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Heterocycles Structurally Influenced by a Side Chain. I. 3-Phenacyl-2(1*H*)-quinoxalinones and 3-Phenacyl-2*H*-1,4-benzoxazin-2-ones[1]

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Seven phenacyl derivatives of 2(1*H*)-quinoxalinone and 2*H*-1,4-benzoxazin-2-one (IV and V) have been synthesized to introduce a common structural element $-CH_2-CO-$ into their 3-positions. Their structures are compared with those of the related compounds described previously. The main purpose of the present study was to see whether or not their ring double bonds ($-N=\overset{|}{C}-$) have ever been displaced onto the side chains, constituting an enamine so as to form $=CH-CO-$, the carbonyl of which is hydrogen bonded with the secondary amino group of the rings thereby formed. Consequently, existence as the enamine form, facilitated by an intramolecular hydrogen bonding, has been evidenced by IR and NMR spectral data. It is, therefore, fitting to call them by the more practical expression "3-phenacylidene-3,4-dihydro-2(1*H*)-quinoxalinone" (IVa), and so on. Hydrolysis of IV gave the corresponding 3-methyl-2-(1*H*)-quinoxalinones (VI) and benzoic acid (VII), while that of V afforded the starting substances, *o*-aminophenols (III) and benzoylpyruvic acid (VIII) which had been partially decomposed into pyruvic acid (IX) and VII.

One of the authors reported[2–7] in and after the year of 1961 that many nitrogen-containing heterocycles having a *β*-carbonyl on their side chains introduced onto the carbon adjacent to the nitrogen atom tend to isomerize so that the carbon-nitrogen double bond is displaced onto the side chain to form an *α*,*β*-unsaturated carbonyl group. Isomerization is facilitated by the resulting intramolecular hydrogen bonding[3] between the carbonyl and the secondary amino group thus newly formed.

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[2] Y. Iwanami, *Nippon Kagaku Zasshi*, **82**, 778, 780 (1961); **83**, 100, 161, 316, 590, 597 (1962).

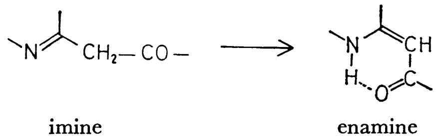
[3] Y. Iwanami, *ibid.*, **83**, 593 (1962).

[4] H. Sasaki, H. Sakata, and Y. Iwanami, *ibid.*, **85**, 704 (1964).

[5] Y. Iwanami, Y. Kenjo, K. Nishibe, M. Kajiura, and S. Isoyama, This Bulletin, **37**, 1740 (1964).

[6] Y. Iwanami, S. Isoyama, and Y. Kenjo, *ibid.*, **37**, 1945 (1964).

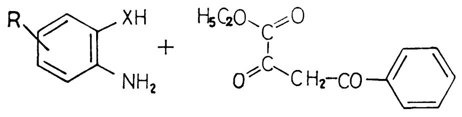
[7] Y. Iwanami, *ibid.*, **44**, 1311 (1971).



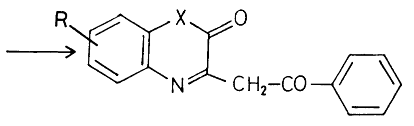
However, we recently encountered[8] an exceptional case of alkyl isoxanthopterin-6-acetates, which exist in the imine form indicating a converse predominance.

We have, therefore, extended our study to 3-phenacyl-2(1*H*)-quinoxalinones (IV) and 3-phenacyl-2*H*-1,4-benzoxazin-2-ones (V).

Condensation of ethyl benzoylpyruvates (I) with *o*-phenylenediamine (IIa), *o*-aminophenol (IIIa) and some of their derivatives (IIb, c, and IIIb—d) gave the corresponding 3-phenacyl-2(1*H*)-quinoxalinones (IVa—c) and 3-phenacyl-2*H*-1,4-benzoxazin-2-ones (Va—d). Five of the products except IVa and Va are new compounds.



