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Synthesis of Dihydrooxadiazinones and Study of Geometrical Isomerism in α-Ketol Carbethoxyhydrazones

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A series of α-ketols and α-diketones are shown to be readily transformed to carbethoxyhydrazones II, IV, and thence to dihydrooxadiazinones III. These new derivatives of 1,3,4-oxadiazine may serve as useful intermediates for the conversion of such carbonyl compounds to olefins under nonreductive conditions. Evidence is presented which indicates that the urethano group is generally *syn* to the hydroxyl or carbonyl function in the intermediate carbethoxyhydrazones. A mechanism which accounts for this stereoselectivity is proposed.

In a previous note we reported the preparation of the diphenyldihydrooxadiazinone IIIa from benzoin and carbethoxyhydrazine.[1] Our interest in these heretofore unknown 1,3,4-oxadiazine derivatives was kindled by the observation that thermal decomposition of IIIa at 200° led to the loss of carbon dioxide and nitrogen and the formation of a mixture of *cis*- and *trans*-stilbene in good yield. Since in principle many other dihydrooxadiazinones were available from α-ketols by a simple two-step sequence (Fig. 1), the method constituted a potentially useful one for the removal of such oxygen functions under nonreductive conditions, and we have therefore sought to examine its generality. The present paper describes the preparation and properties of several dihydrooxadiazinones. Their pyrolysis will be treated in a subsequent report.

Results

We found that the carbethoxyhydrazones indicated in Fig. 1 were conveniently prepared by treatment of the α-ketols with equimolar quantities of carbethoxyhydrazine in an alcohol solution containing a catalytic amount of acetic acid. Their cyclization could be effected in moderate to good yield with a variety of base catalysts such as potassium carbonate or sodium hydride in benzene, sodium ethoxide in ethanol, or potassium *t*-butoxide in *t*-butyl alcohol. The progress of this latter reaction is easily observed by following the disappearance of the rather intense amide II band[2] (6.7 μ) in the infrared spectrum of the starting material.

With the exception of the carbethoxyhydrazone of the 2-hydroxy-2-methylbutanone (IIe), all of the α-ketol transformation products examined were easily characterized crystalline materials. These are listed in Table I. All of these substances were observed to decompose with gas evolution and without darkening below 200°.

In addition to these carbethoxyhydrazones, the C_8-, C_9-, and C_{10}- acyloins gave some of the dicarbethoxyhydrazone derivatives of the corresponding α-diketones. These are listed in Table II, along with several monocarbethoxyhydrazone derivatives of α-diketones prepared directly from the diketones. Of these, only benzil gave two isomeric monocarbethoxyhydrazones, of which the higher melting isomer was formed preponderantly.

Both this latter substance, as well as the corresponding derivative of cyclodecanedione (IVb) and of diacetyl (IVc), were readily reduced with sodium borohydride to the carbethoxyhydrazone of the related α-ketol. How-

TABLE I

	Carbethoxyhydrazone				Dihydrooxadiazinone			
		Yield,	Analyses, %			Yield,	Analyses, %	
α-Ketol	Mp., °C.	%	Calcd.	Found	M.p., °C.	%	Calcd.	Found
Benzoin α	175	77	C, 68.44	68.81	192	99[a]	C, 71.40	71.41
			H, 6.08	6.02		80[b]	H, 5.13	4.79
			N, 9.39	9.34		83[c]	N, 11.59	11.11
β	129	87[f]	C,	68.48				
			H,	6.03				
			N,	9.61				
2-Hydroxycyclooctanone	105	49	C, 57.89	57.98	96	46[d]	C, 59.34	58.54
			H, 8.77	8.68			H, 7.69	7.39
			N, 12.28	12.28				
2-Hydroxycyclononanone	114	48	C, 59.48	59.43	164	59[d]	C, 61.22	61.28
			H, 9.23	9.12			H, 8.16	8.36
			N, 11.50	11.70			N, 14.28	14.52
2-Hydroxycyclodecanone	119	36	C, 60.91	60.74	163	45[d]	C, 62.82	63.39
			H, 9.44	9.15		38[e]	H, 8.63	8.59
			N, 10.93	10.73		24[a]	N, 13.32	13.27
2-Hydroxy-2-methylbutanone	115 (1 mm.)	54			76	35[d]	C, 50.70	51.06
							H, 7.04	7.30
							N, 19.71	19.90
1-Acetylcyclohexanol	75	93	C, 57.89	57.81	119	82[d]	C, 59.43	59.43
			H, 8.77	8.61			H, 7.69	7.87
							N, 15.38	15.68
2-Hydroxy-2-butanone					60–61.5	5.5[e]	C, 46.87	46.75
							H, 6.29	6.23
							N, 21.87	21.75

