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INTRAMOLECULAR REARRANGEMENT—IV.[1]

INTRAMOLECULAR ALKYL REARRANGEMENTS AND TAUTOMERISM OF QUINAZOLINONE DERIVATIVES[2]

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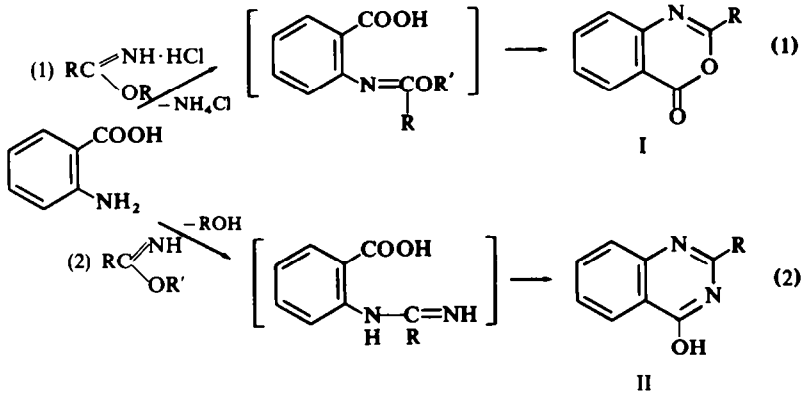
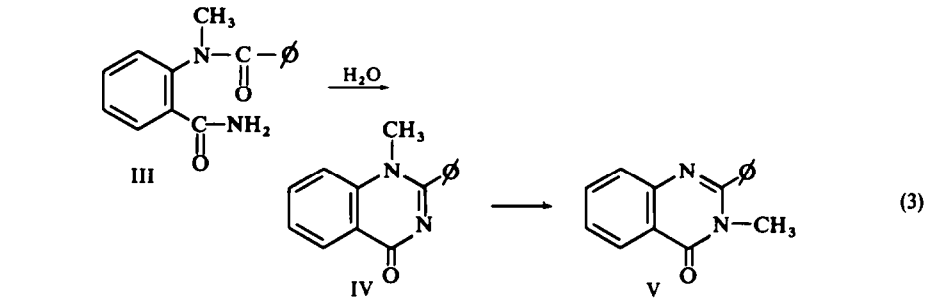
Abstract—The structure of a condensation product of anthranilic acid with ethyl benzimidate was determined on the basis of the comparison of its NMR, IR, UV data and elemental analyses with those of model compounds. The IR, UV and NMR spectra show that the most stable tautomer among three possible structures is 2-phenyl-4(3*H*)-quinazolinone. This conclusion is supported by the fact that the Me group of 1-methyl-2-phenyl-4(1*H*)-quinazolinone rearranges intramolecularly to give 3-methyl-2-phenyl-4(3*H*)-quinazolinone when the former is heated at elevated temperatures.

THE condensation products obtained by the interaction of anthranilic acid with alkyl imidate[3] and its hydrochloride[4] have been reported to be a 4-quinazolinol (II) and benzoxazinone derivatives (I), respectively.



The present paper deals with the intramolecular alkyl rearrangement of 1-methyl-2-phenyl-4(1*H*)-quinazolinone (IV) to 3-methyl-2-phenyl-4(3*H*)-quinazolinone (V) and the structural determination of tautomers (II, VI, VII) obtained in the reaction of anthranilic acid with alkyl imidate. Pakrashi and Bhattacharyya,[5] recently reported that quinazolone alkaloids such as glycorine exist in equilibrium form.

In the structure VI, the >C=N— double bond is located at a β,γ-unconjugated position to the CO group, and the latter is stabilized by amide-resonance. The structure II proposed by Ried *et al.*[3] can be considered as an enol-form of the structure VI, and it is stabilized by aromatization. The third structure VII was postulated by T. Shono *et al.*[7] and the >C=N— double bond is located at an α,β-conjugated position to the CO group.