IIa: R=H, X=NH
IIb: R=4-Cl, X=NH
IIc: R=Benzo[*d*], X=NH
IIIa: R=H, X=O
IIIb: R=4-CH$_3$, X=O
IIIc: R=4-Cl, X=O
IIId: R=Benzo[*c*], X=O



IVa: R=H, X=NH
IVb: R=7-Cl, X=NH
IVc: R=Benzo[*g*], X=NH
Va: R=H, X=O
Vb: R=6-CH$_3$, X=O
Vc: R=6-Cl, X=O
Vd: R=Benzo[*f*], X=O

IR spectra of these compounds were measured for KBr disks. The absorption bands of carbonyls and carbon-carbon double bonds (both in the side chains) are shown in all cases (Table 1). The results suggest that a nitrogen-carbon double bond in the ring is just visionary and the double bond has ever been displaced onto the side chain. Moreover, the carbonyl bands are not in the region 1670—1663 cm^{-1} expected[9] for an α,β-α',β'-unsaturated ketone, but in a lesser wave-number region 1623—1620 cm^{-1}. This lower frequency shift is probably accounted for an intramolecular hydrogen bonding of the carbonyl with the amino group of the ring. The secondary amino group can not occur unless the imaginary nitrogen-carbon double bond has been displaced onto the side chain. Thus, these compounds exist in the enamine form, which is attributable to the internal hydrogen bond by the analogy of a number of their related compounds.[2-7]

Table 1. IR absorption bands of the products (cm^{-1})

Compound	$\nu_{C=O}$			$\nu_{C=C}$
	Lactone	Lactam	Ketone	
IVa		1689	1622	1613
IVb		1690	1622	1613
IVc		1693	1620	1610
Va	1755		1620	1611
Vb	1755		1621	1613
Vc	1757		1623	1612
Vd	1750		1620	1613

All spectra were measured for KBr disks.

The enamine structure is further evidenced by NMR spectra determined for dimethyl sulfoxide-d_6 solutions (the solubilities of these compounds in the usual solvents are not high enough for spectroscopy). The NMR spectra of IVa and Vb are shown in Fig. 1. In the spectrum of IVa (above), no signals appear in the region between 6.91 and 0 ppm, except for those due to protons of the solvent, but a singlet appears at 6.91 ppm (δ scale). Therefore, we can conclude that IVa does not involve methylene but a methine group in its structure. Bands at lower fields are due to aromatic protons, and the carbonyl adjacent to the phenyl ring would displace the signals due to the *ortho* protons down-field giving the band at *ca.* 8.07. Consequently, the carbonyl group does not exist as an enol in IVa. The two broad signals at 12.09 and 13.88 ppm are due to amino protons. Existence of amino protons is also proper only to the enamine form. Hydrogen bonding between the carbonyl and amino groups is suggested by the lowest-field position of the amino proton signal. The structure consistent with these chemical shifts is designated as "3-phenacylidene-3,4-dihydro-2(1*H*)-quinoxalinone."

This is not exceptional to the existing forms of many other related compounds.[2-7]

Similarly, Vb showed a methine, an amino, and aromatic *ortho* (to a carbonyl) proton signal (Fig. 1, below). In this case, Vb possesses a methyl group attached to the benzoxazine ring, and the corresponding signal appears at 2.32 ppm. The relative intensity of the methine singlet represents exactly one proton when compared to three protons of another singlet due to the ring methyl group. Presence of the methine group in Vb is thus satisfactory from this quantitative point of view. The customary name of V, 3-phenacyl-2*H*-1,4-benzoxazin-2-one, is not fitting, and the most practical designation would be "3-phenacylidene-3,4-dihydro-2*H*-1,4-benzoxazin-2-one."

The NMR spectra of the other products (IVb and Va,c,d), except for that of IVc sparingly soluble in dimethyl sulfoxide-d_6, are essentially the same as those of IVa and Vb described above. The broad amino proton signals of Vc and Vd are indistinctly observed because of their insufficient solubility. The δ values of the methine, amino benzoyl *ortho* protons are listed in Table 2. The IR spectra were measured for potas-

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8) Y. Iwanami, This Bulletin, **44**, 1314 (1971).

9) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Co., London (1958), p. 132.

