51. *Chalkones: Production of* iso*Oxazoles from Some Chalkone Derivatives.*

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The action of hydroxylamine in presence of alkali on a chalkone dibromide (IV) provides an unambiguous synthesis of the resulting *iso*oxazole (II), and the reaction can therefore be employed to determine which of the two possible *iso*oxazoles, (II) or (III), is obtained from the related dibenzoylmethane (I) and hydroxylamine. No simple relation can be traced between the substituents in (I) and the structure of the preferred *iso*oxazole.

The action of hydroxylamine on unsymmetrical dibenzoylmethanes (I) normally proceeds

as shown at (*a*), one or other, but seldom both (see footnote **4** to the table), of the corresponding isomeric 3 : 5-diaryl substituted *iso*oxazoles (II) and (III) being produced :

$$(a)\quad \underset{\text{(I.)}}{R_1\cdot CO\cdot CH_2\cdot CO\cdot R_2} \xrightarrow{NH_2\cdot OH} R_1\cdot C\!<\!\begin{matrix}CH{:}CR_2\\ |\\ N\!-\!O\end{matrix}\ \text{(II.)}\quad \text{or}\quad R_1\cdot C\!<\!\begin{matrix}CH\cdot CR_2\\ ||\\ O\!-\!N\end{matrix}\ \text{(III.)}$$

The determination of which of the isomers (II) and (III) is produced in (*a*) requires that there should be available a simple unambiguous synthesis of these compounds. The action of hydroxylamine in alcoholic solution on the chalkone dibromide (IV) in presence of alkali proceeds thus

$$(b)\quad \underset{\text{(IV.)}}{R_1\cdot CO\cdot CHBr\cdot CHBrR_2} \xrightarrow[NaOH]{NH_2\cdot OH} \text{(II)}$$

and provides an easy method for determining the course of reaction (*a*). This statement is based on the following considerations :

(1) Weygand and Bauer (*Annalen*, 1927, **459**, 123) synthesised the two isomeric 3 : 5-phenyl-*p*-anisyl*iso*oxazoles by the following unambiguous method :

$$(c)\quad R_1\cdot CCl(:NOH) + NaC{:}CR_2 \longrightarrow \text{(II)}$$

and confirmed reaction (*b*) for (IV; R_1 = Ph, R_2 = *p*-anisyl) and for (IV; R_1 = *p*-anisyl, R_2 = Ph).

(2) Auwers and Brink (*J. pr. Chem.*, 1932, **133**, 159) prepared 5-phenyl-3-methyl*iso*oxazole by the application of reaction (*b*) to Me·CO·CHCl·CHClPh; the structure of the two 3 : 5-phenylmethyl*iso*oxazoles had already been fixed by Weygand and Bauer (*loc. cit.*) using reaction (*c*).

(3) Auwers and Brink (*loc. cit.*, p. 156) obtained 5-phenyl-3-styryl*iso*oxazole by the action of hydroxylamine in presence of alkali on Ph·CH:CH·CO·CHBr·CHBrPh; the structure was fixed by the previous preparation of the 3-phenyl-5-styryl isomer by Ciusa and Terni (*Atti R. Accad. Lincei*, 1911, [v], **20**, ii, 25) from Ph·CH:CH·CH(NH·OH)·CH_2·C(:NOH)Ph by oxidation.

(4) Blatt (*J. Amer. Chem. Soc.*, 1931, **53**, 1133) showed that the oxime of *p*-bromophenyl αβ-dibromo-β-phenylethyl ketone gave with alkali the same *iso*oxazole (3-*p*-bromophenyl-5-phenyl*iso*oxazole) as was obtained by the action of alkali and hydroxylamine on *p*-bromophenyl αβ-dibromo-β-phenylethyl ketone (IV; R_1 = *p*-bromophenyl, R_2 = phenyl)-

(5) Weygand and Bauer (*loc. cit.*) also employed reaction (*c*) to show that the action of hydroxylamine in weak acid, neutral or alkaline solution on the two isomeric enol ethers Ph·CO·CH:C(OMe)·C_6H_4·OMe (*p*) and *p*-C_6H_4(OMe)·CO·CH:C(OMe)Ph proceeded thus :

$$(d)\quad \underset{\text{(V.)}}{R_1\cdot CO\cdot CH{:}C(OAlk)R_2} \xrightarrow{NH_2\cdot OH} \text{(III)}$$

so that when reactions (*b*) and (*d*) apply, the related compounds (IV) and (V) yield isomeric 3 : 5-disubstituted *iso*oxazoles. In mineral acid solution, (V) is immediately hydrolysed to (I) (see Claisen, *Ber.*, 1926, **59**, 144).

