

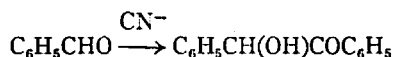
SYNTHESES AND STRUCTURES OF ACETYLFORMOIN AND RELATED COMPOUNDS

BY RYOZO GOTO AND YO MIYAGI

A series of formoin* has been synthesized and their structures have been determined from infrared and ultraviolet spectral studies. The chemistry of formoins is a tautomerism between two structures. Solvation and substituent have great effects on this tautomerism.

Introduction

A condensation of an aromatic aldehyde in the presence of cyanide ion gives a benzoin: (the benzoin condensation):



Similarly an α -ketoaldehyde (a substituted glyoxal) undergoes a condensation of the benzoin type in the presence of cyanide ion



to give a kind of acyloin, the so-called "formoin* ". Formoins, which have been synthesized, are: benzoylformoin¹⁾ ($\text{C}_6\text{H}_5\text{COCH}(\text{OH})\text{COCOC}_6\text{H}_5$),

p-methoxybenzoylformoin²⁾ ($\text{CH}_3\text{O}-\text{C}_6\text{H}_4\text{COCH}(\text{OH})\text{COCOC}_6\text{H}_4-\text{OCH}_3$),

p-chlorobenzoylformoin³⁾ ($\text{Cl}-\text{C}_6\text{H}_4\text{COCH}(\text{OH})\text{COCOC}_6\text{H}_4-\text{Cl}$),

p-bromobenzoylformoin³⁾ ($\text{Br}-\text{C}_6\text{H}_4\text{COCH}(\text{OH})\text{COCOC}_6\text{H}_4-\text{Br}$),

mesitoylformoin⁴⁾ ($(\text{CH}_3)_3-\text{C}_6\text{H}_2\text{COCH}(\text{OH})\text{COCOC}_6\text{H}_2-(\text{CH}_3)_3$),

acetylformoin^{5,6)} ($\text{CH}_3\text{COCH}(\text{OH})\text{COCOCH}_3$),

(Received June 30, 1964)

* Söderbaum gave the name of benzoylformoin to the condensation product of phenylglyoxal. The condensation products of the other glyoxals have been named "acylformoin" after benzoylformoin, such as acetyl-, isobutyryl-, neopentoyl, mesitoyl-formoin. So, the word "formoin" is used here as a class name. However, "formoin" should be used only for the case of acylformoin because alkylformoin is nothing but acyloin.

1) P. W. Abenius and H. G. Söderbaum, *Ber.*, **24**, 3033 (1891); **25**, 3468; P. W. Abenius, *ibid.*, **27**, 706 (1894)

2) P. Karrer and A. v. Segesser, *Helv. Chim. Acta*, **18**, 273 (1935)

3) P. Karrer and C. Musante, *ibid.*, **18**, 1140 (1935)

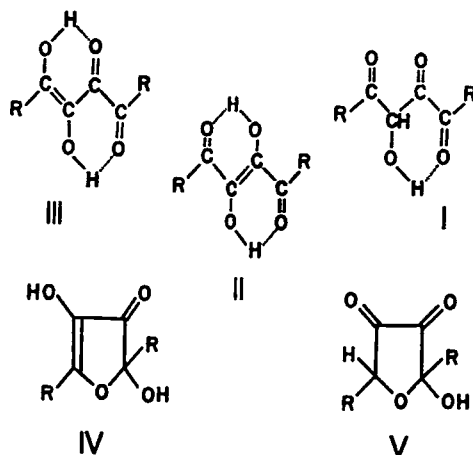
4) A. R. Gray and R. C. Fuson, *J. Am. Chem. Soc.*, **56**, 1367 (1934)

5) R. Nodzu and S. Kunichika, *Bull. Chem. Soc. Japan*, **45**, 211 (1940)

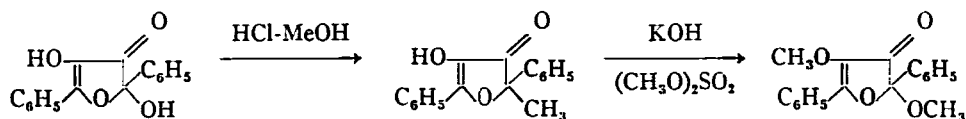
6) E. Steinbauer and E. Waldman, *Monat.*, **89**, 569 (1958)

neopentoylformoin⁷⁾ $((\text{CH}_3)_3\text{CCOCH}(\text{OH})\text{COCOC}(\text{CH}_3)_3)$,
and isobutyrylformoin⁸⁾ $((\text{CH}_3)_2\text{CHCOCH}(\text{OH})\text{COCOC}(\text{CH}_3)_2)$.

In the condensation of aromatic glyoxals and tert-butylglyoxal, the products have been generally isolated in good yields. On the other hand, in the case of aliphatic glyoxal the yield is low*. Low yield may be caused by side reactions or the conversion to other compounds in isolation steps: for example, phenylhydrazones of pyruvic acid and acetol have been isolated from an aqueous solution of methylglyoxal and sodium cyanide¹⁰⁾.



Possible structures for formoins are shown in I-V. Blatt¹¹⁾ considered only I-IV, but structure V should be involved. First of all, the structure of benzoylformoin has been studied¹¹⁾¹¹⁾. It has been found that benzoylformoin has two hydroxyl groups of different reactivity. With an absolute alcoholic solution of an mineral acid, only one of the two hydroxyl groups is etherated to give a mono-O-alkyl derivative. The other hydroxyl group is etherated with alkali-dimethylsulfate. The etherification by alcohol-acid is characteristic of the glycosidic ether linkage and hence suggests structure VI ($\text{R}=\text{C}_6\text{H}_5$) for O-alkyl derivatives. Benzoylformoin reacts with phenylenediamine to give a quinoxaline VII, suggesting structure III. Blatt¹¹⁾ considered that the structure of benzoylformoin in the solid state was IV and that



* However the quantitative proceed of the condensation of methylglyoxal was proved by the titration of enediol group by the Tillman reagent⁹⁾.

7) Y. Miyagi and R. Goto, *Bull. Chem. Soc. Japan*, **36**, 650 (1963)

8) *Idem.*, *ibid.*, **36**, 921 (1963)

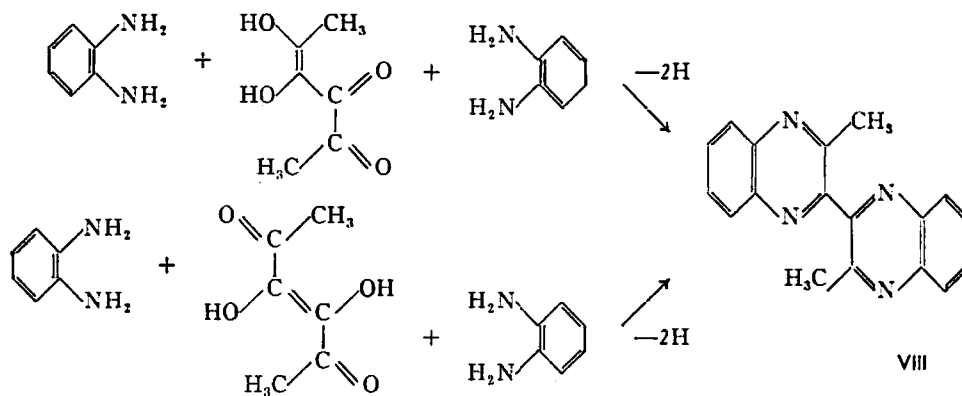
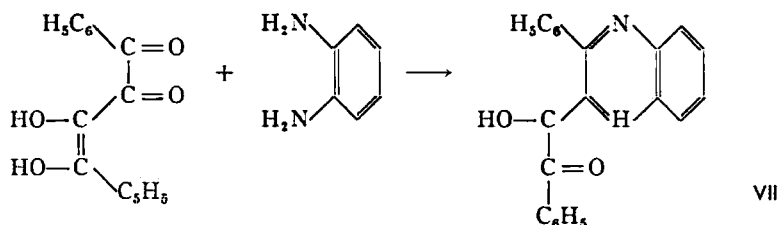
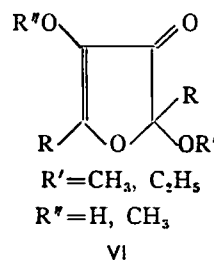
9) B. Görlich, *Ber.*, **89**, 2135 (1956)

10) V. Franzen, *ibid.*, **89**, 2154 (1956)

11) A. H. Blatt, *J. Am. Chem. Soc.*, **57**, 1103 (1935); **58**, 1894 (1936)

an equilibrium between IV and III occurred in solution. Steinbauer and Waldman⁶⁾ obtained a quinoxaline VIII by the reaction of acetylformoin with phenylenediamine.