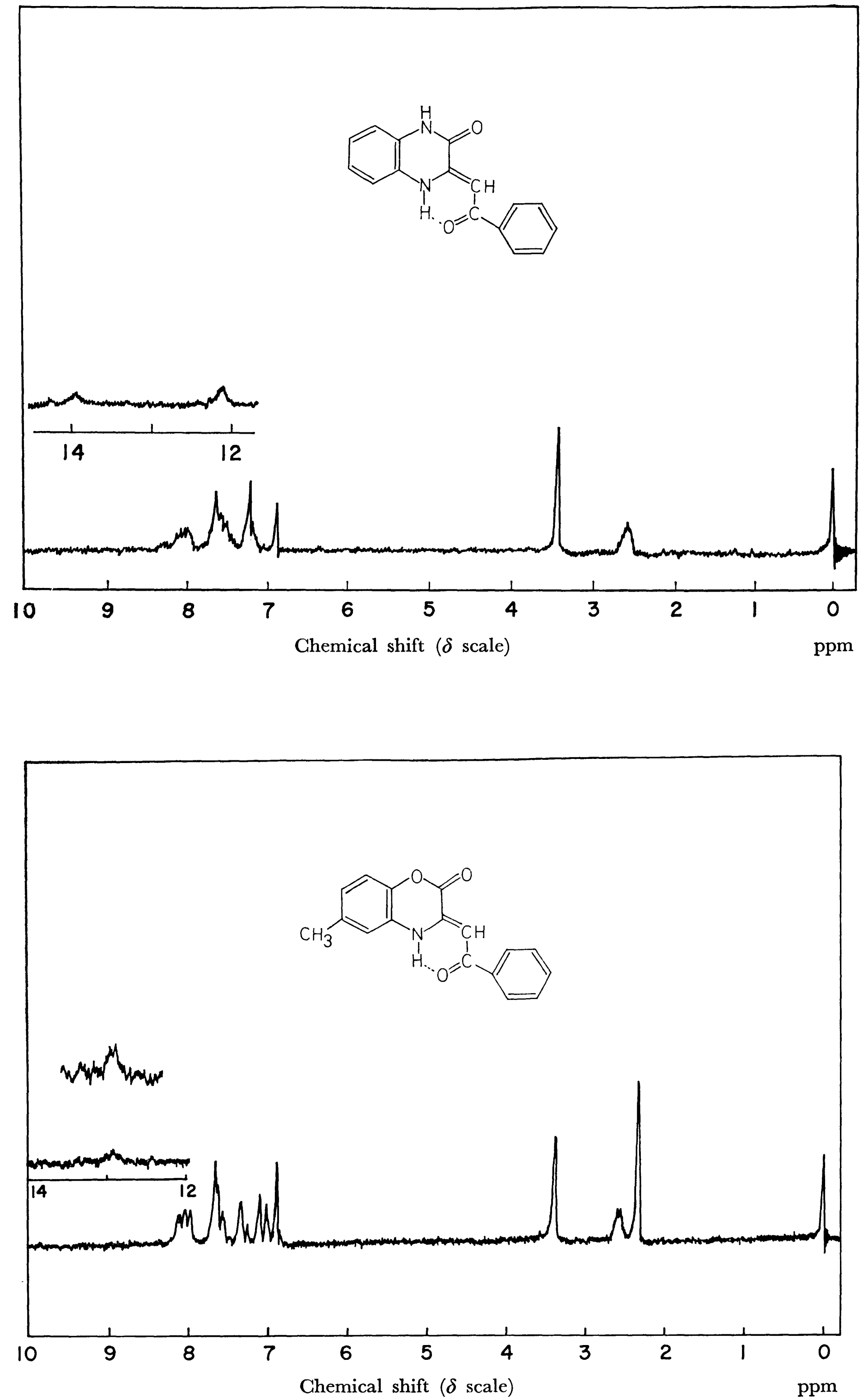

Fig. 1. NMR spectra (60 MHz) of 3-phenacylidene-3,4-dihydro-2(1*H*)-quinoxalinone (IVa) (above), and 6-methyl-3-phenacylidene-3,4-hydro-2*H*-1,4-benzoxazin-2-one (Vb) (below) in DMSO-d_6 (internal TMS).

sium bromide disks (Table 1) and the NMR spectra for dimethyl sulfoxide-d_6 solutions (Table 2). Structure in solution or crystalline state has, therefore, been confirmed to be the same (the enamine form) by both spectroscopies.

