoint, the pathway of the well-known reaction between benzoxazine (I) and primary amine should be reexamined. The widely accepted route of this reaction is the one shown in Chart 7.[3] This mechanism requires the nucleophilic attack of amine at position 4 of benzoxazine (I) as the first step. The resultant diamide (III) needs a drastic condition to afford the corresponding 4-quinazolone by intramolecular dehydration. The present work suggests that initial attack of a primary amine at position 2 with subsequent ring-opening to carboxylic acid (XVII) followed by recyclization to give 4-quinazolone, may be a more probable route of this reaction (Chart 8).[7]

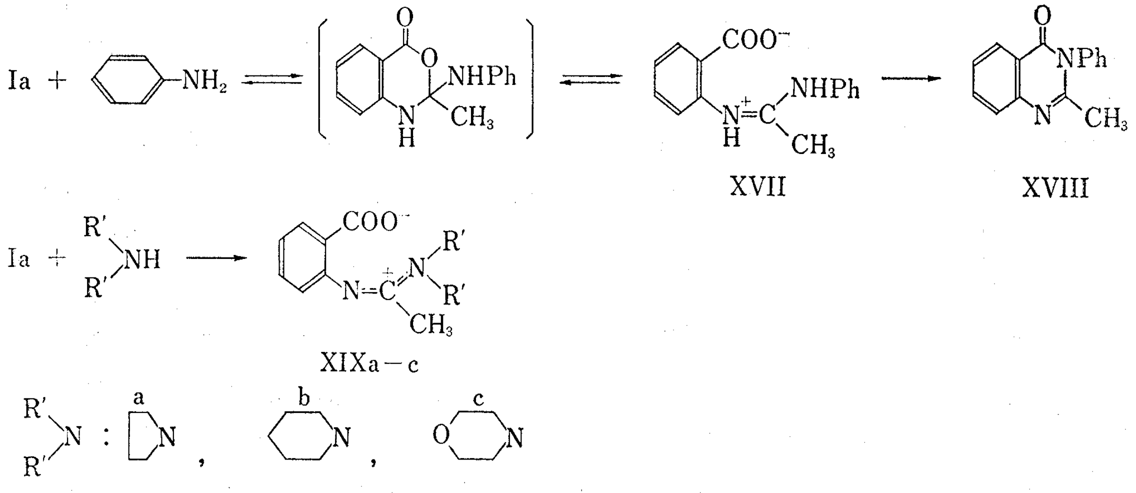

Chart 8

To obtain further evidence for this mechanism, the reaction of benzoxazine (Ia) with aniline was investigated. The solution of Ia and aniline in benzene was allowed to stand at room temperature for 15—60 minutes. White crystalline powder precipitated and its IR spectrum in Nujol showed the presence of a carboxylate structure. Benzoxazine carbonyl or amide carbonyl did not appear in the spectrum. The NMR spectrum in $CDCl_3$ showed two signals of the CH_3 group, the former of which coincided with that of the CH_3 group of benzoxazine (Ia). The IR spectrum of the crystalline powder in the same solvent showed two carbonyl absorptions, carboxylate ($1590\ cm^{-1}$) and benzoxazine ($1760\ cm^{-1}$). This evidence leads to the conclusion that the crystalline powder has the structure XVII in solid state and exists as an equilibrium mixture of XVII and Ia in $CDCl_3$ solution. Also the crystalline powder was converted quantitatively to 4-quinazolone (XVIII) at room temperature within 48 hr. This reaction pathway was further confirmed by the reaction of Ia with secondary amines, *i.e.*, pyrrolidine, piperidine and morpholine. Since these amines have only

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7) We presented this opinion at 6th Congress of Heterocyclic Chemistry, November, 1973, Nagoya, Japan. Recently, Errede *et al.* reported on the pathway of the 4-quinazolone formation in the reaction of acylanthranil with aniline. Their conclusion was entirely agreed with our opinion. See, *a*) L.A. Errede, J.J. McBrady, and H.T. Oien, *J. Org. Chem.*, **41**, 1763 (1976); *b*) L.A. Errede, J.J. McBrady, and H.T. Oien, *ibid.*, **41**, 1765 (1976); *c*) L.A. Errede, H.T. Oien, and D.R. Yarian, *ibid.*, **42**, 12 (1977); *d*) L.A. Errede, J.J. McBrady and H.T. Oien, *ibid.*, **42**, 656 (1977).