In the experiments above described, the structure of benzoylformoin has been estimated with reaction products of benzoylformoin with reagents. In a system where an equilibrium may be involved,



however, reaction products can not become unequivocal evidences, because the equilibrium may be shifted by an exclusive reaction of one tautomer to give a sole product.

Results

Infrared spectral study⁷⁾⁸⁾¹²⁾¹⁵⁾

Acetylformoin shows quite different infrared spectra in chloroform¹²⁾ and in tetrahydrofuran¹⁵⁾

12) R. Goto, Y. Miyagi and H. Inokawa, *Bull. Chem. Soc. Japan*, **36**, 147 (1963)

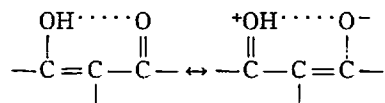
13) R. S. Rasmussen, D. D. Tunnicliff and R. B. Brattain, *J. Am. Chem. Soc.*, **71**, 1068 (1949)

14) L. J. Billamy, "*Infrared Spectra of Complex Molecules*", Methuen, London (1958), pp. 104, 142

15) Y. Miyagi, *Bull. Chem. Soc. Japan*, **37**, 12 (1964)

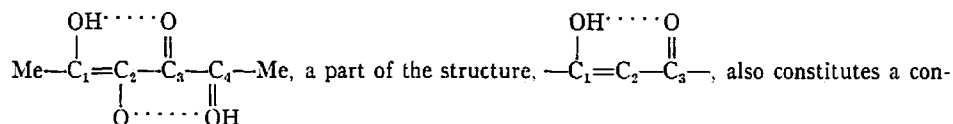
(Fig. 1): in the former solvent a broad and weak band of the OH stretching absorption is observed between 3600 and 2800 cm^{-1} and the CO stretching absorption band arises at a low frequency, 1625 cm^{-1} ; in the latter solvent a distinct band of the OH stretching absorption is observed at 3280 cm^{-1} and the CO and C=C stretching absorption bands are located at 1705 and 1640 cm^{-1} respectively.

Rasmussen *et al.*¹³⁾ found the anomaly of the infrared spectra of enolic β -diketones that the CO stretching absorption band is widely shifted close to 1600 cm^{-1} and that the OH stretching absorption band becomes very weak and broad. They attributed the anomaly to resonance structures:



This chelation has been termed "conjugate chelation" to distinguish it from the normal hydrogen bonding¹⁴⁾. The infrared spectrum of acetylformoin has exactly the same type of anomaly. In structure II, enediol $\text{C}(\text{OH})=\text{C}(\text{OH})$ serves to form conjugate chelation on both sides of the carbonyl groups and hence a stronger chelation may be expected.

In structure III where carbon atoms are numbered as



jugate chelation and can show such an anomaly as has been observed. However a part of the structure, $-\text{C}_2-\text{C}_3-\text{C}_4-$, is a β -oxyketone constituting a simple hydrogen bonding: the CO stretching absorption will arise at a higher frequency, probably close to 1700 cm^{-1} and the hydroxyl group attached to C_2 will show some distinct absorption bands.

In enolic β -diketones, the C=C stretching absorption band can not be observed. Rasmussen stated that this is to be accounted for by its being hidden by the remarkably strong CO band or by its being shifted out of the double-bond region because of its loss of a double-bond character. Furthermore, it is not too difficult to comprehend the disappearance of the C=C stretching absorption band of acetylformoin when due attention is paid to the fact that C=C is fully and symmetrically substituted in structure II.

The infrared spectra of acetylformoin in tetrahydrofuran is most compatible with structure VI. The absorption bands at 1640 , 1705 and 3280 cm^{-1} may be attributed to the C=C, CO and OH stretching absorptions respectively: the absorption of two hydroxyl groups may be considered to arise at the same position.

Another assignment to structure III is also possible. The absorption at 1705 cm^{-1} comes from $\text{C}_4=\text{O}$ and that at 1640 cm^{-1} comes from a conjugate chelation, $\text{C}_1=\text{C}_2-\text{C}_3$: the hydroxyl group attached to C_2 may show the absorption around 3280 cm^{-1} because it constitutes only a simple hydrogen bonding. The above assignment, however, is excluded on the basis of reasons mentioned later.

The infrared spectrum of isobutylformoin (Fig. 2) in chloroform is quite similar to that of acetylformoin in this solvent⁸⁾: a weak broad band of OH stretching absorption from 3600 beyond over 2800 cm^{-1} ; the CO stretching absorption at 1630 cm^{-1} . Accordingly isobutyrylformoin may be considered to have structure II in chloroform. The infrared spectrum of isobutyrylformoin in tetrahydrofuran is also similar to that of acetylformoin in this solvent: a distinct band of the OH stretching absorption at 3290 cm^{-1} ; the CO and C=C stretching absorption at 1705 and 1630 cm^{-1} respectively. Hence, structure IV may be suggested for isobutylformoin in tetrahydrofuran. The infrared spectrum of isobutyrylformoin in the solid state, is rather similar to that of isobutyrylformoin in tetrahydrofuran: the CO and C=C stretching absorptions are observed at 1690 and 1605 cm^{-1} respectively; two bands of the OH stretching absorption arise.

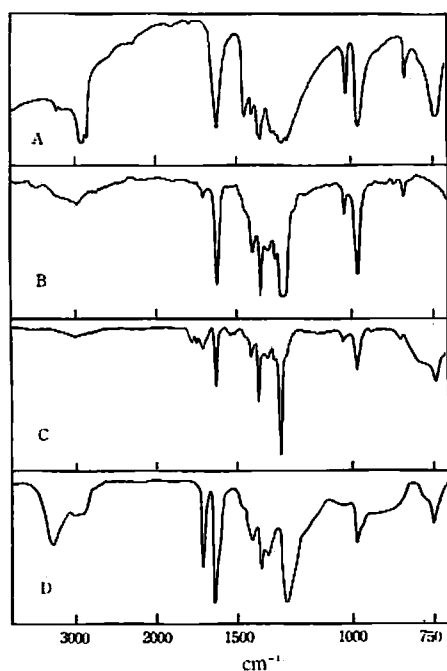


Fig. 1 Infrared spectra of acetylformoin in Nujol (A), chloroform (B), carbon tetrachloride (C) and tetrahydrofuran (D)