Profiles of the NMR spectra, measured for trifluoroacetic acid solutions, were greatly different. Three or four singlets appeared in the region 6.98—4.39 ppm (Table 2). This probably accounted for the tautomerism as follows:

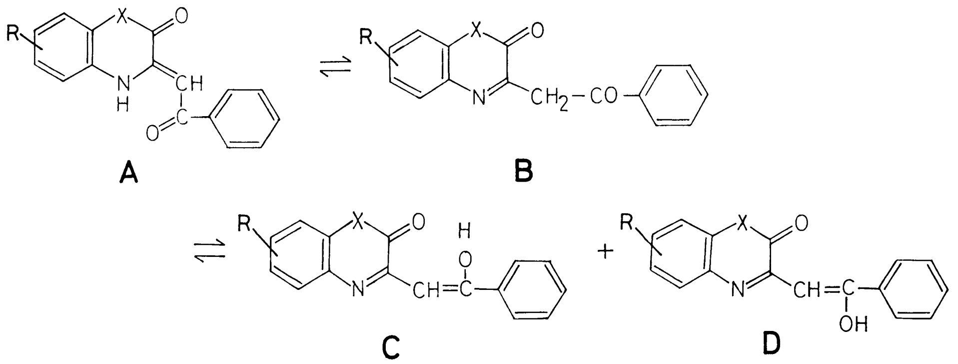

Table 2. Chemical shifts of the products

Compound	DMSO-d_6			CF$_3$COOH	
	=CH	Benzoyl(*ortho*)	NH	=CH	CH$_2$
IVa	6.91	*ca.* 8.07	13.88 12.09	6.59 5.70	4.79
IVb	6.92	*ca.* 8.10	13.68 12.12	6.78 6.43 5.54	4.39
IVc	—	—	—	6.98 6.55 5.69	4.79
Va	6.98	*ca.* 8.13	12.97	6.26 5.35	4.53
Vb	6.89	*ca.* 8.05	12.92	6.65 6.45 5.55	4.65
Vc	7.07	*ca.* 8.19	(12.02)	6.44 5.56	4.65
Vd	7.11	*ca.* 8.13	(12.18)	6.97 6.43 5.56	4.69

Values are on δ scale, unmeasurable: —, and indistinct: ( ).

In crystalline state or in dimethyl sulfoxide, these compounds exist as A, as already mentioned. In a strongly ionizing solvent like trifluoroacetic acid, however, the solvent forces them to tautomerize between A and B, B and C (or D), and possibly A and C (or D). This effect of the ionizing solvent would be due to solvation with proton and the anion. The mechanism can be explained by a simultaneous attack (concerted reaction) of an anion and a proton,[10] analogous to similar phenomena observed[7,8] on the related compounds in trifluoroacetic acid or sulfuric acid.

The interconversions are supported by the following interpretations and experiments. In trifluoroacetic acid, a methylene (–CH$_2$–) proton signal (Table 2) is shown in every case. This is satisfactory for B. Although no direct evidences are given to the presence of both tautomers C (*cis*) and D (*trans*), occurrence of three methine (=CH–) ptoron signals (Table 2) can be interpreted as that one methine belongs to A and the two others to C and D. Since intramolecular hydrogen bonding possibly occurs as well in C as in A, a couple of the signals both fallen in a range 6.98—6.43 ppm would be attributable to the methines of A and C. Thus, the remaining signal in the higher field 5.70—5.35 ppm is likely to be that of D (when only two methine signals appear, one form may be minimized or two of the three signals overlapped). Moreover, the typical benzoyl (*ortho*) proton signals observed in dimethyl sulfoxide-d_6 are weakened in trifluoroacetic acid. Enolized forms C and D explain this felicitously.