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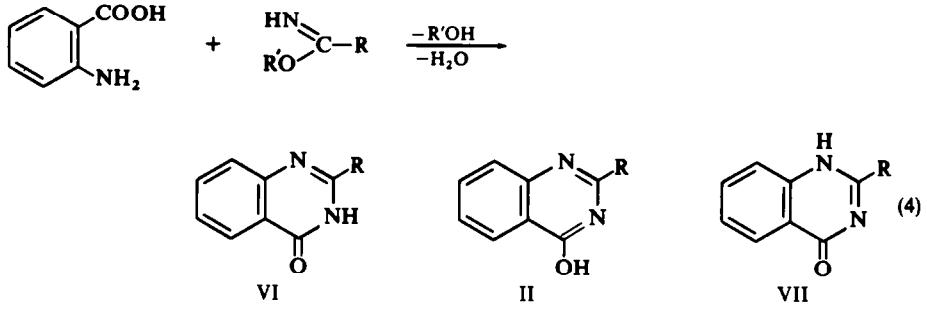

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Among three tautomers which may exist as the condensation product of anthranilic acid with ethyl benzimidate, it is reasonably presumed that the most stable one is 2-phenyl-4(3*H*)-quinazolinone, since it is stabilized by amide resonance. In order to ascertain the structure by IR, UV and NMR spectral evidence, closely related model compounds are prepared, in which the $\rangle C{=}N-$ double bond is fixed at either an α,β- or β,γ-position to the CO group in the quinazolinone ring systems.

The model compounds are prepared according to the known methods, and the physical properties elemental analyses, and IR and UV data are summarized in Table 1. The CO bands in the IR spectra of the product and the model compounds are shown in Fig. 1 and the UV spectra are shown in Figs 2 and 3. These data are summarized in Table 2. It was found that 3-methyl-2-phenyl-4(3*H*)-quinazolinone (V) was obtained by heating the corresponding 1-Me derivative IV at 260° as shown in Eq. (3). The reaction path was followed by measuring UV absorption bands at 308 mμ and 275 mμ in the temperature range of 234° to 305°. The results are summarized in Fig. 4. It is clear from Fig. 4 that 1-methyl-2-phenyl-4(1*H*)-quinazolinone (IV) was obtained quantitatively by heating 2'-carbamoyl-N-methylbenzanilide (III) at 234° for 30 min. The absorption maximum at 308 mμ of 1-methyl-2-phenyl-4(1*H*)-quinazolinone (IV) gradually decreases at higher temperatures and a new absorption at 278 mμ of 3-methyl-2-phenyl-4(3*H*)-quinazolinone (V) appears. The spectrum of the final product at 305° is identical with that of an authentic sample of 3-methyl-2-phenyl-4(3*H*)-quinazolinone (V). It is, therefore presumed that 1-methyl-2-phenyl-4(1*H*)-quinazolinone (IV) is kinetically controlled product and an intramolecular 1,3-alkyl shift takes place at elevated temperatures to form a thermodynamically more stable product, 3-methyl-2-phenyl-4(3*H*)-quinazolinone (V).

TABLE 1. PHYSICAL PROPERTIES, IR AND UV DATA OF 4(1*H*)-QUINAZOLINONE AND 4(3*H*)-QUINAZOLINONE DERIVATIVES

NO	Compound	m.p.	IR[a]	UV[b]		Elemental analyses		
			$\nu_{C=O}$ (cm^{-1})	λ^{max} (mμ)	log ε	C (%)	H (%)	N (%)
VIII	2-Phenyl-4(3*H*)-quinazolinone	231–232°	1667 (s)	233	4·42	calc. 75·85	4·57	12·81
				291	4·18	found 75·68	4·51	12·61
XII	2,3-Diphenyl-4(3*H*)-quinazolinone	177°	1679 (s)	229	4·52	calc. 80·22	4·79	9·45
				279	4·20	found 80·54	4·70	9·40
V	3-Methyl-2-phenyl-4(3*H*)-quinazolinone	132·5–3·5°	1676 (s)	228	4·46	calc. 76·07	5·12	12·00
				278	4·02	found 76·37	5·01	11·86
				306 (sh)[c]	3·80			
				318 (sh)	3·60			
XI	1,2-Diphenyl-4(1*H*)-quinazolinone	261°	1646 (s)	236	4·40	calc. 80·34	4·77	9·70
				306	4·05	found 80·55	4·70	9·39
				316 (sh)	3·98			
IV	1-Methyl-2-phenyl-4(1*H*)-quinazolinone	165–166°	1638 (s)	240	4·41	calc. 76·38	5·20	11·81
				280 (sh)	3·80	found 76·27	5·01	11·86
				308	4·00			
				318 (sh)	3·95			

[a] IR absorption taken by KBr disc.

[b] UV absorption maxima measured in 99·5% ethanol.

[c] (s): strong, (sh): shoulder.