This production of isomeric *iso*oxazoles from (IV) and (V) has now been confirmed for the cases when R_1 and R_2 are respectively phenyl, 6-bromo-3 : 4-methylenedioxyphenyl; phenyl, *p*-tolyl; *p*-tolyl, phenyl; β-naphthyl, phenyl; *p*-anisyl, *p*-tolyl; and *p*-tolyl, *p*-anisyl. These results and those of Weygand and Bauer are summarised in the table (columns 1—4; rows 1—8). Columns 3 and 4 give the m. p.'s of the *iso*oxazoles (II) and (III) obtained from (IV) and (V) by reactions (*b*) and (*d*) respectively. The results for the related compounds given in rows 1 and 2, 4 and 5, and 7 and 8 are interesting; taking rows 1 and 2 in detail, it will be seen that the *iso*oxazole obtained from (IV) in row 1 is the same as that formed from (V) in row 2 and *vice versa*; similar results were obtained with the other pairs.

(6) The course given for reaction (*b*) is further supported by a consideration of the

probable mechanism of the reaction. Weygand and Bauer (*loc. cit.*) pointed out that (V), which is a final product of the prolonged action of alkali in alcoholic solution on (IV), could not in view of the production of (III) in (*d*) be an intermediate in (*b*); they suggested, therefore, the possibility of the intermediate formation of the acetal $R_1{\cdot}CO{\cdot}CH_2{\cdot}C(OAlk)_2R_2$. Such acetals are, however, only formed from (IV) in quantity in certain instances (see Kohler and Addinall, *J. Amer. Chem. Soc.*, 1930, **52**, 3728; cf. Auwers and Seyfried, *Annalen*, 1930, **484**, 186). The monobromochalkone $R_1{\cdot}CO{\cdot}CBr{:}CHR_2$ (VI), which is always the first product of the restricted action of alkali on (IV) (see Nadkarni *et al.*, J., 1937, 1798), is more likely as an intermediate. (VI), like the parent chalkone $R_1{\cdot}CO{\cdot}CH{:}CHR_2$, can be made to react with hydroxylamine to yield an oxime (see, for example, Auwers and Brink, *Annalen*, 1932, **493**, 218). This oxime with alkali, or (VI) with hydroxylamine and alkali, gives (II) (Weygand and Bauer, *loc. cit.*; Auwers and Brink, *loc. cit.*). The production of (II) from (IV) is therefore to be expected.

These considerations confirm the view stated above, and already implied by previous workers (see Allen *et al.*, *Canadian J. Res.*, 1932, **7**, 643; 1934, **11**, 388), that reaction (*b*) provides a simple unambiguous synthesis of 3 : 5-diaryl substituted *iso*oxazoles, and may therefore be employed to determine the course of reaction (*a*).

The table (column 5) gives the m. p.'s of *iso*oxazoles prepared from (I) either in the present research or previously, for which data are available to fix the structure. This