[a] Potassium carbonate in refluxing benzene. [b] Sodium hydride in refluxing benzene. [c] Potassium *t*-butoxide in *t*-butyl alcohol. [d] Sodium ethoxide in ethanol. [e] Directly from monocarbethoxyhydrazone of α-diketone with sodium borohydride in ethanol. [f] By reduction of benzil monocarbethoxyhydrazone, β-isomer, with sodium borohydride in ethanol.

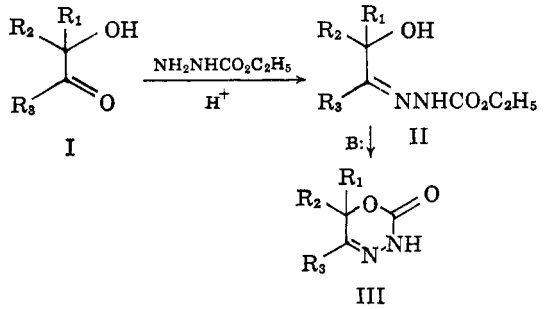
(1) M. Rosenblum and H. Moltzen, *Chem. Ind.* (London), 1480 (1956).

(2) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 203.

TABLE II

α-Diketone	Monocarbethoxyhydrazone M.p., °C.	Monocarbethoxyhydrazone Analyses, % Calcd.	Monocarbethoxyhydrazone Analyses, % Found	Dicarbethoxyhydrazone M.p., °C.	Dicarbethoxyhydrazone Analyses, % Calcd.	Dicarbethoxyhydrazone Analyses, % Found
Benzil α	128	C, 68.90	69.14	211	C, 62.80	62.77
		H, 5.44	5.13		H, 5.75	5.85
		N, 9.46	9.64		N, 14.70	15.41
β	114		C, 68.98			
			H, 5.48			
			N, 9.51			
Phenanthraquinone	174	C, 69.38	69.95			
		H, 4.80	4.81			
		N, 9.52	9.97			
Cyclohexanedione				129	C, 50.70	50.78
					H, 7.04	7.03
					N, 19.72	19.66
Cyclooctanedione				180	C, 53.84	53.59
					H, 7.69	7.47
Cyclononanedione				201	C, 55.21	54.72
					H, 8.03	8.09
					N, 17.17	17.16
Cyclodecanedione	132	C, 61.39	61.75	223	C, 56.45	56.45
		H, 8.72	8.99		H, 8.29	8.39
					N, 16.46	15.60
Diacetyl	145	C, 48.83	48.84	255 d.	C, 46.51	46.28
		H, 7.03	7.04		H, 7.00	7.23
		N, 16.27	16.15		N, 21.70	21.94

ever, when these reactions were carried out with excess borohydride, the intermediate α-ketol carbethoxyhydrazones underwent concurrent cyclization to the dihydrooxadiazinone (Fig. 2). Thus α-diketones may be



a, $R_1 = H$, $R_2 = R_3 = C_6H_5$ d, $R_1 = H$, $R_2 = R_3 = (CH_2)_8$
b, $R_1 = H$, $R_2 = R_3 = (CH_2)_6$ e, $R_1, R_2, R_3 = CH_3$
c, $R_1 = H$, $R_2 = R_3 = (CH_2)_7$ f, $R_1 = R_2 = (CH_2)_5$, $R_3 = CH_3$

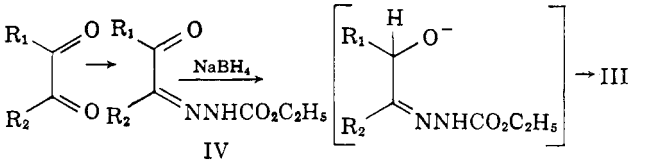
Figure 1.

made to serve as starting materials in the synthesis of these heterocyclic derivatives, and the degradative sequence, exemplified by the transformation of benzoin, may in principle be applied to these substances, as to α-ketols.