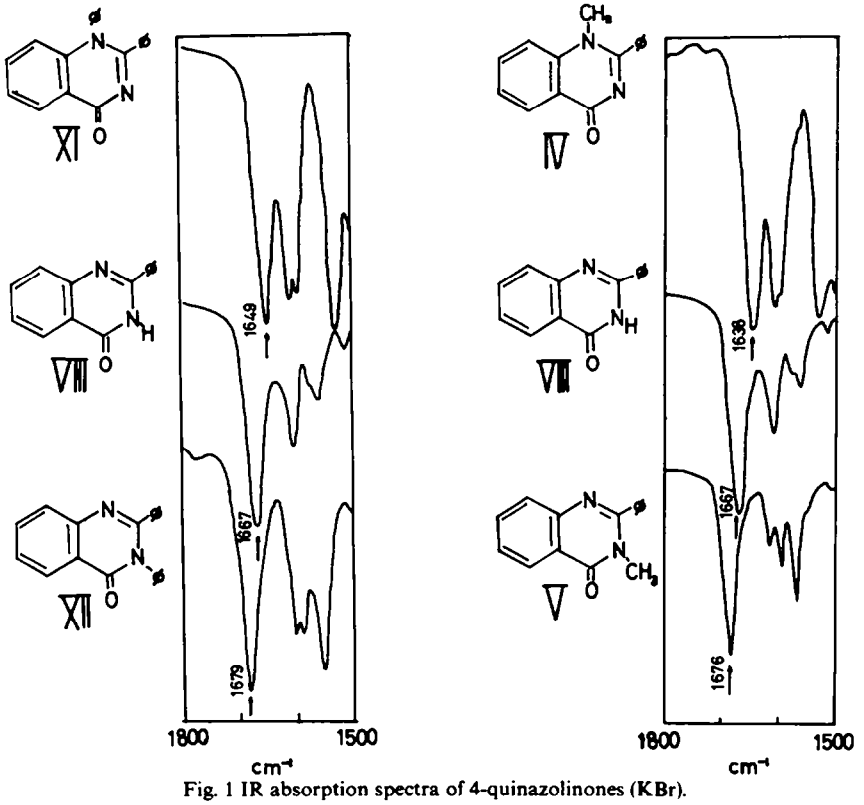


Fig. 1 IR absorption spectra of 4-quinazolinones (KBr).

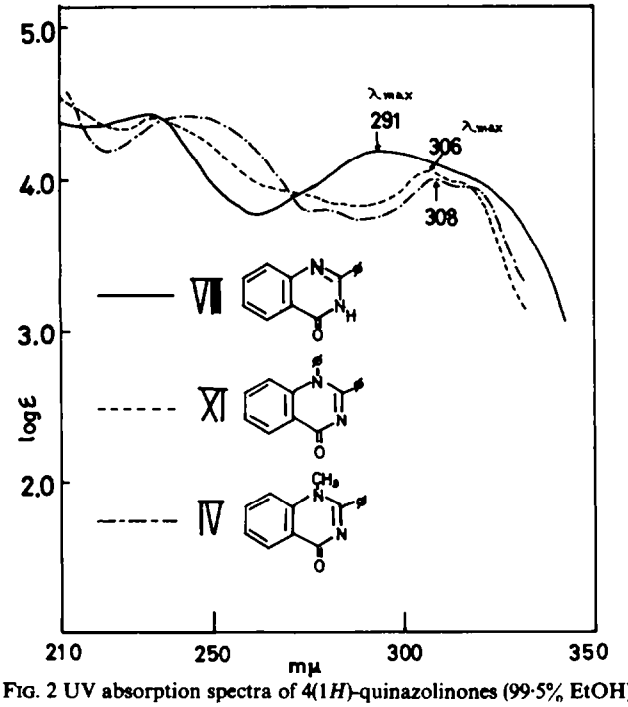
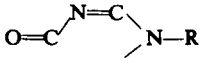
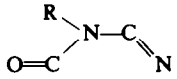


FIG. 2 UV absorption spectra of 4(1*H*)-quinazolinones (99·5% EtOH).