1	2	3	4	5	6
		M. p. of the *iso*oxazole (II), 3-R_1—5-R_2, from (IV) by reaction (*b*).	M. p. of the *iso*oxazole (III), 5-R_1—3-R_2, from (V), in presence of dil. acetic acid, or in neutral or alkaline solution, by reaction (*d*).	M. p. of *iso*oxazole from (I) by reaction (*a*).	Carbonyl carbon atom (×) which is linked to N in the *iso*oxazole obtained from (I) by reaction (*a*).
R_1.	R_2.				$R_1{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}R_2$.
1	Ph	*p*-$C_6H_4{\cdot}OMe$	128° [1]	121° [2]	121° [1, 2]		×
2	*p*-$C_6H_4{\cdot}OMe$	Ph	121 [2]	128 [2]	,,	×	
3	Ph	3 : 4-CH_2O_2:$C_6H_2Br(6)$	157 [3]	179 [3]	157 [3]	×	
4	,,	*p*-C_6H_4Me	136 [3]	125 [2]	125 [4]		×
5	*p*-C_6H_4Me	Ph	125 [3]	136 [2]	,,	×	
6	β-$C_{10}H_7$	,,	152 [3]	160 [3]	160 [3]		×
7	*p*-$C_6H_4{\cdot}OMe$	*p*-C_6H_4Me	148 [3]	130 [3]	130 [3]		×
8	*p*-C_6H_4Me	*p*-$C_6H_4{\cdot}OMe$	130 [3]	148 [3]	,,	×	
9	*o*-$C_6H_4{\cdot}OH$	Ph	231 [3]	—	231 [3]	×	
10	Ph	3 : 4-CH_2O_2:C_6H_3	130 [3]	—	130 [3]	×	
11	*p*-Ph·C_6H_4	Ph	195 [5]	—	182 [5]		×
12	*p*-$C_6H_4{\cdot}CH{:}CH$	,,	144 [6]	—	138 [6]		×
13	*p*-C_6H_4Cl	3 : 4-CH_2O_2:C_6H_3	180 [7]	—	180 [7]	×	
14	*p*-C_6H_4Me	,,	135 [8]	—	135 [8]	×	
15	,,	3 : 4-CH_2O_2:$C_6H_2Br(6)$	127 [8]	—	127 [8]	×	
16	Ph	*p*-$C_6H_4{\cdot}NO_2$	—	—	221 [9]		×
17	,,	Me	—	43 [10, 12]	68 [10]		×
18	Me	Ph	68 [11]	68 [10, 12]	,,	×	

[1] Pond and Shoffstall, *J. Amer. Chem. Soc.*, 1900, **22**, 658. [2] Weygand and Bauer, *Annalen*, 1927, **459**, 123. [3] Present research. [4] Present research, but Weygand (*Annalen*, 1927, **459**, 104) states that a mixture of the isomeric *iso*oxazoles is obtained. Kohler *et al* (*J. Amer. Chem. Soc.*, 1919, **41**, 1697) found that $Ph{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}CMe_3$ gave a mixture of *iso*oxazoles with hydroxylamine. No other report of the production of other than a single *iso*oxazole from an unsymmetrical 1 : 3-diketone has been traced. [5] Allen and Ball, *Canadian J. Res.*, 1932, **7**, 643. [6] Auwers and Brink, *J. pr. Chem.*, 1932, **133**, 156; Ryan and Dunlea, *Proc. Roy. Irish Acad.*, 1913, **32B**, 1. [7] Allen *et al.*, *Canadian J. Res.*, 1934, **11**, 382. [8] Nadkarni *et al.*, J., 1937, 1798. [9] Wieland (*Ber.*, 1904, **37**, 1151) showed this compound to be 5-phenyl-3-*p*-nitrophenyl*iso*oxazole by a method involving reduction. [10] Claisen, *Ber.*, 1926, **59**, 144. [11] Auwers and Brink (*loc. cit.*, p. 159); the dichloride was used. [12] As Weygand and Bauer (*loc. cit.*) point out, the enol ethers of benzoylacetone do not react with hydroxylamine as shown in reaction (*d*). Here oximation occurs, so that the same *iso*oxazole is obtained from (IV) and (V) (cf. row 18, columns 3 and 4).

structure can be deduced by comparison of the m. p.'s in column 5 with those of the *iso*-oxazoles obtained in reaction (*b*), which are, as explained above, given in column 3; the results obtained in reaction (*d*), which are given in column 4, are available in a number of cases, and, as previously mentioned, support the results given by (*b*). The structure of one *iso*oxazole (row 16) has been otherwise determined. The structures of the *iso*-oxazoles obtained from (I) are indicated in column 6.

An examination of the results given in column 6 shows that with *p*-nitro-, *o*-hydroxy-, *p*-methoxy- and *p*-methyl-dibenzoylmethanes, the phenyl group is in the 5-position in the *iso*oxazoles resulting from (I); that is, the carbonyl carbon atom to which the nitrogen atom becomes linked is remote from the phenyl group. With 3 : 4-methylenedioxy-, 6-bromo-3 : 4-methylenedioxy-, and *p*-phenyl-dibenzoylmethanes, and with $Ph{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}CH{:}CHPh$, and $Ph{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}C_{10}H_7$ (β), 3-phenyl*iso*oxazoles are formed. *p*-Tolyl takes the 3-position in preference to *p*-anisyl and to the methylenedioxyphenyl group; the latter also takes the 5-position in the product from 4-chloro-3′ : 4′-methylenedioxydibenzoylmethane.