On the other hand, the spectra determined in trifluoroacetic acid-*d* exhibit no methylene nor methine proton signals, *i.e.* all hydrogens on the aliphatic carbon have been replaced with deuterium. As an example, two of the possible exchange mechanisms would be as

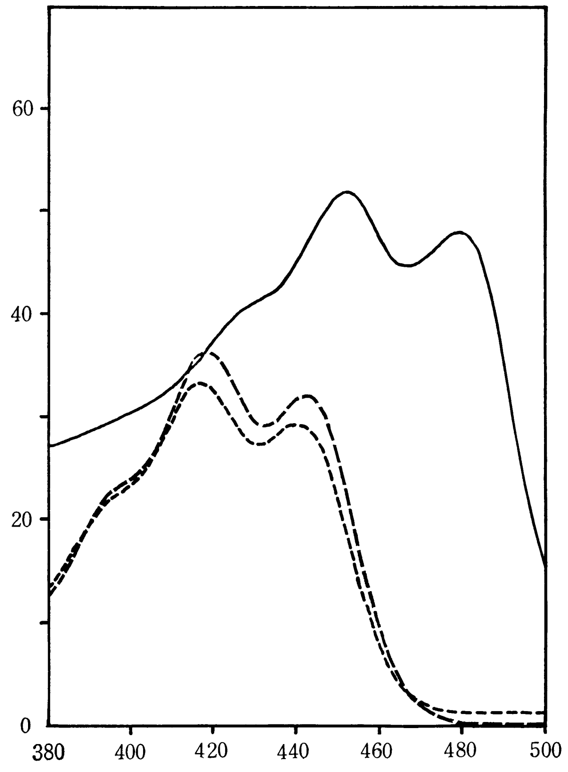

Fig. 2. Electronic absorption spectra of 3-phenacylidene-3,4-dihydro-2(1*H*)-quinoxalinone (IVa); in EtOH: ------, in DMSO: ----, and in CF$_3$COOH: ——.

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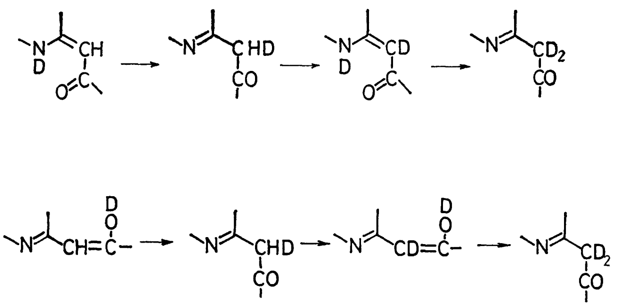
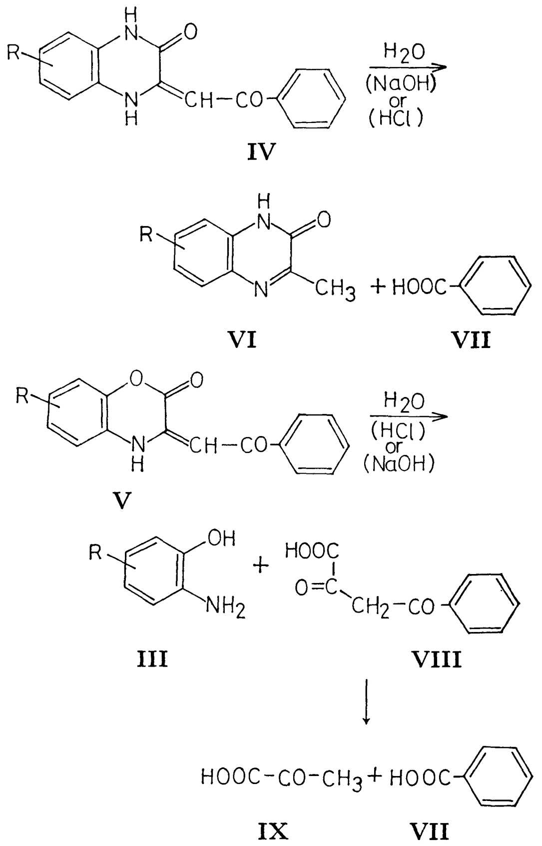
[10] E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., Inc., London (1960), p. 385.

follows:



Besides the interconversion between A and B[7] (above), the keto-enol tautomerism involving B, C, and D (below) probably contributes to the deuterium exchange. At least, disappearance of the signals is consistent with the above tautomerisms forced by the acid.