TABLE 2. IR ABSORPTION AND UV ABSORPTION SPECTRA OF 4-QUINAZOLINONES

Structure	R	IR $\nu_{C=O}$, cm^{-1}		UV λ^{max}, mμ	
			$\Delta\nu$		$\Delta\lambda^{max}$
	CH_3	1638	(−29)	308	(+17)
	ϕ	1649	(−18)	306	(+15)
Product	H	1667	(0)	291	(0)
	CH_3	1676	(+9)	278	(−13)
	ϕ	1679	(+12)	279	(−14)

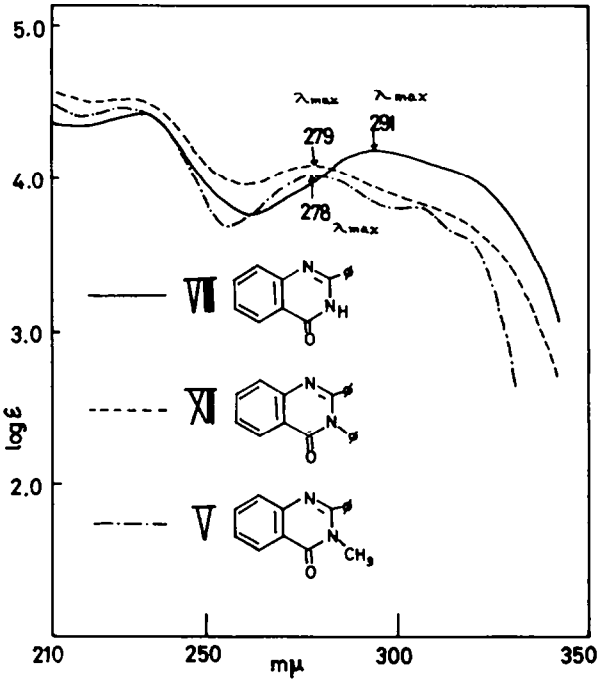


FIG. 3 UV absorption spectra of 4(3*H*)-quinazolinones (99·5% ErOH).

The intramolecular alkyl rearrangement of this type was recently reported by Paudler[6] in the N-methylation of *s*-triazolo[4,3-a] pyridine, whereby the N-2 methiodides could be thermally rearranged to the N-1 methiodides. Model compounds having CO group conjugated with a $\rangle C{=}N-$ bond have CO absorption bands at low wave numbers (1649 cm^{-1} or 1639 cm^{-1}), whereas those having a β,γ-unsaturated CO group show bands at 1679 cm^{-1} or 1676 cm^{-1}. The difference of these compounds is about 30 cm^{-1}. On the other hand, the CO band of the compound in question appears at 1667 cm^{-1}, which is more close to those of the β,γ-unsaturated compounds. From the results, it is reasonably presumed that the product is a β,γ-unsaturated 4(3*H*)-quinazolinone.

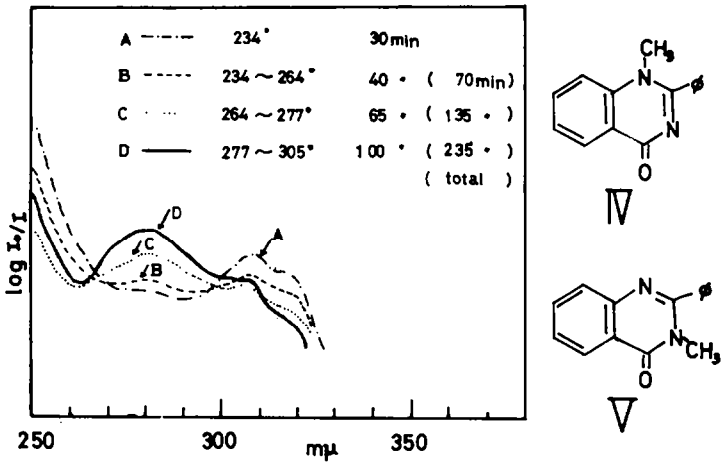


FIG. 4 Rearrangement of 1-methyl-2-phenyl-4(1*H*)-quinazolinone (99·5% EtOH).