one proton on nitrogen, the corresponding intermediates could not be cyclized to 4-quinazolone and were isolated. The results of the analysis of the intermediates revealed that they had amidine structures (XIXa—c), ruling out diamide structures. These facts show that the formation of 4-quinazolone from benzoxazine with amine proceeds at least mainly *via* an amidine intermediate rather than *via* a diamide as formerly thought.

Experimental

All melting points are uncorrected. IR spectra were obtained with a Hitachi 215 spectrophotometer. NMR spectra were recorded on a Varian T-60 spectrometer using tetramethylsilane (TMS) as an internal standard.

Materials——a) 6-Chloro-N-acylanthranilic acids were prepared by the acylation of methyl anthranilates with corresponding acylchlorides in pyridine, followed by the hydrolysis of ester moiety with NaOH in aqueous EtOH. N-Acetyl-6-fluoroanthranilic acid was obtained by the oxidation of 3-fluoro-2-methylacetanilide[8] with $KMnO_4$. These are listed in Table II. 6-Chloro-N-benzoylanthranilic acid, 6-chloro-N-cinnamoylanthranilic acid and 6-chloro-N-phenylacetylanthranilic acid were prepared in the similar manner described previously.[9] N-Isobutyroyl-[10] and N-pivaloylanthranilic acid[11] were prepared by the known method.

TABLE II. 6-Halogeno-N-acylanthranilic Acid

Acyl	Halogen	mp (°C)	Formula	Analysis Calcd. C	Calcd. H	Found C	Found H
CH_3CO	F	199—201	$C_9H_8FNO_3$	54.83	3.49	54.86	4.09
$CH_3\diagdown$ CHCO $CH_3\diagup$	Cl	149—150	$C_{11}H_{12}ClNO_3$	54.67	5.01	54.31	5.02
$CH_3\diagdown$ CH_3-C-CO $CH_3\diagup$	Cl	148—149	$C_{12}H_{14}ClNO_3$	56.37	5.52	56.20	5.35
$CH_3(CH_2)_6CO$	Cl	131—133	$C_{15}H_{20}ClNO_3$	60.50	6.77	60.26	6.83

b) 2-Substituted 4-oxo-3,1-benzoxazines, Ia,[12] Ib,[13] Id,[12] Ie[13] and If[10] were prepared by the known method. Ii, Ik, Il and Im were prepared by the dehydration of the corresponding N-acylanthranilic acid with acetic anhydride in the similar manner described previously.[9] Ic, Ig, Ih, and Ij were newly prepared in this paper from corresponding N-acylanthranilic acids and showed in Table III.

TABLE III. New 2-Substituted 4-Oxo-3,1-benzoxazines

Comp. No.	Yield (%)	IR ν_{max} cm^{-1} (C=O)	NMR (δ ppm) of substituent at position 2 (in $CDCl_3$)
Ic	87	1760	2.43 (3H, singlet)
Ig	37	1765	1.35 (6H, doublet) 2.90 (1H, multiplet)
Ih	96	1760	1.50 (9H, singlet)
Ij	92	1760	0.90 (3H, triplet) *ca.* 1.40 (10H, multiplet) 2.71 (2H, triplet)

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[8] G. Lock, *Chem. Ber.*, **69**, 2253 (1936).

[9] H. Asakawa, Y. Fukushima, E. Imamiya, and Y. Kawamatsu, *Chem. Pharm. Bull.* (Tokyo), **27**, 522 (1979).

[10] R. Andrisano and A. Chiesi, *Ateneo Parmense*, **32**, 671 (1961) [*C.A.*, **58**, 3428 (1963)].

[11] F. Piozzi, M. Dubini, and M. Cecere, *Gazz. Chim. Ital.*, **89**, 2342 (1959).