In addition to these supports,[11] another evidence for C and D is obtained from electronic absorption. The spectra of IVa are shown in Fig. 2. The absorptions in ethanol and in dimethyl sulfoxide are almost the same, whereas that in trifluoroacetic acid shows a bathochromic shift. This is consistent with the enol forms C and D, since the enol double bond connects two aromatic rings so as to intensify the resonance through this new conjugated double bond.



Hydrolysis of IV gave the corresponding 3-methyl-2(1*H*)-quinoxalinones (VI) and benzoic acid (VII), while that of V afforded the starting substances, *o*-aminophenols (III) and benzoylpyruvic acid (VIII) which had been partially decomposed into pyruvic acid (IX) and VII.

The reasons why V gave starting materials whereas IV preserved its quinoxaline ring would be exactly the same as those given for their analogues.[5]

Experimental

IR spectra were measured for KBr disks with a Nippon Bunko DS-301 spectrophotometer, NMR spectra were determined on a Hitachi H-60 spectrometer, and electronic absorption spectra were taken on a Hitachi 124 spectrophotometer.

The starting material, ethyl benzoylpyruvate (I), was prepared according to the method of Beyer and Claisen.[12] All melting points are uncorrected.

*3-Phenacylidene-3,4-dihydro-2(1*H*)-quinoxalinone (IVa).* Preparation was essentially the same as that reported.[13] Yield 95%. Recrystallization from acetone gave IVa as yellow needles; mp 268—269°C (lit.[13,14] mp 267—268°C). Found: C, 72.84; H, 4.64; N, 10.38%.

*7-Chloro-3-phenacylidene-3,4-dihydro-2(1*H*)-quinoxalinone (IVb).* Into a solution of IIb (0.7 g) in ethanol (20 m*l*), a solution of sodium salt of I (1.4 g) 50% acetic acid (25 m*l*) was dropped with stirring. After the mixture had been stirred for further 2 hr, it was allowed to stand overnight. The precipitated crystals (84% yield) were recrystallized from hot dimethyl sulfoxide to give IVb as yllow prisms; mp 323°C.

Found: C, 64.58; H, 3.88; N, 9.37%. Calcd for $C_{16}H_{11}O_2N_2Cl$: C, 64.34; H, 3.68; N, 9.38%.

The other compounds were synthesized in a similar manner.

*3-Phenacylidene-3,4-dihydro-2(1*H*)-benzo[g]quinoxalinone (IVc).* Yield 61%. Orange-yellow needles from dimethyl sulfoxide; mp 343°C.

Found: C, 76.62; H, 4.59; N, 9.27%. Calcd for $C_{20}H_{14}O_2N_2$: C, 76.42; H, 4.49; N, 8.91%.

*3-Phenacylidene-3,4-dihydro-2*H*-1,4-benzoxazin-2-one (Va).* Yield 72%. Orange-yellow prisms from acetone; mp 200—201°C (lit.[15,16] mp 201°C). Found: C, 72.65; H, 4.20; N, 5.60%.

*6-Methyl-3-phenacylidene-3,4-dihydro-2*H*-1,4-benzoxazin-2-one (Vb).* Yield 86%. Yellow prisms from acetone; mp 174.5—175°C.

Found: C, 73.40; H, 4.81; N, 5.31%. Calcd for $C_{17}H_{13}O_3N$: C, 73.11; H, 4.69; N, 5.02%.

*6-Chloro-3-phenacylidene-3,4-dihydro-2*H*-1,4-benzoxazin-2-one (Vc).* Yield 74%. Yellow prisms from acetone; mp 212—213°C.

Found: C, 64.25; H, 3.42; N, 4.80%. Calcd for $C_{16}H_{10}O_3NCl$: C, 64.12; H, 3.36; N, 4.67%.

*3-Phenacylidene-3,4-dihydro-2*H*-naphtho[2,1-b]-1,4-oxazin-2-one (Vd).* Yield 89%. Orange fibers from acetone; mp 200—200.5°C.