In this case the CO band of the compound is lower than those of the model compounds by about 10 cm^{-1} because of the amide resonance. It is supported by the fact that ε-caprolactam has a CO band at 1668 cm^{-1} which is lower than that of N-Me caprolactam (1676 cm^{-1}) by about 8–10 cm^{-1}. This phenomenon may be well explained in terms of the amide resonance and it is clear that β,γ-unconjugated 2-phenyl-4(3*H*)- quinazolinone is stabilized by the amide resonance. It is reasonable to conclude therefore that the product is 2-phenyl-4(3*H*)-quinazolinone. This conclusion is also supported by the comparison of UV spectra. Figs 2 and 3 show that the spectrum of the compound resembles those of the β,γ-unsaturated 4(3*H*)-quinazolinone derivatives and is quite different from those of the α,β-unsaturated 4(1*H*)-quinazolinone derivatives. The λ_{max} of the product, however, is higher than those of the β,γ-unsaturated compounds by about 13 mμ. This phenomenon is explained in terms of the resonance stabilization as indicated in the IR spectra. An NMR spectrum of the 4(3*H*)-quinazolinone derivative (VI) in DMSO is shown in Fig. 5. The signals centered around 8·10 ppm are due to four benzene ring protons. The low-field shift of these signals is due to fused aromatic rings. The structure VI rather than the conjugated keto form VII or enol form II is supported by the following observations. In the case of 4-quinazolinone derivatives, Pakrashi *et al.*[5] reported that the signals of the proton at a peri-position to the CO group appeared at 8·1–8·3 ppm. Fig. 5 shows NMR spectra of the product and the related model compounds. The chemical shift was found to be at 8·10–8·23 ppm, which was assigned to the proton at a peri-position to the CO group. The proton signal of the β,γ-unsaturated compound V appeared as a doublet centered at 8·10 ppm, which is higher by 0·13 ppm than in the α,β-unsaturated compound IV. The proton signal of the product appeared at 8·13 ppm and this indicates that the product is a β,γ-unsaturated compound. It is concluded on the basis of these facts that the condensation product of anthranilic acid with ethyl benzimidate has a β,γ-unsaturated 2-phenyl-4(3*H*)-quinazolinone structure, which is

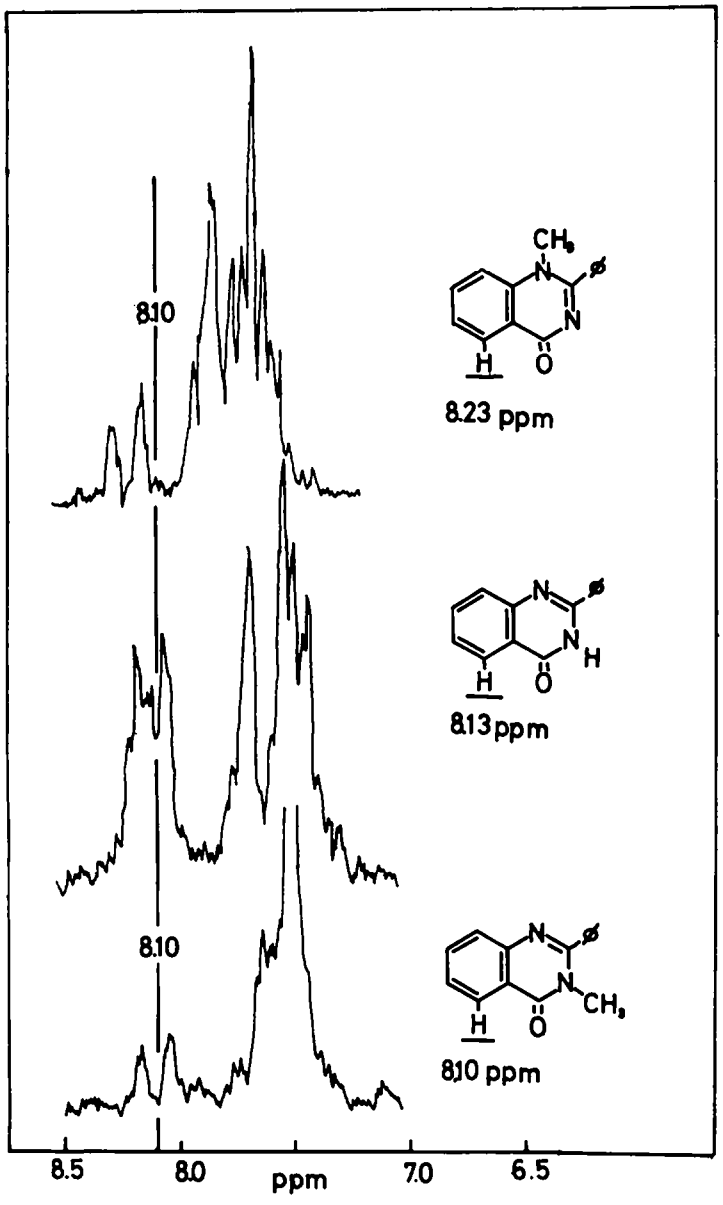
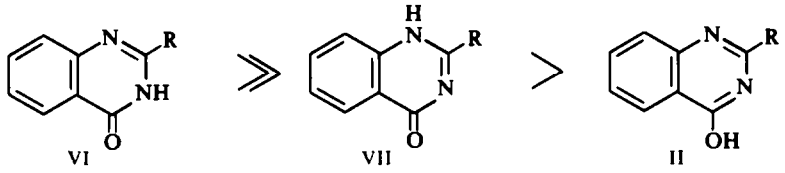