Discussion

Since successful application of the degradative sequence required cyclization of the α-ketol carbethoxyhydrazones, we were particularly interested in defining the limitations of this step, particularly those imposed by geometrical isomerism. The fact that all the carbethoxyhydrazones studied were cyclized under relatively mild conditions requires that either *syn–anti* interconversion in these substances is a facile process, or that all possess the *syn*-hydroxyl configuration.

The latter assumption did not appear particularly plausible especially for the ketol carbethoxyhydrazones IIe and IIf. Nevertheless, there is very little evidence to suggest that isomeric carbethoxyhydrazones would readily equilibrate. Thus, while the rates of *syn–anti* interconversion of some oximes appear to be appreciable below 100° and to be subject to base catalysis,[3] most oximes are considerably more resistant to such isomerization.[4] Unfortunately, very little is known about the energy barrier for interconversion of geometrically isomeric semicarbazones which are more closely related to the carbethoxyhydrazones than are the oximes. Isomeric semicarbazones and substituted semicarbazones derived from benzoin alone have been isolated,[5] but there would appear to be ample evidence, based on n.m.r. studies, for the wider occurrence of such isomers.[6]



a, $R_1 = R_2 = C_6B_5$; b, $R_1 = R_2 = (CH_2)_8$; c, $R_1 = R_2 = CH_3$

Figure 2.

The isolation of the two geometrically isomeric monocarbethoxyhydrazones of benzil provided the means by which each of the above hypotheses could be examined. Stereochemical assignments for each of the isomers may be inferred from a comparison of the position of N–H proton resonance in these substances (Table III). On these grounds, the higher melting α-isomer must have the *syn*-keto configuration since its lower field N–H proton resonance reflects the anticipated deshielding effect of the proximate carbonyl group. Further evidence for these assignments is provided by a comparison of the n.m.r. spectra of the isomeric benzoin carbethoxyhydrazones, obtained by reduction of the benzil derivatives with sodium borohydride. As expected, each of the isomeric benzoin derivatives exhibits the same relative disposition of N–H proton resonance as do the parent benzil derivatives. Of these substances, the α-isomer derived from α-benzil carbethoxyhydrazone

(3) R. J. W. LeFevre and J. Northcott, *J. Chem. Soc.*, 2235 (1949); E. Jordan and C. R. Hauser, *J. Am. Chem. Soc.*, **58**, 1304 (1936); T. S. Patterson and H. H. Montgomerie, *J. Chem. Soc.*, 2100 (1912).

(4) E. G. Vassian and R. K. Murmann, *J. Org. Chem.*, **27**, 4309 (1962); W. Theilacker and L. H. Chou, *Ann.*, **523**, 143 (1936).

(5) I. Hopper, *J. Chem. Soc.*, 1282 (1925).

(6) G. J. Karabatsos, J. D. Graham, and F. M. Vane, *J. Am. Chem. Soc.*, **84**, 753 (1962).

TABLE III

CHEMICAL SHIFTS OF N–H PROTON RESONANCE IN CARBETHOXYHYDRAZONES

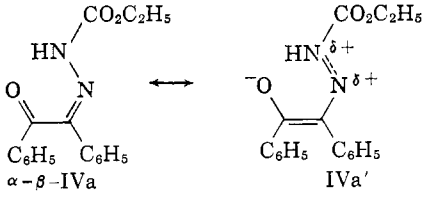
Parent compound	N–H chemical shifts, τ[a] CDCl$_3$	DMSO[b]
Acetone	2.28	0.45
Pinacolone	2.46	
Benzophenone	2.21–2.92[c]	
2-Hydroxycyclooctanone	2.13	
2-Hydroxycyclononanone	2.04	
2-Hydroxycyclodecanone	2.08	
2-Hydroxy-2-methylbutanone	2.15	
1-Acetylcyclohexanol	1.90	
Benzoin		
syn-Hydroxy (m.p. 175°)	..[e]	−1.01
anti-Hydroxyl (m.p. 129°)	2.27	1.31
Diacetyl[d]	1.66	
1,2-Cyclodecanedione[d]	1.78	
Benzil[d]		
syn-Keto (m.p. 128°)	1.31	−0.93
anti-Keto (m.p. 114°)	1.83–2.50[c]	−0.13
Phenanthraquinone	−4.10	