[12] D.T. Zentmyer and E.C. Wagner, *J. Org. Chem.*, **17**, 967 (1949).

[13] S. Somasekhara, V.S. Dighe, and S.L. Mukhevjee, *Curr. Sci.*, **35**, 594 (1966).

3-(2-Carboxy-3-chlorophenyl)-5-chloro-2-methyl-4-quinazolone (VIIb)——a) A solution of benzoxazine (Ia, 3.2 g) and 6-chloroanthranilic acid (IVb, 3.4 g) in EtOH (10 ml) was refluxed for 2 hr, concentrated *in vacuo* to remove EtOH and the residue was triturated with ether to solidify. The solid (2 g) was recrystallized from EtOH to give colorless prisms. mp 273—275°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1720 (COOH), 1700 (C=O). NMR (in d_6-DMSO) δ ppm: 2.14 (3H, CH_3, s), 7.5—7.8 (6H, arom. H, m). *Anal.* Calcd. for $C_{16}H_{10}Cl_2N_2O_3$: C, 55.04; H, 2.87; N, 8.02. Found: C, 55.17; H, 2.71; N, 8.07.

b) Benzoxazine (Ib, 1 g) and anthranilic acid (VIa, 0.7 g) were treated as above to give colorless prisms (0.5 g), which were identical with the above sample (VIIb) on mixed melting point test and spectral comparison.

c) A solution of 6-chloroanthranilic acid (IVb, 3 g) and acetoiminoester hydrochloride (2.4 g) in EtOH (10 ml) was refluxed for 1 hr and concentrated *in vacuo* to remove EtOH. The residue was triturated with water to solidify. The solid (2.5 g, 81%) was recrystallized from EtOH to give colorless prisms, which were identical with above samples (VIIb).

Dimeric Condensation of Ia——A solution of Ia (900 mg) in MeOH (10 ml) was refluxed for 8 hr and concentrated *in vacuo* to remove MeOH. The residue was triturated with ether to solidify. The solid (640 mg) was chromatographed on silica gel using $CHCl_3$–acetic acid–ether (500:1:30 v/v) as solvent. Evaporation of the first eluate afforded 150 mg (18%) of VIIIa. mp 225—226°[14] (from EtOH). MS *m/e*: 298 (M$^+$). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1690 (COOH), 1660, 1530 (–CONH–). NMR (in d_6-DMSO) δ ppm: 2.10 (3H, CH_3, s), 7.05—8.30 (8H, arom. H), 12.47, 13.87 (1H each, NH, COOH). *Anal.* Calcd. for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.33; H, 4.62; N, 9.41.

The second eluate with $CHCl_3$–acetic acid–MeOH (500:1:50 v/v) was evaporated to afford 480 mg (58%) of VIIa. mp 249—250°.[14] MS *m/e*: 280 (M$^+$). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1690 (COOH, C=O). NMR (in d_6-DMSO) δ ppm: 2.15 (3H, CH_3, s), 7.4—8.3 (8H, arom. H). *Anal.* Calcd. for $C_{16}H_{12}N_2O_3$: C, 68.57; H, 4.32; N, 9.99. Found: C, 68.60; H, 4.15; N, 10.11.

Dimeric Condensation of Ib——A solution of Ia (1.00 g) in EtOH (10 ml) was refluxed for 2 hr and concentrated to remove EtOH. The residue was triturated with ether to afford 0.63 g (70%) of VIIb. When MeOH was used as solvent almost the same result was obtained.

Dimeric Condensation of Ic——A solution of Ic (2.5 g) in EtOH was refluxed for 40 hr and concentrated to remove EtOH. The residue was triturated with ether to solidify. The solid (1.2 g, 50%) was recrystallized from EtOH to afford VIIc. mp 237—238° (dec.). MS *m/e*: 316 (M$^+$). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1720 (COOH), 1695 (C=O). NMR (in $CDCl_3$) δ ppm: 2.00 (3H, CH_3, s), 7.0—7.8 (6H, arom. H, m). *Anal.* Calcd. for $C_{16}H_{10}F_2N_2O_3$: C, 60.76; H, 3.19; N, 8.86. Found: C, 60.63; H, 3.13; N, 8.53.