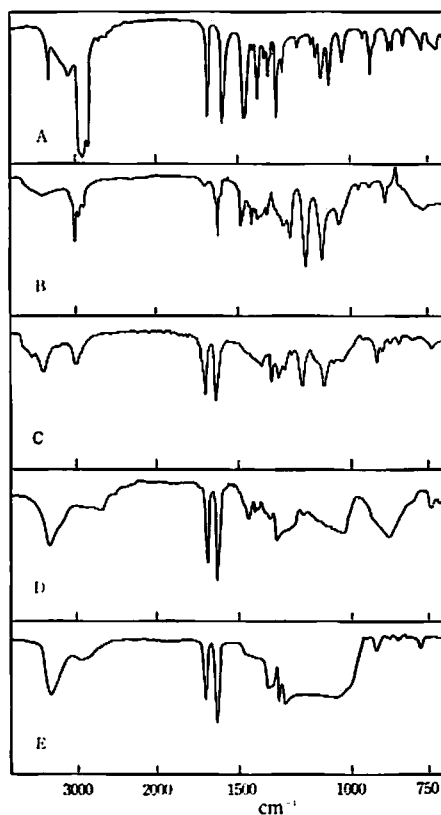


Fig. 2 Infrared spectra of isobutyrylformoin in Nujol (A), chloroform (B), acetonitrile (C), tetrahydrofuran (D) and ether (E)

Neopentoylformoin¹⁶⁾ shows the infrared spectrum (Fig. 3) characteristic of structure IV in ether, tetrahydrofuran and acetonitrile: the CO, C=C and OH stretching absorptions are located at 1705, 1630 and around 3300 cm^{-1} respectively. The infrared spectrum of neopentoylformoin in the solid state⁷⁾ is similar to that of isobutyrylformoin in the solid state: the CO and C=C stretching absorptions at 1690

and 1605 cm^{-1} and the OH stretching absorption at 3330 and 3180 cm^{-1} . The low solubility and rapid oxidation of neopentoylformoin in chloroform makes it impossible to measure the infrared spectrum in this solvent.

Benzoylformoin shows the infrared spectrum (Fig. 4) characteristic of structure IV in tetrahydrofuran¹⁵⁾ solution and the solid state¹²⁾. In the former state, the C=C, CO and OH stretching absorptions are located at 1615 , 1705 and 3240 cm^{-1} respectively. In the latter state, the C=C and CO stretching absorptions arise at 1605 and 1685 cm^{-1} and the OH stretching absorption does at 3270 and 3500 cm^{-1} .

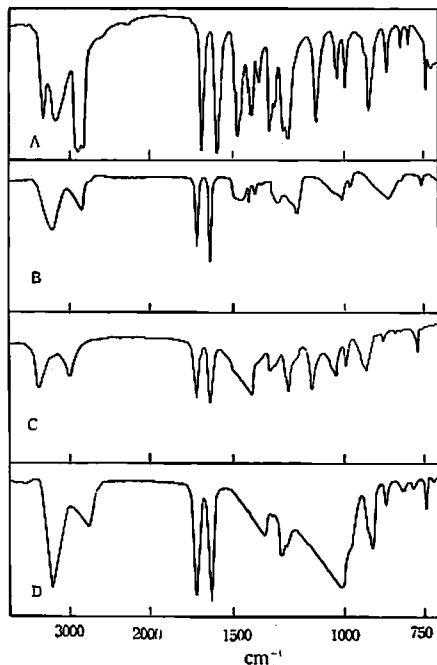


Fig. 3 Infrared spectra of neopentoylformoin in Nujol (A), tetrahydrofuran (B), acetonitrile (C) and ether (D); in ether a 0.2 mm cell was used

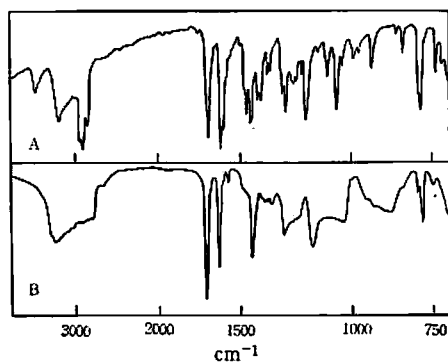


Fig. 4 Infrared spectra of benzoylformoin in Nujol (A) and tetrahydrofuran (B)

In summary, the spectral characteristics are thus: in the solid state, structure IV shows the CO stretching absorption at 1690 cm^{-1} the C=C stretching absorption at 1605 cm^{-1} and two bands of the OH stretching absorption; in solution, structure IV shows the CO stretching absorption at 1710 cm^{-1} , the C=C stretching absorption at 1620 cm^{-1} and the OH stretching absorption at around 3300 cm^{-1} ; structure II shows a broad weak band of the OH absorption between $3600\text{--}2800\text{ cm}^{-1}$ and the CO stretching absorption at 1620 cm^{-1} .

Ultraviolet spectral study⁸⁾¹⁵⁾

Ultraviolet spectra also vary with changing solvents.

Ultraviolet absorption of acetylformoin in tetrahydrofuran is observed at $303\text{ m}\mu$ with moderate intensity (ϵ_{max} , 7500) and at $360\text{ m}\mu$ with increased intensity (ϵ_{max} , 15000) in chloroform (Fig. 5). Since infrared spectral evidence has established structure IV for tetrahydrofuran solution and structure

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Table 1 Infrared absorption bands of formoins, cm^{-1}

Formoin	Phase	ν_{OH}	$\nu_{\text{C=O}}$	$\nu_{\text{C=C}}$
Acetyl	Nujol	broad and weak	1620	
	CHCl_3		1625	
	CCl_4		1630	
	THF*	3280	1705	1640
Isobutyryl	Nujol	3340	3100	1685
	CHCl_3	broad and weak		1605
	THF	3290	1705	1630
	CH_3CN	3380	1705	1630
	Et_2O	3320	1710	1635
Neopentoyl	Nujol	3330	3180	1690
	THF	3280	1705	1605
	CH_3CN	3400	1705	1630
	Et_2O	3240	1703	1627
Benzoyl	Nujol	3500	3210	1685
	THF	3240	1705	1605

* THF; tetrahydrofuran

Table 2 Ultraviolet absorption bands of formoins

Formoin	Solvent	$\lambda_{\text{max}}, \text{m}\mu$	ϵ_{max}
Acetyl	THF*	303	7300
	StOH	303	7500
	CHCl_3	355	15000
Isobutyryl	EtOH	305	7200
	THF	305	7350
	Et_2O	305	7400
	CH_3CN	{ 305 360	6000 2950
	CHCl_3	360	14200
Neopentoyl	EtOH	308	7350
	THF	308	7750
	Et_2O	308	7850
	CH_3CN	307	7750
	CHCl_3	311	6330
Benzoyl	EtOH	{ 354 240	12000 10800
	THF	{ 354 240	13700 11300
	Et_2O	{ 350 240	14600 13000
	CHCl_3	{ 367 240	* * —

* THF; tetrahydrofuran

** see Experimental

II for chloroform solution, the 303 $m\mu$ and 355 $m\mu$ bands are ascribable to structures IV and II respectively. In ethanol solution, the 303 $m\mu$ band is also dominant. There is, however, a slight difference between the ultraviolet spectrum in ethanol and that in tetrahydrofuran: a slight but distinct shoulder beyond 350 $m\mu$ in the latter solvent suggests the existence of a small amount of structure II.

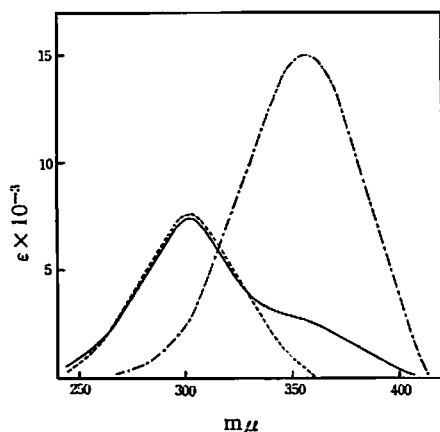


Fig. 5 Ultraviolet spectra of acetylformoin in tetrahydrofuran (—), chloroform (---) and ethanol (.....)