[a] All spectra were determined at a concentration of approximately 60 mg./cc. and recorded at 60 Mc. with a Varian Model V-4300 spectrometer. Peak positions were calibrated against tetramethylsilane as internal standard by side banding with a standard deviation of ±2 c.p.s. [b] Deuteriodimethyl sulfoxide. [c] N–H peak position obscured by aromatic proton resonance. [d] Monocarbethoxyhydrazone. [e] Not sufficiently soluble in CDCl$_3$.

was identical with the product obtained directly from benzoin.

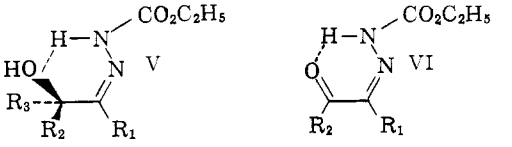
The most convincing evidence for the stereochemistry of these latter isomers was obtained by heating each in benzene solution in the presence of anhydrous potassium carbonate. After 24 hr. of such treatment, the α-isomer had undergone quantitative cyclization to IIIa, while 50% of the β-isomer was recovered unchanged and the remainder yielded only 1.4% of IIIa. Aside from confirming the stereochemical assignments, these results demonstrate that these isomers, and very likely all of the carbethoxyhydrazones studied, are not readily interconverted.[7] Furthermore, the β-isomer was not cyclized in the presence of ethoxide ion, although this reagent was found to be the most generally effective catalyst for the conversion of α-ketol carbethoxyhydrazones to their corresponding dihydrooxadiazinones. It is therefore improbable that the cyclization of these latter derivatives proceeds *via* initial addition of ethoxide ion to the hydrazone linkage. Moreover, the carbethoxyhydrazone of cyclodecanolone, prepared either directly from the acyloin or by borohydride reduction of the diketone monocarbethoxyhydrazone, could also be cyclized in benzene solution in the presence of potassium carbonate, albeit in lower yield than with ethoxide. It seems probable, therefore, that all these derivatives possess the *syn*-hydroxyl geometry.

(7) This conclusion is probably not valid for monocarbethoxyhydrazones of α-diketones. Thus, the two isomeric derivatives of benzyl were observed to be slowly interconverted on heating in benzene solution. The more facile equilibration of these isomers is accounted for in terms of contributions of the dipolar resonance form IVa′ which effectively lowers the energy barrier for *syn–anti* interconversion.

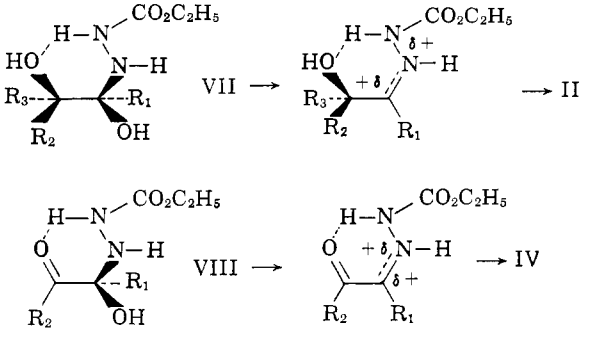


Peak positions for the N–H proton resonance of all of the carbethoxyhydrazones prepared are summarized in Table III. These exhibit a downfield shift for α-ketol and α-diketone carbethoxyhydrazones, compared with derivatives of the simple ketones, consistent with the above conclusions. While deshielding of the amido proton in the α-ketol carbethoxyhydrazones is to be attributed to internal hydrogen bonding as in V, such interactions may be relatively weak in the α-diketone derivatives, and the chemical shift of the N–H proton in these substances may be largely conditioned by proximity to the carbonyl group. Thus, the gross deshielding effect of the N–H proton in these substances is much less pronounced than in the hydrogen-bonded Schiff bases of acetylacetone recently discussed by Dudek and Holm.[8] Several factors may account for this difference, not the least of which is the steric interaction of groups bonded to the trigonal carbon atoms, which is maximized in the S-*cis* conformation (VI) required for effective hydrogen bonding in these substances. Such interactions would be expected to be greatest in the *syn*-benzil carbethoxyhydrazone, and indeed the infrared N–H absorption in this substance is at 2.99 μ while that of the *anti* isomer is at 3.00 μ. By contrast, the O–H and N–H infrared absorptions for the isomeric benzoin derivatives are clearly distinguishable and, as can be seen from the data of Table III, the difference in chemical shifts for the N–H proton in these substances is significantly greater than in the benzil derivatives.