Dimeric Condensation of Id——A solution of Id (1.00 g) in MeOH (10 ml) was refluxed for 8 hr and concentrated *in vacuo* to remove MeOH. The residue was dissolved in 10% $NaHCO_3$ and the solution was washed with ether, acidified with 2 N HCl and extracted with $CHCl_3$. The $CHCl_3$ layer was evaporated to afford 0.65 g of solid, which was chromatographed on silica gel (100 g).

The first eluate with $CHCl_3$–acetic acid–ether (500:1:20 v/v) was 325 mg of VIIId. mp 208° (from EtOH). MS *m/e*: 312 (M$^+$). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1690 (COOH), 1650, 1530 (CONH). NMR (in d_6-DMSO) δ ppm: 1.10 (3H, CH_3, t), 2.35 (2H, CH_2, q), 7.1—8.3 (8H, arom. H). 12.60, 12.97 (1H each, NH, COOH). *Anal.* Calcd. for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.16; N, 8.97. Found: C, 65.01; H, 5.02; N, 8.80.

The second eluate with $CHCl_3$–acetic acid–MeOH (500:1:50 v/v) was 310 mg of VIId. mp 229—230° (from EtOH). MS *m/e*: 294 (M$^+$). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1710 (COOH), 1660 (C=O). NMR (in d_6-DMSO) δ ppm: 1.13 (3H, CH_3, t), 2.30 (2H, CH_2, q), 7.3—8.2 (8H, arom. H). *Anal.* Calcd. for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 68.87; H, 4.72; N, 9.23.

Dimeric Condensation of Ie——A solution of Ie (1.00 g) in EtOH (10 ml) was refluxed for 5 hr and treated as described above in the case of Ib to afford 560 mg of VIIe. mp 250—251°. MS *m/e*: 362 (M$^+$). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1720 (COOH, C=O). NMR (in d_6-DMSO) δ ppm: 1.17 (3H, CH_3, t), 2.47 (2H, CH_2, q), 7.4—7.8 (6H, arom. H). *Anal.* Calcd. for $C_{17}H_{12}Cl_2N_2O_3$: C, 56.22; H, 3.33; N, 7.71. Found: C, 55.74; H, 2.93; N, 7.70.

Dimeric Condensation of Ig——A solution of Ig (0.70 g) in EtOH (7 ml) was refluxed for 10 hr and treated as described above in the case of Ib to afford 270 mg of VIIg. mp 281—283° (dec.). MS *m/e*: 376 (M$^+$). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1720 (COOH, C=O). NMR (in d_6-DMSO) δ ppm: 1.10 (3H, CH_3, d), 1.33 (3H, CH_3, d), 7.4—7.9 (6H, arom. H). *Anal.* Calcd. for $C_{18}H_{14}Cl_2N_2O_3$: C, 57.31; H, 3.74; N, 7.43. Found: C, 56.83; H, 3.57; N, 7.58.

Dimeric Condensation of Ij——A solution of Ij (5 g) in EtOH (50 ml) was refluxed for 7 hr and concentrated *in vacuo* to remove EtOH. The residue was dissolved in 10% $NaHCO_3$ and the solution was extracted with ether. The water layer was acidified to afford 2.5 g of VIIj. mp 121—122° (from aqueous EtOH). MS *m/e*: 432 (M$^+$). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1710 (COOH, C=O). NMR (in $CDCl_3$) δ ppm: 0.91 (3H,

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14) Z. Ecsery *et al.* reported that the melting points of VIIIa and VIIa were 226—227° and 241—242°, respectively. See reference 4).

CH_3, t), *ca.* 1.1 (10H, $-(CH_2)_5-$), 2.5 (2H, $-CH_2-$), 7.1—7.7 (6H, arom. H). *Anal.* Calcd. for $C_{22}H_{22}Cl_2N_2O_3 \cdot H_2O$: C, 58.55; H, 5.36; N, 6.21. Found: C, 58.56; H, 5.16; N, 6.27.