Isobutyrylformoin shows an ultraviolet absorption at 305 $m\mu$ with moderate intensity (ϵ_{\max} , 7250) in ethanol (Fig. 6). In ether and tetrahydrofuran the 305 $m\mu$ band is dominant and also as in acetylformoin a tailing beyond 350 $m\mu$ is observed. In acetonitrile isobutyrylformoin shows the 305 $m\mu$ band with somewhat decreased intensity (ϵ_{\max} , 6000), and a shoulder at 360 $m\mu$, suggesting an equilibrium between structure IV and II. In chloroform the ultraviolet absorption is shifted to 360 $m\mu$ with increased intensity, indicating structure II.

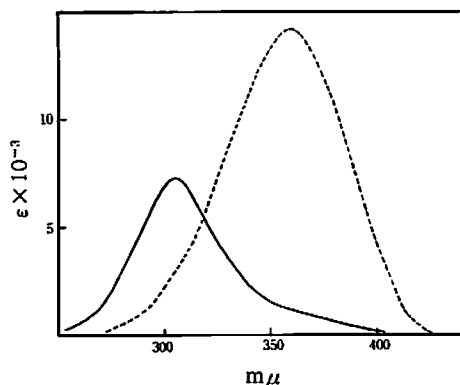


Fig. 6a Ultraviolet spectra of isobutyrylformoin in tetrahydrofuran (—) and chloroform (.....)

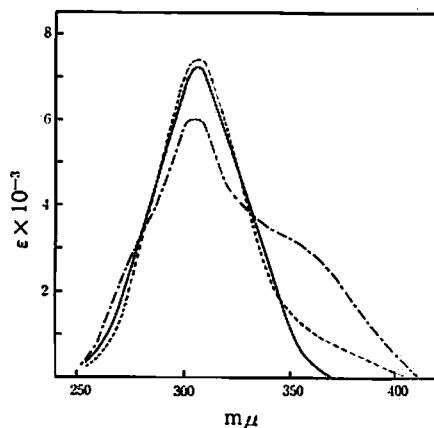


Fig. 6b Ultraviolet spectra of isobutyrylformoin in ethanol (—), acetonitrile (---) and ether (.....)

The ultraviolet absorption of neopentoylformoin in ethanol arises at 308 $m\mu$ with moderate intensity (Fig. 7). In ether, tetrahydrofuran and acetonitrile, the 308 $m\mu$ band predominates and such a

tailing beyond $350\text{ m}\mu$ as in acetylformoin and isobutyrylformoin is not observed. This fact may suggest the dominance of structure IV in any solvent.

As previously mentioned, neopentoylformoin is rapidly oxidized in chloroform so that the ultraviolet spectrum in this solvent was measured in a cell sealed in vacuo (Fig. 8). The absorption arises at $311\text{ m}\mu$ with a slight shoulder at $275\text{ m}\mu$. When the sealed cell is opened, the $311\text{ m}\mu$ band diminishes. This fact indicates structure IV also for chloroform solution of neopentoylformoin and the disappearance of the $310\text{ m}\mu$ band which is ascribable to oxidation.

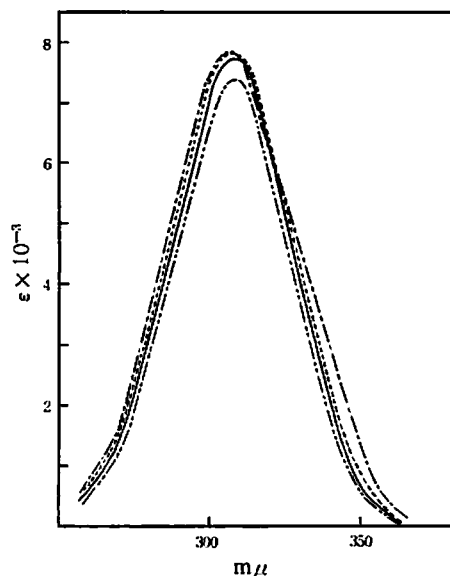


Fig. 7 Ultraviolet spectra of neopentoylformoin in tetrahydrofuran (—), acetonitrile (---), ethanol (····) and ether (— · — · —)

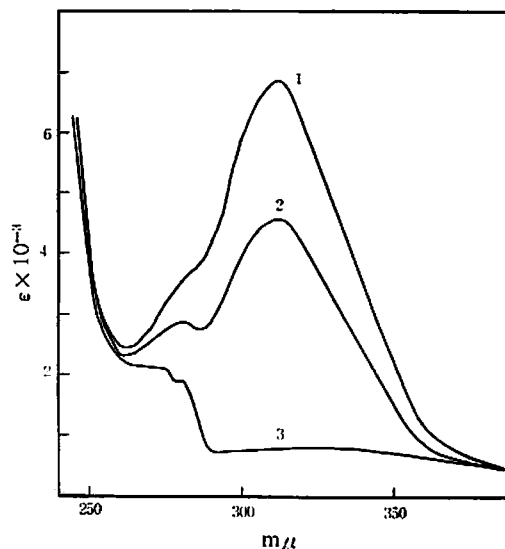


Fig. 8 Ultraviolet spectra of neopentoylformoin in chloroform: (1) in vacuo; (2) 5 hours after breaking the seal; (3) 1 day after breaking the seal

The ultraviolet absorption of benzoylformoin is located at 354 and $240\text{ m}\mu$ in tetrahydrofuran (Fig. 9). Since structure IV is established for tetrahydrofuran solution by the infrared spectral evidence, the 354 and $240\text{ m}\mu$ bands should be attributed to structure IV. The ultraviolet absorptions arising from the enone chromophore of structure IV may be shifted to longer wave lengths by a conjugation with a phenyl group. The ultraviolet spectra in ethanol and ether are quite similar to those in tetrahydrofuran.

Since benzoylformoin is also rapidly oxidized in a chloroform solution, the ultraviolet absorption was measured in a cell sealed in vacuo (Fig. 10). When the sealed cell is broken the 370 and $240\text{ m}\mu$ band disappears and another absorption arises at $262\text{ m}\mu$, which is ascribable to diphenyltetraketone¹⁷.

O-alkyl derivatives of formoins

The chemical behavior of benzoylformoin was mentioned previously. Neopentoylformoin has similar reactivities as benzoylformoin¹¹. Neopentoylformoin suffers methanolysis with methanolic hydrogen chloride to give a mono-O-methyl derivative and ethanolysis with ethanolic hydrogen chloride to give a mono-O-ethyl derivative. Furthermore, the mono-O-methyl derivative is converted to the

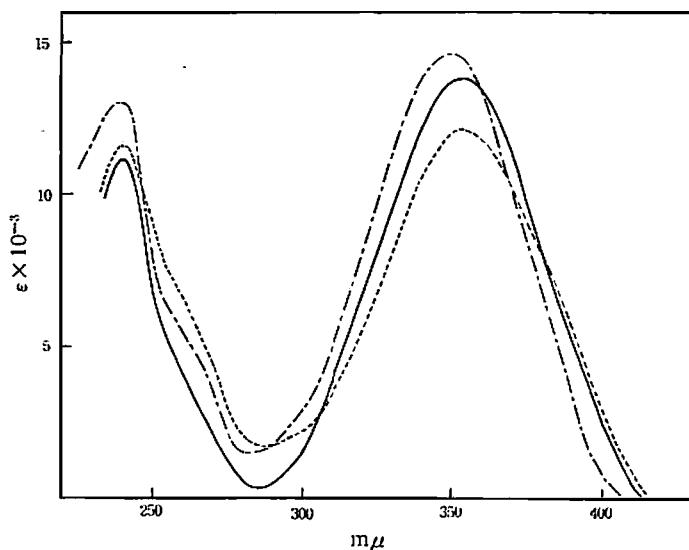


Fig. 9 Ultraviolet spectra of benzoylformoin in tetrahydrofuran (—), ether (---) and ethanol (.....)