The monocarbethoxyhydrazones of cyclodecanedione (IVb) and of diacetyl (IVc) must have the *syn*-keto configuration since each is converted on reduction with excess sodium borohydride to the corresponding dihydrooxadiazinone. None of the isomeric derivatives of these compounds could be isolated and each is transformed by further treatment with carbethoxyhydrazine to dicarbethoxyhydrazones identical with those formed directly from the diketones. These latter derivatives must therefore possess the *syn–anti* or the *syn–syn* configuration.



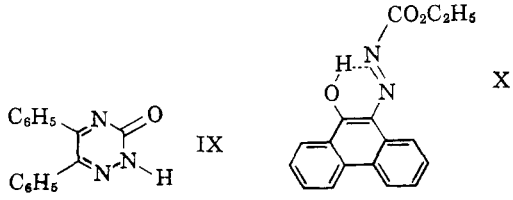
The preferential formation of carbethoxyhydrazone derivatives in which the urethan group is *syn* to the carbonyl or hydroxyl function is best accommodated by assuming that the initial intermediates undergo product-determining dehydration through their internally hydrogen-bonded forms VII or VIII. It is perhaps significant that in the case of benzil, in which stabilization of such an intermediate is likely to be quite small, both of the geometrically isomeric carbethoxyhydrazones may be isolated.



(8) G. O. Dudek and R. H. Holm, *J. Am. Chem. Soc.*, **83**, 2099, 3914 (1961); **84**, 2691 (1962); G. O. Dudek, *ibid.*, **85**, 694 (1963).

Similar stereochemical control is apparently manifest in the formation of semicarbazones of benzoin and benzil. Each of these derivatives is reported to be readily converted to the same diphenyltriazinone IX, the former apparently through oxidative disproportionation.[9] The relative stabilities reported for a number of α-alkoxy ketone phenylhydrazone[10] and 2,4-dinitrophenylhydrazone[11] isomers are likewise explicable in these terms.

Of the diketones, phenanthraquinone alone gave a derivative which is best formulated as 9-hydroxy-10-carbethoxyazophenanthrene (X). Its n.m.r. spectrum exhibited single proton absorption at -4.10 τ, which is significantly lower than that observed for either of the related benzil derivatives, but quite close to the hydroxyl proton absorption reported for the related 6-methyl-6-hydroxy-2-phenylazofulvene.[12] Unlike the 2- and 4-arylazo-1-naphthols,[13] the substance does not appear to be in equilibrium with its ketohydrazone tautomer, since its infrared spectrum exhibits broad absorption between 3.1 and 3.4 μ and no carbonyl absorption near that found in the spectra of the benzil derivatives. The compound is assigned a *trans*-azo stereochemistry, since it is not converted to the expected oxadiazinone on treatment with a variety of basic reagents. Further efforts directed toward the preparation of this cyclic transformation product are being continued, since it may serve as an interesting precursor of phenanthryne.



IX

X

Experimental

The cyclic C_8-, C_9-, and C_{10}-α-ketols were prepared by acyloin condensations following procedures given in the literature. The remaining starting materials were commercially available.

Preparation of α-Ketol Carbethoxyhydrazones.—Three typical procedures for the preparation of these derivatives are given.

1-Acetylcyclohexanol Carbethoxyhydrazone (IIf).—A solution of 24.0 g. (0.196 mole) of 1-acetylcyclohexanol, 17.6 g. (0.196 mole) of carbethoxyhydrazine,[14] m.p. 46–48°, and 2 ml. of acetic acid in 110 ml. of absolute ethanol was refluxed for 24 hr. The solvent was removed *in vacuo* and the residue was taken up in 200 ml. of ether. The ether solution was washed with 10 ml. of saturated bicarbonate solution, then with saturated salt solution, and dried over magnesium sulfate. Removal of solvent left 39.1 g. of viscous oil which solidified on scratching. Recrystallization from ether–petroleum ether solutions gave 35.9 g. (93%) of the carbethoxyhydrazone.