FIG. 5 NMR spectra of 4-quinazolinones (60 MC, in DMSO).

more stabilized by the amide resonance than the other two possible tautomeric structures. Furthermore, the conclusive evidence of thermodynamical stability of 4(3*H*)-quinazolinone rather than 4(1*H*)-quinazolinone was obtained by the intramolecular alkyl rearrangement of 1-methyl-2-phenyl-4(1*H*)-quinazolinone (IV), and α,β-unsaturated model compound, which is obtained by the thermal dehydration of 2′-carbamoyl-N-methylbenzanilide. On the basis of these thermal experiments together with the results of the UV, IR and NMR measurements, it is confirmed that

the condensation product of anthranilic acid with ethyl benzimidate is 2-phenyl-4(3*H*)-quinazolinone. It is concluded that the 4(3*H*)-quinazolinone structure is the most thermodynamically stable one among the three possible tautomeric structures.



EXPERIMENTAL

Ethyl benzimidate.[7] An equimolar mixture of benzonitrile and EtOH was maintained at −5° and HCl was bubbled for 1 hr. The mixture was kept for 48 hr in an ice box. The solid obtained was crushed, dispersed in ether and neutralized with K_2CO_3 aq under ice cooling. The ethereal layer was dried and distilled and the residue was further distilled in vacuum. An 82% yield of ethyl benzimidate yas obtained: b.p. 74° 2·5 mmHg, IR (oil) 1635 cm^{-1} (—C=N). (Found: C, 72·45; H, 7·39; N, 9·45. Calc. for $C_9H_{11}NO$: C, 72·84; H, 7·37; N, 9·39%).

2-*Phenyl*-4(3H)-*quinazolinone* (VII). A mixture of 1·37 g (0·01 mol) of anthranilic acid and 1·49 g (0·01 mol) of ethyl benzimidate was refluxed for 3 hr in isoamyl alcohol. The mixture was cooled to room temp, and white crystals were obtained. The product was recrystallized from EtOH, yield, 104 g (46·9%); m.p. 231–232°, IR, 1668 cm^{-1} (C=O). (Found: C, 75·85; H, 4·57; N, 12·81. Calc. for $C_{14}H_{10}N_2O$: C, 75·68; H, 4·51; N, 12·61%).

2,3-*Diphenyl*-4(3H)-*quinazolinone* (XII). A mixture of 1·12 g (0·005 mol) 2-phenyl-4*H*,3,1-benzoxazin-4-one, 1·01 g. (0·011 mol) aniline, and a catalytic amount of $ZnCl_2$ was kept at 250°. EtOAc was added to the reaction mixture and, on cooling, white crystals were deposited, which were recrystallized from EtOAc to give 1·13 g (75% yield) of XII as white crystals: m.p. 177°; IR (KBr), 1680 cm^{-1} (CO). (Found: C, 80·22; H, 4·79; N, 9·45%. Calc. for $C_{20}H_{14}N_2O$: C, 80·54; H, 4·70; N, 9·40%).

2′-(*Methylcarbamoyl*)*benzanilide* (XII). Phenyl-4*H*-3,1-benzoxazin-4-one (1·12 g) was refluxed in EtOH for 8 hr with excess $MeNH_2$. EtOH was removed and a white residue was obtained (1·19 g, 88% yield). Recrystallization from EtOH gave XII as white crystals: m.p. 160°; IR (KBr), 1662, 1647 cm^{-1} (CO). (Found: C, 70·6; H, 5·58; N, 10·89. Calc. for $C_{15}H_{14}N_2O_2$: C, 70·9; H, 5·52; N, 11·02%).