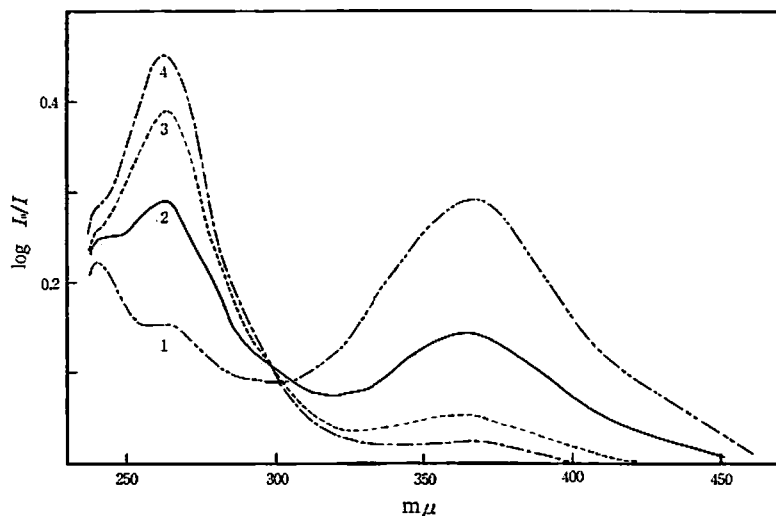


Fig. 10 Ultraviolet spectra of benzoylformoin in chloroform: (1) *in vacuo*; (2) 2 hours after breaking the seal; (3) 4 hours after breaking the seal; (4) 1 day after breaking the seal

O-ethyl derivative and vice versa. Another methoxy group was introduced into the O-alkyl derivatives by the methylation with dimethyl sulfate or methyl iodide. The di-O-methyl derivative is converted to the O-ethyl-O-methyl derivative in the presence of ethanolic hydrogen chloride.

As mentioned previously, the infrared spectral study can not exclude structure III completely. Hence a careful study of ultraviolet spectra of neopentoylformoin and benzoylformoin and their O-alkyl derivatives are undertaken¹⁵.

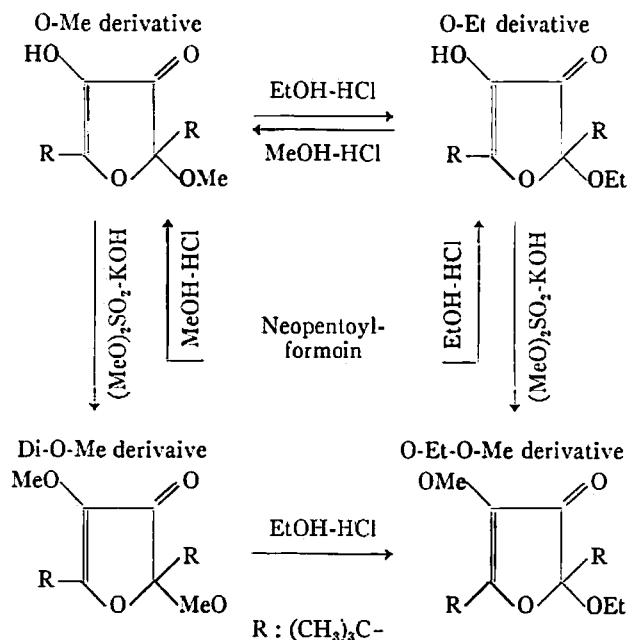


Table 3 Ultraviolet and infrared absorption bands of O-methyl derivatives of benzoyl- and neopentoyl-formoin

	Ultraviolet absorption bands			Infrared absorption bands cm^{-1}		
	Solvent	λ_{max} , $m\mu$	ϵ_{max}	Solvent	ν_{OH}	$\nu_{C=O}$ $\nu_{C=C}$
1st mono-O-methyl benzoylformoin	EtOH	355	14500	$CHCl_3$	3530	1705 1625
		241	11800		3340-3100	1585
di-O-methyl benzoylformoin	EtOH	342	12800	CCl_4		1710 1612
		243	10300			1590
2nd mono-O-methyl benzoylformoin	EtOH	342	12400	THF*	3580-3600	1710 1614
		237	10100		3240	
	$CHCl_3$	342	12200	$CHCl_3$	3580	1705 1610
		244	9200		3260	
mono-O-methyl neopentoylformoin	EtOH	309	7250	Nujol	3310	1690 1610
di-O-methyl neopentoylformoin	EtOH	296	7850	CCl_4		1710 1610

* THF; tetrahydrofuran

Neopentoylformoin shows an ultraviolet spectrum quitesimilar to that of mono-O-methyl neopentoylformoin as is shown in Fig. 11. Since the structure of mono-O-methyl neopentoylformoin was established as VI ($R=C(CH_3)_3$, $R'=CH_3$, $R''=H$), neopentoylformoin may be considered to have structure IV. Similarly the ultraviolet spectrum of the first mono-O-methyl benzoylformoin (Fig. 12), which is identical

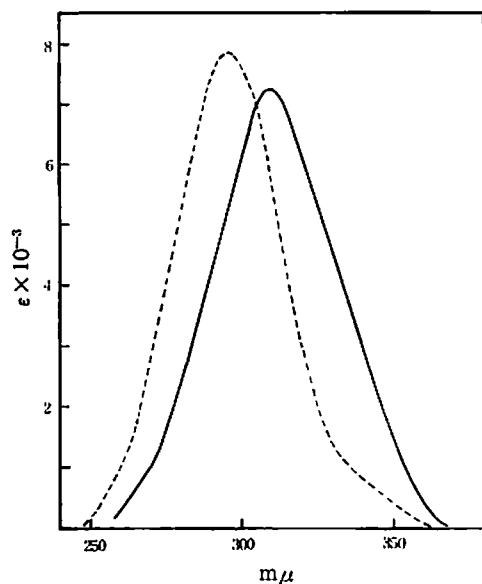
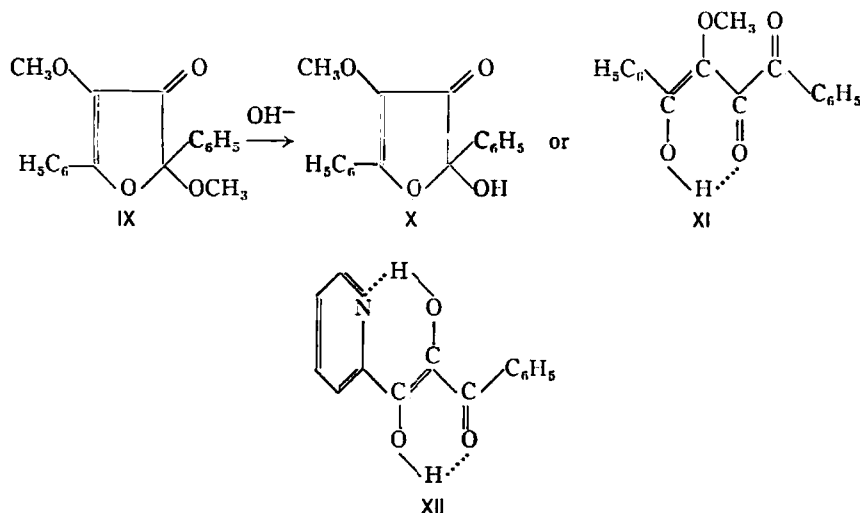


Fig. 11 Ultraviolet spectra of derivatives of neopentoylformoin in ethanol: mono-O-methyl neopentoylformoin (—); di-O-methyl neopentoylformoin (-----)

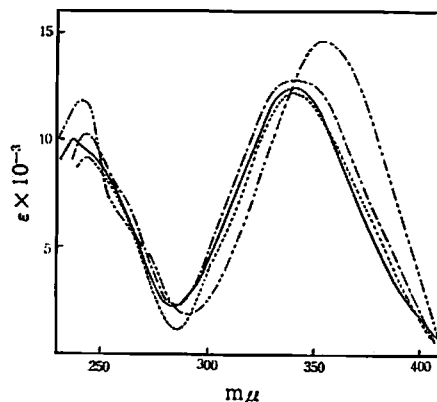
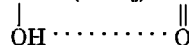


Fig. 12 Ultraviolet spectra of derivatives of benzoylformoin: 1st mono-O-methyl benzoylformoin in ethanol (---); di-O-methyl benzoylformoin in ethanol (-.-.-); 2nd mono-O-methyl benzoylformoin in tetrahydrofuran (—) and chloroform (.....)

with that of the parent benzoylformoin, indicates structure IV for benzoylformoin.