Found: C, 75.90; H, 4.15; N, 4.72%. Calcd for $C_{20}H_{13}O_3N$: C, 76.18; H, 4.16; N, 4.44%.

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[11] IR spectral data also support a lactam structure of IV, as shown in the structurel formulae, but not lactim. This partial structure is the same in dimethyl sulfoxide-d_6, as proved by NMR spectroscopy. In spite of a reasonable interpretation of the NMR spectra in trifluoroacetic acid, the possibility of decomposition in the acid may not be ruled out because of the variety of signals.

[12] C. Beyer and L. Claisen, *Ber.*, **20**, 2181 (1887).

[13] S. Fatutta and A. Stener, *Gazz. Chim. Ital.*, **88**, 89 (1958).

[14] Reported as 3-phenacyl-2(1*H*)-quinoxalinone.

[15] E. Biekert, D. Hoffmann, and F. J. Meyer, *Chem. Ber.*, **94**, 1664 (1961).

[16] Reported as 3-phenacyl-2*H*-1,4-benzoxazin-2-one.

Hydrolysis of IVa. A suspension of IVa (0.75 g) in 2 N sodium hydroxide (25 m*l*) was refluxed for 1 hr. The reaction mixture soon turned into a solution upon heating. Into the solution, after cooling, 6 N hydrochloric acid was dropped with stirring until it remained slightly alkaline. The hydrolysate was repeatedly extracted with chloroform. From the combined extracts, the solvent was removed *in vacuo*, and the residue was recrystallized from ethanol to give 3-methyl-3, 4-dihydro-2(1*H*)-quinoxalinone (VIa) (0.28 g) as colorless needles; mp 243—244°C, undepressed on admixture with a sample which had been prepared.[2] Found: N, 17.57%.

The aqueous layer was acidified with 6 N hydrochloric acid, and extracted with ether repeatedly. Ether was removed from the combined extracts, and the residue was recrystallized from ethanol to afford benzoic acid (VII) (0.29 g) as colorless plates; mp 122—122.5°C, undepressed on admixture with a commercial sample. The product VII was UV-spectroscopically identical with the sample.

Hydrolysis of Va. A solution of Va (1.20 g) in a mixture of acetic acid (40 m*l*) and 6 N hydrochloric acid (20 m*l*) was refluxed for 2 hr. After it had been cooled, the hydrolysate was extracted with benzene three times. The combined extracts were dried over anhydrous sodium sulfate, and the solvent was removed. The residue (0.61 g) was recrystallized from ether to give benzoylpyruvic acid (VIII) as yellowish prisms; mp 155—156°C. (lit.[11] mp 155—156°C), undepressed on admixture with a sample prepared according to literature. Its identity was also proved by UV spectroscopy. The acidity of the aqueous layer was reduced to pH 5 by adding sodium hydrogencarbonate powder, and the aqueous solution was extracted with ether three times. The combined extracts were dried over anhydrous sodium sulfate, and ether was removed. The residue was recrystallized from ethanol to afford *o*-aminophenol (IIIa) (0.48 g); mp 172—174°C, undepressed on admixture with a commercial sample used for the synthesis of Va. UV spectra proved its identity.

From the mother liquors, small amounts of VII and pyruvic acid (IX) were isolated (IX was precipitated as its 2,4-dinitrophenylhydrazone). They were identified by mixed melting points and UV spectroscopy. When Va was refluxed with 6 N hydrochloric acid for 3 hr, the yields of VII and IX which were probably derived from the partial hydrolysis of VIII, increased.

Hydrolyses of the Other Compounds. The hydrolyses of IVb, c and Vb–d were performed in a similar manner to that described above. The corresponding 3-methyl-2(1*H*)-quinoxalinones (VIb,c) were obtained from IVb,c in similar yields and were identical with the respective samples prepared[3] by the mixed melting points and by comparison of their UV spectra. From Vb–d, the corresponding *o*-aminophenols (IIIb–d) and VIII were formed, and their identity with those used for the syntheses of Vb–d was similarly checked by means of melting points and UV spectra.

Similar results were obtained from the hydrolyses of IVa–c with hydrochloric acid and those of Va–d with sodium hydroxide.