Ether extract was evaporated to afford 0.4 g of oil, which was identical with ethyl octanoate on comparison of IR and NMR spectra.

Dimeric Condensation of Im——A solution of Im (0.50 g) in EtOH (5 ml) was refluxed for 30 hr and treated as usual to afford 130 mg of VIIm. mp 241—242° (from aqueous EtOH). MS *m/e*: 424 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1730 (COOH), 1695 (C=O). NMR (in d_6-DMSO) δ ppm: 3.87 (2H, CH_2, q), 6.5—7.9 (11H, arom. H). *Anal.* Calcd. for $C_{22}H_{14}Cl_2N_2O_3$: C, 62.14; H, 3.32; N, 6.59. Found: C, 61.95; H, 3.02; N, 6.39.

Reaction of Ia with Aniline——A solution of Ia (400 mg) and aniline (230 mg) in benzene (15 ml) was allowed to stand for 1 hr with stirring to afford crystalline precipitates (470 mg, 75%). IR ν_{max}^{Nujol} cm^{-1}: 1610, 1590 (carboxylate). No absorption was observed at 1760 cm^{-1}, however, it appeared when the spectrum was obtained in $CDCl_3$. NMR showed the signals at δ 2.20 and 2.47 in $CDCl_3$ and at δ 2.10 and 2.40 in d_6-DMSO. After storage in solid state for 24 hr a new signal appeared in the NMR spectrum of this substance at δ 2.25 in $CDCl_3$ and at δ 2.13 in d_6-DMSO. This substance was completely converted to 2-methyl-3-phenyl-4-quinazolone (XVIII) by the storage in the solid state for 48 hr. mp 146—147°.[15] MS *m/e*: 236 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1685 (C=O). NMR (in d_6-DMSO) δ ppm: 2.13 (3H, CH_3, s), 7.3—8.2 (9H, arom. H). *Anal.* Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.87. Found: C, 76.44; H, 4.96; N, 11.66.

Reaction of Ia with Morpholine——To a solution of Ia (0.80 g) in benzene (3 ml), morpholine (0.43 g) was added. After addition of petroleum ether (2 ml) to the mixture, oily substance was separated. On cooling in a refrigerator for 3 days it solidified to afford XIXc (0.75 g, 59%). mp 150—151°. MS *m/e*: 248 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1700, 1620. NMR (in d_6-DMSO) δ ppm: 2.33 (3H, CH_3, s), *ca.* 3.6 (8H, morpholine, m), 7.2—7.6 (4H, arom. H, m). *Anal.* Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.82; H, 6.51; N, 11.14.

Reaction of Ia with Pyrrolidine——To a solution of Ia (1.6 g) in benzene (10 ml), pyrrolidine (0.71 g) was added. A small amount of petroleum ether was added to the mixture under stirring to afford XIXa (0.95 g, 41%). mp 164—165°. MS *m/e*: 232 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1600, 1580 (carboxylate). NMR (in d_6-DMSO) δ ppm: *ca.* 2.0 (4H, $-CH_2-CH_2-$, m), 2.33 (3H, CH_3, s), *ca.* 3.6 (4H, CH_2NCH_2-, m), 6.9—8.1 (4H, arom. H, m). *Anal.* Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.09. Found: C, 67.00; H, 6.72; N, 11.92.

Reaction of Ia with Piperidine——To a solution of Ia (8.0 g) in benzene–petroleum ether (3: 5, 80 ml), piperidine (4.2 g) was added. After addition of petroleum ether (50 ml), XIXb was precipitated (9.0 g, 71%). mp 90—92°. MS *m/e*: 246 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1580 (carboxylate). NMR (in d_6-DMSO) δ ppm: 1.67 (6H, $-(CH_2)_3-$, m), 2.20 (3H, CH_3, s), 3.63 (4H, $-CH_2NCH_2-$ m), 6.8—8.1 (4H, arom. H, m). *Anal.* Calcd. for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.03; H, 7.21; N, 11.31.

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