A basic hydrolysis of di-O-methyl benzoylformoin eliminates only the glycosidic methoxy group to give the second mono-O-methyl benzoylformoin¹¹⁾, for which structures X and XI are possible. The latter compound shows an ultraviolet spectrum in chloroform, identical with that in ethanol (Fig. 12). Moreover, both spectra are similar to that of the parent di-O-methyl benzoylformoin, the structure of

which has been established as IX by chemical evidences. There are found little differences between the infrared spectrum of the second mono-O-methyl benzoylformoin in chloroform and that in tetrahydrofuran (Fig. 14): the CO and C=C stretching absorptions are located at 1705 and 1610 cm^{-1} respectively. In structure XI a partial structure, $\text{—C=C(OCH}_3\text{)—C—}$, constitutes a conjugate



chelation. If the second mono-O-methyl benzoylformoin were of structure XI, it would show a broad weak band of the OH stretching absorption and the CO stretching absorption around 1620 cm^{-1} and the ultraviolet absorption at 340 $\text{m}\mu$ would be shifted to longer wave lengths. For instance, 1-benzoyl-2- α -pyridyl-ethenediol¹⁶ (XII) shows a broad band of the OH stretching absorption, the CO stretching

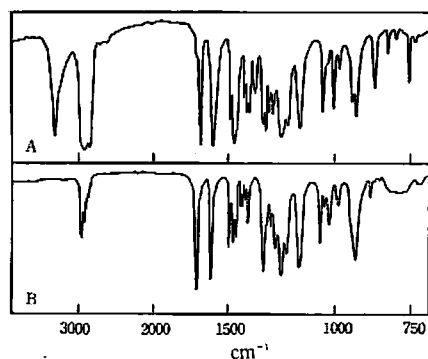


Fig. 13 Infrared spectra of derivatives of neopentoylformoin:
mono-O-methyl neopentoylformoin in Nujol (A); di-O-methyl neopentoylformoin in carbon tetrachloride (B)

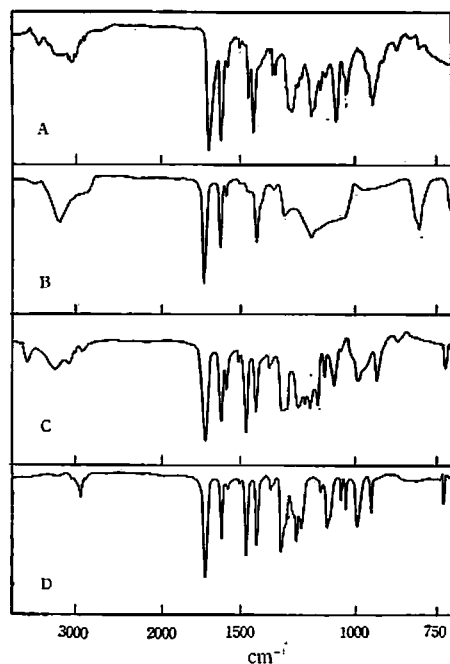


Fig. 14 Infrared spectra of derivatives of benzoylformoin:
1st mono-O-methyl benzoylformoin in chloroform (A); 2nd mono-O-methyl benzoylformoin in tetrahydrofuran (B) and chloroform (C); di-O-methyl benzoylformoin in carbon tetrachloride (D)

16) B. Eistert and H. Munder, *Ber.*, **91**, 1415 (1958)

absorption band at 1603 cm^{-1} and an ultraviolet absorption at $405\text{ m}\mu$. The above results indicate that the structure of the second mono-O-methyl benzoylformoin is X in both type solvents.

Consideration

The above results are summarized in Table 4; therein, A-type solvents are tetrahydrofuran, ether, ethanol; B-type solvents are chloroform and carbon tetrachloride. In the case of acetylformoin and isobutyrylformoin, a tautomerism between structure II and IV arises in solution; in A-type solvent, structure IV is dominant and in B-type, structure II predominates.

Table 4 Structures of formoins

Formoin	R	Solid state	Solution	
			A-type solvent	B-type solvent
Acetyl	CH_3	II	IV	II
Isobutyryl	$\text{CH}(\text{CH}_3)_2$	IV	IV	II
Neopentoyl	$\text{C}(\text{CH}_3)_3$	IV	IV	IV
Benzoyl	C_6H_5	IV	IV	IV

The A-type solvent can act as a proton acceptor. Since it is reasonable to consider that a tautomer predominating in a solution is stabilized by solvation, such a specific solvation may be supposed to occur in A-type solvent as depicted in Fig. 15, where the hydroxyl groups of formoins constitute hydrogen

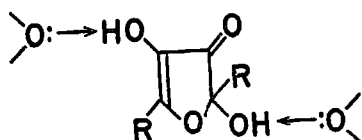


Fig. 15

bondings with solvent molecules. Furthermore ethanol can act not only as a proton acceptor but also as a proton donor to form a hydrogen bonding with the carbonyl group of structure IV as shown in Fig. 16. It means the capacity of solvation of ethanol is larger than ethers. This large solvation may

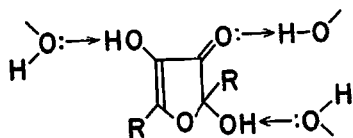


Fig. 16

explain the disappearance of the tailing of ultraviolet absorption bands beyond $350\text{ m}\mu$ of acetylformoin and isobutyrylformoin in ethanol.

The B-type solvent has not the facility of forming such a specific solvation. It may be considered that the lack of the specific solvation makes structure II to predominate in B-type solvent in the case of acetylformoin and isobutyrylformoin. This sequence of consideration means structure II is more

stable than structure IV in these formoins when the solvation is not involved.

On the other hand, it apparently seems that the tautomerism does not arise in the case of neopentoylformoin and benzoylformoin; both formoins have spectral characteristics of structure IV even in chloroform, which contains about 1% of ethanol as a stabilizer. However structure IV can not be unequivocally concluded because the behavior of benzoylformoin is rather complicated. Eistert¹⁷⁾ found that benzoylformoin shows up an ultraviolet absorption at 400 m μ in ethanol-free chloroform *in vacuo* suggesting structure II. By our re-examination the above fact has proved true. Moreover neopentoylformoin shows the main absorption at 312 m μ with a shoulder at 360 m μ in ethanol-free chloroform *in vacuo*¹⁹⁾. Structure II certainly arises but the condition is critical. What is the reason why structure II does not arise in chloroform containing ethanol? The solvation? The amount of ethanol, however, is too small to bring about the specific solvation to stabilize structure IV. It has been reported¹⁸⁾ that an absorption arises at 400 m μ in a solution of benzoylformoin in cyclohexane containing 1% of ether and diminishes rapidly in the existence of air. Eistert¹⁷⁾ is of opinion that benzoylformoin reacts ethanol present in chloroform to give the first mono-O-ethyl benzoylformoin which shows an ultraviolet absorption at 355 m μ * since he isolated the first mono-O-ethyl benzoylformoin from the solution. He also suggested¹⁷⁾ the infrared spectral change by the standing of acetylformoin in chloroform¹²⁾ is ascribable to the same reaction of acetylformoin.