Ring closure of 2′-(*methylcarbamoyl*)*benzanilide* (XIII). (a) A 1·00 g portion of XII was kept at 200° for 2 hr. The starting material was quantitatively recovered. (b) In the presence of catalytic amount of $ZnCl_2$, 1·00 g of XII was heated at 260° for 2 hr. Crystallization of the product from ligroin gave V in a quantitative yield as white crystals: m.p. 132·5–133·5°; IR (KBr), 1676 cm^{-1} (CO). (Found: C, 76·07; H, 5·12; N, 12·00. Calc. for $C_{15}H_{12}N_2O$: C, 76·27; H, 5·01; N, 11·86%). (c) A 1·50 g portion of XIII was heated at 200° in 300 ml polyphosphoric acid for 2 hr under N_2 atm. The reaction mixture was poured into water and after neutralization with Na_2CO_3, was extracted with EtOAc. The EtOAc was removed after the soln had been dried with Na_2SO_4 and a white residue was obtained. Recrystallization from ligroin gave white crystals. The crystals were identified as 2-phenyl-4*H*-3,1-benzoxazin-4-one by comparison with an authentic sample. (d) A 370 mg portion of XII was refluxed for 2 hr in 50 ml of a mixture of two parts Ac_2O and one part pyridine. The solvent was removed and the residue was crystallized from alcohol with Norit decolorization to give 400 mg (63% yield) of 2-phenyl-4*H*-3,1-benzoxazin-4-one. (e) An 810 mg portion of XIII was refluxed in 100 ml 10% KOH aq in alcohol for 5 hr. The soln was concentrated, poured into water and neutralized with HCl. The ppt was starting material, quantitatively recovered.

N-*Phenylbenzimidoyl chloride.*[9] A 3·8 g portion of benzanilide was refluxed in 2·3 g (1·5 mol eq) $SOCl_2$ for 3 hr, and excess $SOCl_2$ was removed under reduced press. Distillation of the residue *in vacuo* gave 3·0 g (72%) of colorless liquid: b.p. 120°/2·5 mmHg. (Found: C, 72·58; H, 4·71; N, 6·46; Cl, 16·58. Calc. for $C_{13}H_{10}NCl$: C, 72·39; H, 6·46; N, 6·50; Cl, 16·47%).

Methyl o-(N-*phenylbenzimidoyloxy*)*benzoate.*[9] To an ice bath cooled soln of 0·44 g of Na metal in 30 ml alcohol, a soln of 2·8 g methyl salicylate and 2·7 g N-phenylbenzimidoyl chloride in 20 ml anhydrous ether was added. The mixture was allowed to stand at room temp overnight and the solvent was removed. The

residue was washed with water and crystallized from EtOH to give 3·4 g (82%) of white crystals; m.p. 105°; IR (KBr), 1711 cm^{-1} (CO), 1660 cm^{-1} ($\rangle C{=}N-$). (Found: C, 76·00; H, 5·34; N, 4·24. Calc. for $C_{21}H_{17}NO_3$: C, 76·13; H, 5·14; N, 4·23%).

Methyl N-benzoyl-N-phenylanthranilate.[9] A 1·5 g portion of methyl *o*-(N-phenylbenzimidoyloxy)-benzoate was added in a test tube equipped with a thermometer and the tube was placed in an oil bath at 280°. The temp reached 285° before it began to fall. The test tube was maintained in the oil bath for 3 min. The reaction mixture was cooled to room temp and EtOH was added. White ppt began to deposit. Recrystallization from EtOAc gave a rearranged product (1·14 g, 76% yield) as white crystals; m.p. 124·5°; IR, 1722, 1651 cm^{-1} (CO). (Found: C, 75·40; H, 5·31; N, 4·16. Calc. for $C_{21}H_{17}NO_3$: C, 76·13; H, 5·14; N, 4·23%).

N-Benzoyl-N-phenylanthranilic acid.[9] A 2·4 g portion of metallic Na was dissolved in 100 ml EtOH and then 20 ml water was added. Three ml of this soln, 4 ml water, and 6 ml alcohol were mixed and to this mixture was added 1 g methyl N-benzoyl-N-phenylanthranilate. After refluxing for 1 hr, the alcohol removed under the reduced press and the residue was neutralized in water with HCl. The product was recrystallized from alcohol to give white crystals.

1,2-Diphenyl-4(1H)-quinazolinone (XI).[9] A 610 mg portion of N-benzoyl-N-phenylanthranilic acid was dissolved in 5 ml $POCl_3$. The soln was refluxed for 19 hr, and excess $POCl_3$ was removed under the reduced press. The residue was dissolved in CH_2Cl_2 and NH_3 gas was bubbled for about 15 min into this soln. The mixture was allowed to stand at room temp for 1 hr. After being washed with water, the CH_2Cl_2 layer was dried over Na_2SO_4 and CH_2Cl_2 was removed. The residue was crystallized from alcohol with Norit decolorization to give white crystals; m.p. 261°; IR (KBr), 1640 cm^{-1} (CO). (Found: C, 80·34; L, 4·77; N, 9·70. Calc. for $C_{20}H_{14}N_2O$: C, 80·55; H, 4·70; N, 9·39%).