Benzoin Carbethoxyhydrazone (IIa).—A mixture of 11 g. (0.052 mole) of benzoin and 5.4 g. (0.052 mole) carbethoxyhydrazine, dissolved in 300 ml. of ethanol containing 1 ml. of glacial acetic acid, was refluxed for 8 hr. and then allowed to stand overnight at room temperature. The solution was concentrated to half its volume and 300 ml. of water was added. The first crop of material, m.p. 170–173°, weighed 9.8 g. On standing, an additional 2.3 g. of material, m.p. 170–173°, was obtained. These crops were combined and recrystallized from ethanol to give 11.5 g. of product, m.p. 175–176° (77%).

Cyclooctanolone Carbethoxyhydrazone (IIb).—A solution of 3.8 g. (0.027 mole) of cyclooctanolone and 2.8 g. (0.027 mole) of carbethoxyhydrazine in 20 ml. of ethanol containing 0.3 ml. of glacial acetic acid was kept at room temperature in a nitrogen atmosphere for 24 hr. Solvent was then removed *in vacuo* and the gummy residue was taken up in 50 ml. of ether. After standing for several hours in the cold, 3.0 g. (49%) of crystalline product, m.p. 105–107°, was collected.

Concentration of the mother liquors yielded, after several recrystallizations from ethanol, 0.4 g. of 1,2-cyclooctanedione dicarbethoxyhydrazone, m.p. 180–182°.

Preparation of Dihydrooxadiazinones.—Three examples of these cyclization reactions are given.

From Cyclodecanolone.—Cyclodecanolone carbethoxyhydrazone (1.28 g., 5 mmoles) was added to a freshly prepared solution of sodium ethoxide (0.5 mmole) in 40 ml. of ethanol. The solution was refluxed in a nitrogen atmosphere for 16 hr., then cooled and diluted with 150 ml. of water. The aqueous ethanol solution was extracted twice with 100-ml. portions of ether and the combined ether extract was washed to neutrality and dried over magnesium sulfate. Removal of solvent left a partially crystalline material which was crystallized from ethanol to give 470 mg. of cyclized product IIId, m.p. 162–163° (45% yield).

From Benzoin.—A solution of 0.500 g. (1.68 mmoles) of benzoin carbethoxyhydrazone, m.p. 175°, in 20 ml. of dry benzene containing 25 mg. of anhydrous potassium carbonate was refluxed for 24 hr. The material, which crystallized from the cooled solution, was washed with water and dried to give 370 mg. of cyclized product IIIa, m.p. 195–195.5°. An additional 50 mg. of product, m.p. 194–195°, was obtained from the solution; total yield (99%).

From 1-Acetylcyclohexanol.—To a solution of sodium ethoxide (0.02 mole) in 20 ml. of absolute ethanol was added 4.56 g. (0.02 mole) of 1-acetylcyclohexanol carbethoxyhydrazone. The solution was refluxed for 5 days, then cooled, diluted with 75 ml. of water and extracted with 200 ml. of ether in portions. The combined ether extract was washed with saturated salt solution to neutrality and dried over magnesium sulfate. Removal of solvent gave 3.3 g. of crude material, m.p. 120–127° (IIIf). Recrystallization of the crude material from ether–petroleum ether solutions gave 2.98 g. of product, m.p. 126–128° (82% yield). An analytical sample melted at 128–129°.

Benzil Monocarbethoxyhydrazones (IVa, α and β).—A solution of 10.5 g. of benzil (0.05 mole), 5.2 g. of carbethoxyhydrazine (0.05 mole), and 1 ml. of glacial acetic acid in 600 ml. of absolute ethanol was heated on the steam bath for 2 hr. and then allowed to stand at room temperature overnight. A total of 8.25 g. of monocarbethoxyhydrazone, m.p. 122–124°, was obtained from several initial crops by recrystallization from ethanol. No attempt was made to isolate the lower melting derivative, but in a second experiment after allowing the reaction to proceed at reflux temperatures for 5 days, the α- and β-isomers were obtained in yields of 13 and 4.7%, respectively. In addition, a 10% yield of the dicarbethoxyhydrazone, m.p. 205–212°, was obtained.