From the above consideration it may be concluded that structure II is not so stable in neopentoylformoin and benzoylformoin as in acetylformoin and isobutyrylformoin. In other words, the stability of structure II depends on the substituent R. In order to ascertain it, the structures of *p*, *p'*-disubstituted benzoylformoin have been examined¹⁹⁾, which are given in Table 5. The results suggest that electron-donating groups in the electromery effect stabilize II, including hyperconjugation.

Table 5 Structures of substituted benzoylformoins

Substituent	Solid state	Solution	
		A-type solvent	B-type solvent
<i>p</i> -tert-butyl	IV	IV	IV
<i>p</i> -methyl	IV	IV	II
2, 4, 6-trimethyl	II	II	II
<i>p</i> -bromo	II and IV	IV	II
<i>p</i> -methoxy	II	IV	II

In addition there is a discrepancy in ultraviolet spectra of structures II. Mesitoylformoin (structure II) absorbs at 380 m μ and any other absorption is not observed at higher wave lengths. On the other

* Eistert stated¹⁷⁾ that the ultraviolet absorption in chloroform containing ethanol shows up at 355 m μ . In our measurement, however, it arises at 370 m μ .

17) B. Eistert, a private communication. We are indebted to him for informing us of their observations prior to publication.

18) H. Munder, his dissertation on "Versuche mit Benzoylformoin und 1-Benzoyl-2-(α -pyridyl)- α -thendiol-1, 2" at Technische Hochschule Darmstadt (1957)

19) Y. Miyagi and R. Goto, in preparation

hand, *p*, *p'*-dimethoxy-benzoylformoin and *p*, *p'*-dibromobenzoylformoin in chloroform (structure II) absorb at 420 and 310 $m\mu$. Further investigation is now proceeding.

The solubility of formoins seems to have a correlation with their structures. While acetylformoin is remarkably soluble in chloroform and carbon tetrachloride (B-type solvents), the other three formoins are slightly soluble in chloroform and quite insoluble in carbon tetrachloride. This difference may be explained with terms of solvation energy and interaction of molecules in the solid state* as follows.

Isobutyrylformoin, neopentoylformoin and benzoylformoin have structure IV in the solid state and in solution in B-type solvents. The C=O and C=C stretching absorptions of these formoins are located at 1690 and 1605 cm^{-1} respectively in the former state, and at 1705 and 1620 cm^{-1} respectively in the latter state; these values are higher by 15 cm^{-1} in solution than in the solid state. On the other hand, the C=O stretching absorption of acetylformoin, which has structure II in the solid state and in solution in B-type solvents, arises at the same position in both states. It means that the intermolecular interaction in the solid is strong in structure IV. A large intermolecular interaction in the solid state suggests a large value of the heat of vaporization ΔH_V .

The specific solvation to structure IV, which was mentioned above, may suggest a large value of solvation energy ΔH_S . It means that the ΔH_S value of structure IV is large in A-type solvent but small in B-type solvent.

In spite of a small ΔH_S value, acetylformoin has a large solubility in B-type solvent because it has structure II in the solid state, in other words, it has a small ΔH_V value. A sum of a large ΔH_V value and a small ΔH_S value results in low solubilities of the other three formoins in B-type solvent.

Conclusion

Formoins show a tautomerism between structure II and IV, dependent on the solvent and the substituent R. The A-type solvent constitutes such a specific solvation as shown in Fig. 15 or 16 to stabilize structure IV. The stability of structure II is dependent on the substituent R.

Experimental

Acetylformoin⁵⁾⁶⁾¹²⁾ The freshly distilled monomer of methylglyoxal was dissolved in cold water (pH value: 2.4) and the solution was stored in a refrigerator overnight. The condensation was effected according to Steinbauer's method⁶⁾, i. e., under a nitrogen stream, a pH-meter being used. An aqueous solution of sodium cyanide (molar ratio to methyl glyoxal: 0.08), previously cooled to 0°C, was added through a dropping funnel to the aqueous methylglyoxal solution; then the pH value rose to 9.5. The temperature of the reaction mixture did not rise above 2°C under cooling with ice-water, though Steindauer and Waldman stated that it rose up to 5°C under cooling. Sodium bicarbonate was

* The solubility is in a sense, an equilibrium constant and hence proportional to $\exp(-\Delta H/RT)$: $\Delta H = \Delta H_V - \Delta H_S$; ΔH , the change of heat content in dissolving; ΔH_V , heat of vaporization; ΔH_S , solvation energy.

added to keep the pH value of the solution between 7~8. When the aqueous methylglyoxal solution was used soon after dissolving, the pH value did not decrease below 8 even though considerable amount of sodium bicarbonate was added. In 30 min, condensation was stopped by adding phosphoric acid (pH: 5.0). The procedure thereafter was as usual. The solution was concentrated to a syrup, and alcohol was added to it. Inorganic salt was filtered off. The filtrate was concentrated to a syrup which was dissolved in ether, and the inorganic salt was filtered off again. The filtrate was dried over sodium sulfate. The syrup obtained by concentrating the ethereal solution was distilled under a vacuum. The yield was about 10%. The purification was effected by vacuum sublimation at 30~35°C. resulting in yellow crystals, m. p. 82~83°C.

Neopentoylformoin⁷⁾ In 100 ml of 70% aqueous alcohol, *t*-butylglyoxal hydrate²⁰⁾ (4 g) was dissolved. The solution was cooled to 0°C. To this solution, a solution of 0.25 g of sodium cyanide in 10 ml of 50% aqueous alcohol was added with stirring. The solution immediately colored yellow. After stirring for 30 min, alcohol was evaporated under reduced pressure. White crystals were collected by filtration and washed with water and dried in vacuo over phosphorus pentoxide. Yield, 2.3 g (73%). Recrystallization was effected from isopropanol. Yield, 18 g (56%). M.p. 170~171°C. Insoluble in ordinary organic solvents except alcohols.

Found: C, 63.04; H, 8.86; mol. wt. (Rast) 219. Calcd. for $C_{12}H_{18}O_4$: C, 63.16; H, 8.77%; mol. wt., 228.

When a crude glyoxal monomer²⁰⁾ was used, the procedure was the same except for purification; crude formoin was dissolved in a minimum amount of alcohol and precipitated with addition of water.

Isobutyrylformoin⁸⁾ Into a solution of 4.5 g of isopropylglyoxal in 150 ml. of 90% aqueous alcohol, a solution of 0.2 g sodium cyanide in 5 ml. of water was added under a nitrogen stream. The entire solution was then cooled at 0°C for about 20 minutes. After the addition of a few drops of phosphoric acid, the solvent was evaporated off under reduced pressure. The faint-colored crystals which appeared were washed with about 50 ml of cold water, then dissolved in a minimum amount of alcohol and crystallized by addition of water: yield, 68%; m. p. 88~93°C.

Found: C, 59.78; H, 7.75; mol. wt. (Rast), 186. Calcd. for $C_{10}H_{16}O_4$: C, 60.00; H, 8.00%; mol. wt., 200.

Benzoylformoin¹²⁾ Phenylglyoxal hydrate (1 g, m. p. 81°C) was dissolved in 35 cc of water, with slight warming if it was necessary. To this solution was added a solution of 0.04 g. of potassium cyanide (molar ratio to phenylglyoxal hydrate: 0.08) in 10 cc of water. Immediately the mixture colored yellow, and crystalline benzoylformoin began to precipitate. After 3 hr., the solution was neutralized with hydrochloric acid. Benzoylformoin was collected by filtration. The yield was about 85%. The recrystallisation was effected from aqueous ethanol. Yellow crystals, m. p., 186~188°C.