N-Methylisatoic anhydride. A 5·2 g portion of N-methylanthranilic acid was dissolved in 11·2 g (3 mol eq) of hot ethyl orthoformate. To this soln 2·24 g (1·2 mol eq) acetyl chloride was added. The soln after heating under reflux for 3 hr, deposited crystals (5·98 g; 98% yield).

o-(Methylamino)benzamide. A 3·60 g portion of N-methylisatoic anhydride was added to 50 ml water, and to this mixture 3 g (2·5 mol eq) NH_4OH was added. The mixture was heated gently on a steam bath and ethanol was added portionwise until the soln became clear. On cooling, the soln deposited 2·75 g (90%) of white crystals of *o*-(methylamino) benzamide; m.p. 155·5–156·5°; IR (KBr), 1635, 1617 cm^{-1}. (Found: C, 63·81; H, 6·65; N, 18·83. Calcd. for $C_8H_{10}N_2O$: C, 64·00; H, 6·67; N, 18·67%).

2'-Carbamoyl-N-methylbenzanilide (III). A 1·77 g portion of *o*-(methylamino) benzamide was dissolved in 25 ml pyridine. To this soln was added portionwise 1·99 g (1·2 mol eq) benzoyl chloride under cooling. After standing at room temp for several min the soln was concentrated to about 10 ml, poured into water and then extracted with EtOAc. From the EtOAc layer, 2·7 g (90%) white crystals was obtain*Id*; m.p. 135–136°; IR (KBr). 1676, 1631 cm^{-1}. (Found: C, 71·00; H, 5·66; N, 11·07. Calc. for $C_{15}H_{14}N_2O_2$: C, 70·86; N, 5·51; N, 11·02%).

Ring closure of 2'-carbamoyl-N-methylbenzanilide (III). (a) A 1·15 g portion of III was heated under N_2 in a test tube in oil bath (temp raised to 300° in 30 min and the test tube maintained at this temp for 10 min. The product was allowed to stand at room temp after EtOH had been added, and white crystals were precipitated. This product was not the expected 1-methyl-2-phenyl-4(1*H*)-quinazolinone. The IR and UV spectra and the elemental analysis were identical with those of authentic V, which was prepared by the Dimroth rearrangement of the Me group, yield, 561 mg (52·5%), m.p. 129·3–129·8°. (Found: C, 76·29; H, 5·16; N, 12·15. Calc. for $C_{15}H_{12}N_2O$: C, 76·27; H, 5·01; N, 11·86%). (b) A 200 mg portion of IV was kept at 220° for 45 min, then at 220–240° for 20 min and finally at 240° for 30 min. To this reaction mixture alcohol was added, and the soln after standing at room temp gave a white ppt. This was identified as the expected IV by means of IR and UV spectra and elemental analysis, yield, 160 mg (16%); m.p. 165–165·5°; IR (KBr), 1638 cm^{-1} (C=O). (Found: C, 76·38; H, 5·20; N, 11·81. Calc. for $C_{15}H_{12}N_2O$: C, 76·27; H, 5·01; N, 11·86%).

REFERENCES

[1] For the previous papers of this series, see M. Kurihara and N. Yoda, *Tetrahedron Letters*, 2597 (1965); *Bull. Chem. Soc. Japan* **39**, 1942 (1966); *Ibid.* **40**, 2429 (1967).

[2] Y. Hagiwara, M. Kurihara and N. Yoda, presented at the Fall Meeting of the Associated Chemical Societies, Tokyo, Japan, on November 29th (1967).

[3] W. Ried, *Chem. Ber.* **95**, 3042 (1962).

[4] F. Weygand, *Ibid.*, **95**, 2264 (1964).

[5] S. C. Pakrashi and J. Bhattacharyya, *Tetrahedron* **24**, 1 (1968); *Ibid.* **19**, 1011 (1963).
[6] W. W. Paudler and R. J. Brumbaugh, *J. Heterocyclic Chem.* **5**, 29 (1968).
[7] M. Saga, T. Shono and K. Shirra, *Kogyokagaku Zasshi* **69**, 1529 (1966).
[8] M. T. Bogert and F. P. Nahenhauer, *J. Am. Chem. Soc.* **27**, 1305 (1905).
[9] M. M. Jamison and E. E. Turner, *J. Chem. Soc.* 1954 (1937).
[10] I. M. Heilbron, *Ibid.*, **126**, 2167 (1925).