Reduction of Benzil Monocarbethoxyhydrazone Isomers. α-Isomer.—Benzil monocarbethoxyhydrazone (m.p. 126–128°, 0.660 g., 2.2 mmoles) was added to a solution of 0.100 g. of sodium borohydride (2.6 mmoles) in methanol. After allowing the reaction to proceed at room temperature in a nitrogen atmosphere for 24 hr., the solution was cooled, acidified with dilute hydrochloric acid, and extracted with ether. The combined ether extract was washed to neutrality and dried over magnesium sulfate. Removal of ether left 0.590 g. of crude product which on fractional crystallization from ethanol gave 0.185 g. of benzoin carbethoxyhydrazone, m.p. 175–176°, identical by mixture m.p. and comparison of infrared spectra with the derivative obtained directly from benzoin. In addition, 0.260 g. of starting material was recovered.

β-Isomer.—To an ethanolic solution of 1.000 g. (3.38 mmoles) of benzil monocarbethoxyhydrazone, m.p. 114–116°, was added 64 mg. (1.73 mmoles) of sodium borohydride in one portion. The mixture was stirred at room temperature for 10 min., then cooled in an ice bath and decomposed with 80 ml. of 0.1 *N* hydrochloric acid. The solution was then neutralized with 20 ml. of 4% sodium bicarbonate solution and the precipitated product was filtered, washed with water, and dried. The yield of product, m.p. 128–129°, was 0.880 g. (87%).

Attempted Cyclization of the β-Isomer.—A mixture of 0.500 g. (1.68 mmoles) of benzoin carbethoxyhydrazone, m.p. 128–129°, and 25 mg. of anhydrous potassium carbonate in 20 ml. of dry benzene was refluxed in a nitrogen atmosphere for 24 hr. The benzene solution was washed with water and dried over anhydrous magnesium sulfate. Removal of solvent gave a yellow oil. Crystallization of this material from ether–petroleum ether solution gave 0.222 g. of starting material. The residue was chromatographed on 15 g. of Merck alumina, containing 3% water. Elution with benzene–ether mixtures led to the isolation of 6 mg. (1.4%) of the dihydrooxadiazinone (IIIa), m.p. 193–195°, and the recovery of an additional 20 mg. of starting material.

Reduction of Benzil Monocarbethoxyhydrazone with Concurrent Cyclization.—Benzil monocarbethoxyhydrazone, (m.p. 126–128°, 0.500 g., 1.7 mmoles) was taken up in 12 ml. of absolute ethanol, and to this solution was added 200 mg. of sodium borohydride. The solution was stirred at room temperature in a nitrogen atmosphere for 18 hr., after which time an additional 200 mg. of sodium borohydride was added and reaction was con-

(9) H. Blitz, *Ann.*, **339**, 243 (1905); J. Thiele and O. Strange, *ibid.*, **283**, 6 (1895).

(10) J. Thesing and D. Witzel, *Ber.*, **88**, 117 (1955).

(11) F. Ramirez and A. F. Kirby, *J. Am. Chem. Soc.*, **76**, 1037 (1954); **75**, 6026 (1953).

(12) K. L. Rinehart and R. E. Bozak, *ibid.*, **84**, 1584 (1962).

(13) K. J. Morgan, *J. Chem. Soc.*, 2151 (1961).

(14) O. Diels, *Ber.*, **47**, 2183 (1914).

tinued for 6 more hours. The solution was cooled, acidified with dilute hydrochloric acid, and extracted with ether. The combined ether extract was washed to neutrality, dried over magnesium sulfate, and solvent was removed. Recrystallization of the crude product gave 0.300 g. of the dihydrooxadiazinone IIIa, m.p. 192–193° (70% yield).

Derivatives of Simple Ketones; Pinacolone Carbethoxyhydrazone.—Pinacolone (3.8 g., 0.038 mole) and carbethoxyhydrazine (4 g., 0.038 mole) were dissolved in 25 ml. of absolute ethanol containing 3 drops of glacial acetic acid. The solution was left to stand for 12 hr. at room temperature, after which time ethanol was removed *in vacuo* and the residue was taken up in 25 ml. of ether. On keeping in the cold, the derivative crystallized to give 3.5 g. of product, m.p. 85–86°.