Mono-O-methyl neopentoylformoin In about 10 ml of 12% methanolic hydrogen chloride, 2 g of neopentoylformoin was dissolved. After standing overnight at room temperature, alcohol and acid were evaporated under reduced pressure. The residue, dried in vacuo over potassium hydroxide, was washed quickly with cold water and dried in vacuo over phosphorus pentoxide. M. p. 100.5~101°C.

20) R. C. Fuson, H. Gray and J. J. Gouza, *J. Am. Chem. Soc.*, **61**, 1937 (1939)

Found C, 64.64; H, 9.25; MeO, 12.75. Calcd. for $C_{13}H_{22}O_4$: C, 64.64, H, 9.07; MeO, 12.81%.

Mono-O-ethyl neopentoylformoin The procedure was the same as in methanolysis. M. p. 77~78°C.

Found: C, 65.41; H, 9.43. Calcd. for $C_{14}H_{24}O_4$: C, 65.52; H, 9.38.

Di-O-methyl neopentoylformoin

Method A. In 20 ml. of water containing 1 g. of potassium hydroxide, mono-O-methyl neopentoylformoin (4 g.) was dissolved. The solution was brilliant yellow. Into this solution, 2 g. of dimethyl sulfate was added during 30 minutes with stirring, and stirring was continued for additional 30 minutes. After the addition of 0.5 g. of potassium hydroxide, the dropping of 1 g. of dimethyl sulfate was continued for 30 minutes at 50°C. During the reaction, the yellow color of the solution was diminished and colorless oil separated. The whole solution was extracted with carbon tetrachloride. The extract was dried over anhydrous sodium sulfate. The solvent was evaporated and the residue of colorless liquid was distilled under reduced pressure. Fraction boiling at 107~108°C/5 mmHg was collected. Yield, 2.3 g (53%).

Found: C, 65.51; H, 9.40; MeO, 24.12. Calcd. for $C_{14}H_{24}O_4$: C, 65.52; H, 9.37; MeO, 24.22%.

Method B. In 30 ml of absolute methanol containing 0.6 g of sodium, mono-O-methyl neopentoylformoin (3.6 g.) was dissolved. The solution colored yellow. After addition of 20 g of methyl iodide, the solution was refluxed for 4 hr. During this period, the color of solution was diminished as in the method A. The solution was stood overnight at room temperature. After the addition of 10 ml of water, methanol was evaporated under reduced pressure. The residue was extracted with ether. The extract was dried over anhydrous sodium sulfate. Ether was evaporated off. The residue of pale yellow liquid was under distilled reduced pressure. Fraction boiling at 107~108°C/5 mmHg was collected. Yield, 2.1 g (58%).

Found: C, 65.51; H, 9.40%.

The infrared spectrum of the product in carbon tetrachloride solution was coincident with that of the product obtained in the method A even in details.

O-ethyl-O-methyl neopentoylformoin—This compound was prepared as in the method A and boiling at 107~108°C/5 mmHg.

Found: C, 66.74; H, 9.41; RO, 27.94. Calcd. for $C_{15}H_{26}O_4$: C, 66.66; H, 9.63; RO, 28.14%.

The conversion of mono-O-methyl neopentoylformoin to mono-O-ethyl neopentoylformoin and vice versa About 0.1 g of mono-O-methyl derivative was dissolved in 1 ml of 8% ethanolic hydrogen chloride and the procedure was the same as above. M. p. 78~79°C. The mixed melting point with the authentic O-ethyl derivative did not show any depression. The procedure was the same in the case of the O-ethyl neopentoylformoin to the O-methyl neopentoylformoin. M. p. 100~101°C. Not any depression of the melting point was observed at a mixed melting point.

The conversion of di-O-methyl neopentoylformoin to O-ethyl-O-methyl neopentoylformoin

A solution of 3 g of di-O-methyl neopentoylformoin in 15 ml of 12% ethanolic hydrogen chloride was stood overnight at room temperature. The solvent and the acid were evaporated under reduced pressure and evaporation was repeated with addition of absolute ethanol and the residue of liquid was dissolved in carbon tetrachloride. The solution was washed with cold water and dried over anhy-

drous sodium sulfate. The removal of the solvent, followed by distillation, gave 2.2 g of liquid boiling at $105\sim 109^{\circ}\text{C}/5\text{ mmHg}$.

Found: C, 66.65; H, 9.36; RO, 28.01%.

The first mono-O-methyl benzoylformoin Benzoylformin (4 g) was dissolved in ca. 10% methanolic hydrogen chloride (80 ml) with slight warming. After standing overnight, the solvent and the acid were evaporated off under reduced pressure. The residue was washed with cold water and dried in vacuo. The recrystallization was carried out from 50 ml. of ethanol: yellow needles; 3 g; m. p. $180\sim 2^{\circ}\text{C}$.

Found: C, 72.15; H, 4.91. Calcd. for $\text{C}_{17}\text{H}_{14}\text{O}_4$: C, 72.33; H, 5.00%. By addition of 10 ml. of water to the mother liquor, 1 g. of the product was collected; m. p., $176\sim 82^{\circ}\text{C}$.

Di-O-methyl benzoylformoin First mono-O-methyl benzoylformoin (2.5 g) was dissolved in a solution of 0.7 g of sodium methoxide in 50 ml of methanol. After an addition of 15 g of methyl iodide, the solution was evaporated off under reduced pressure. Water and ether were added to the residue. The product was obtained as yellow needles by evaporating ether from the ethereal layer and recrystallized from 2 ml. of methanol: 2.1 g; m. p., $79.5\sim 80.5^{\circ}\text{C}$.

Found: C, 72.85; H, 5.29. Calcd. for $\text{C}_{13}\text{H}_{16}\text{O}_4$: C, 72.96; H, 5.44%.

The second mono-O-methyl benzoylformoin—This compound was prepared by the method of Blatt⁽¹¹⁾; m. p., $120\sim 124^{\circ}\text{C}$.

Found: C, 72.19; H, 5.01. Calcd. for $\text{C}_{17}\text{H}_{14}\text{O}_4$: C, 72.33; H, 5.00%.

Ultraviolet spectra of neopentoylformoin and benzoylformoin in chloroform A definite quantity (3 ml) of tetrahydrofuran solution of neopentoylformoin (ca. $5 \times 10^{-5}\text{ M}$) was placed in a bottle A (Fig. 17), which was then attached to a vacuum line through the ground joint B. The solvent was distilled

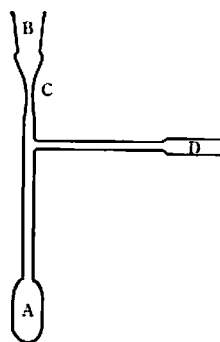


Fig. 17

off under 10^{-4} mmHg . Chloroform (3 ml) was placed in a flask, which was attached to the vacuum line, and chloroform was distilled into the bottle A cooled by liquid air under 10^{-4} mmHg . The thin glass tube C was sealed. After the content of the bottle A reached room temperature it was poured in the cell D and the spectrum was recorded. Consequently the molecular extinction coefficient was nearly correct. In the case of benzoylformoin, about 0.5 mg of crystals was placed in the bottle A and chloroform was distilled in by the same way as above: the intensity in Fig. 10 is arbitrary.

Alkoxy group The alkoxy group content was determined by the method of Hoffman and Wolfrom²¹⁾.

Spectra The infrared spectra were recorded with a Koken model DS-301 and IR-S spectrophotometer, 0.1 mm cells being used. The ultraviolet spectra were recorded with a Shimadzu model QR-50 spectrophotometer.

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21) D. O. Hoffman and M. L. Wolfrom, *Anal. Chem.*, **19**, 225 (1947)