Anal. Calcd. for $C_9H_{18}O_2N_2$: C, 58.06; H, 9.68; N, 15.05. Found: C, 58.05; H, 9.42; N, 15.03.

The carbethoxyhydrazone derivatives of acetone, m.p. 75–76°, and of benzophenone, m.p. 115–117° were similarly prepared.

Anal. Calcd. for $C_6H_{12}N_2O_2$: C, 50.00; H, 8.33; N, 19.44. Found: C, 50.38; H, 8.39; N, 18.89. Calcd. for $C_{16}H_{16}O_2N_2$: C, 71.64; H, 5.97; N, 10.45. Found: C, 71.55; H, 6.03; N, 10.31.

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The Reactions of Phosphorus Compounds. VIII. Kinetics and Mechanism of the Wittig Reaction

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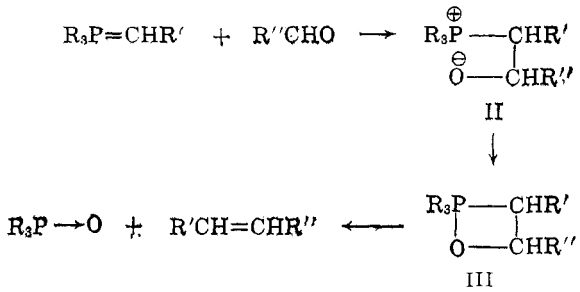
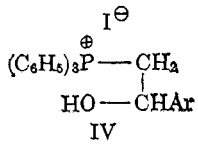
The rates of reaction of carbomethoxymethylenetriphenylphosphorane with a series of aromatic aldehydes have been studied in benzene, chloroform, and methanol. The reaction is cleanly second order, first order in each of ylid and aldehyde. The reaction rate is increased by increasing solvent polarity, by substitution of butyl for phenyl on phosphorus in the ylid, and by electron-withdrawing substituents in the aldehyde. The slope of the $\rho\sigma$ plot is +2.7. The reversibility of betaine formation in the Wittig reaction of stable ylids has been demonstrated by trapping the ylid formed by decomposition of the betaine derived from reaction of a phosphine with an epoxide. A mechanism for the Wittig reaction of stable ylids is proposed and substantiated.

Although the synthetic applications of the Wittig reaction are well known,[1,2] a detailed mechanistic study has not been reported. Investigations from these laboratories[3,4] as well as others[5–8] have treated this reaction in qualitative terms. We wish now to amplify our recent communication[9] of the kinetics, stereochemistry, and mechanism of the Wittig reaction.



The importance of II and/or III has not been definitely established although their existence has been demonstrated by the isolation of IV from reaction of II or III (R = C_6H_5, R′ = H, R″ = Ar) with hydrogen iodide.[5]



Since IV, on heating, gave triphenylphosphine oxide and styrene and only trace amounts of 1,1-diphenylethylene in the presence of benzophenone, irreversible formation of the betaine II was postulated.[5]

In the reaction of the stable triphenyl- and tributylphosphonium fluoreneylids with carbonyl compounds, the betaine intermediate could not be trapped by quenching the reaction with acid.[6a,b] In each case, only the phosphonium salt derived from the starting ylid was isolated. The tributyl ylids furnished much better yields of olefin than did the triphenyl ylids under similar reaction conditions. These data provided evidence for an inherent difference in the mechanistic path for reaction of stable and unstable ylids.[10]

Stable ylids, in their reactions with carbonyl compounds, gave predominantly the *trans*-olefins,[4,11,12] while unstable ylids yielded mixtures of the two possible stereoisomers.[13,14] In an attempt to explain the stereoselectivity of the reaction of methylcarbomethoxymethylenetriphenylphosphorane with acetaldehyde, House and Rasmusson[7] postulated that steric interactions between ylid and aldehyde in the formation of the betaine intermediate were not sufficient to account for the observed product ratio (96.5% methyl tiglate and 3.5% methyl angelate). They proposed instead a mechanism involving rapid, reversible formation of two stereoisomeric betaines, one of which decomposes to olefin and phosphine oxide faster than the other. The transition state for decomposition of the betaine leading to *trans*-olefin would be stabilized by overlap of the π-orbitals of the carbomethoxy group with those of the incipient double bond, while steric interactions between the carbomethoxy group and the eclipsed methyl group would prohibit similar stabilization of the transition

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