These results do not appear to admit of any simple analysis; Bradley and Robinson reached a similar conclusion in regard to the hydrolytic fission of substituted dibenzoylmethanes (J., 1926, 2356).

Experimental.

The compounds were colourless, unless otherwise stated. Recrystallisation was from alcohol unless another solvent is mentioned. Following are the new compounds prepared as intermediates in the production of *iso*oxazoles.

Chalkones.—p-*Anisyl* p-*methylstyryl ketone* (1), m. p. (acetic acid) 126° (Found: C, 81·0; H, 6·2. $C_{17}H_{16}O_2$ requires C, 80·9; H, 6·3%), and β-*naphthyl styryl ketone* (2), m. p. 106° (Found: C, 88·5; H, 5·7. $C_{19}H_{14}O$ requires C, 88·4; H, 5·4%) (cf. Hutchins *et al.*, J., 1938, 1885), were obtained as yellow crystalline powders from the corresponding acetophenones and aldehydes in presence of alcoholic alkali (Sorge, *Ber.*, 1902, **35**, 1069).

Chalkone Dibromides.—o-*Hydroxyphenyl* αβ-*dibromo*-β-*phenylethyl ketone* (16 g.), m. p. (carbon tetrachloride) 192° (Found: Br, 41·6. $C_{15}H_{12}O_2Br_2$ requires Br, 41·7%), was obtained by treating a suspension of *o*-hydroxyphenyl styryl ketone (22 g.) (Feuerstein and Kostanecki, *Ber.*, 1898, **31**, 715) in carbon disulphide (100 c.c.) with a solution of bromine (16 g.) in carbon disulphide (50 c.c.), and volatilising the solvent after 12 hours (Khanolkar, private communication; cf. Warriar *et al.*, *Current Sci.*, 1937, **5**, 476).

p-*Anisyl* αβ-*dibromo*-β-p-*tolylethyl ketone* (3), which was obtained by bromination of (1) in warm glacial acetic acid, separated from acetic acid in colourless needles, m. p. 169° (Found: Br, 38·5. $C_{17}H_{16}O_2Br_2$ requires Br, 38·8%). p-*Anisyl* α-*bromo*-p-*methylstyryl ketone* (Found: Br, 24·5. $C_{17}H_{15}O_2Br$ requires Br, 24·1%), which separated from a cold solution of (3) in pyridine, after it had been heated at the b. p. for ½ min., cooled, and diluted with alcohol, formed yellow crystals, m. p. 129°.

β-*Naphthyl* αβ-*dibromo*-β-*phenylethyl ketone* (4), obtained by bromination of (2) in glacial acetic acid, had m. p. (carbon tetrachloride) 173° (Found: Br, 38·3. $C_{19}H_{14}OBr_2$ requires Br, 38·3%). β-*Naphthyl* α-*bromostyryl ketone*, which separated in yellow needles from alcohol, m. p. 116°, was obtained by the action of pyridine on (4) (Found: Br, 24·0. $C_{19}H_{13}OBr$ requires Br, 23·7%).

The other chalkone dibromides required have previously been described in the literature.

Diketones.—The oil (*p*-anisyl β-methoxy-*p*-methylstyryl ketone) obtained by adding water to a solution of (3) (8 g.) and sodium methoxide (1 g. of sodium) in methyl alcohol, which had been boiled under reflux for 1½ hour, gave a yellow solid (3 g.) after it had been heated with dilute hydrochloric acid for 2 hours. The product, p-*anisoyl*-p-*toluoylmethane* (5) (Found: C, 76·7; H, 5·8. $C_{17}H_{16}O_3$ requires C, 76·1; H, 6·0%), separated from alcohol in yellow needles, m. p. 104°; (5) was also prepared by the action of dilute hydrochloric acid on *p*-tolyl β*p*-dimethoxystyryl ketone, obtained as an oil by the action of methyl-alcoholic sodium methoxide on *p*-tolyl αβ-dibromo-β-*p*-anisylethyl ketone (Nadkarni *et al.*, J., 1937, 1801). *Benzoyl*-β-*naphthoylmethane*, m. p. 99° (Found: C, 82·7; H, 5·2. $C_{19}H_{14}O_2$ requires C, 83·2; H, 5·1%), was similarly obtained from (4) as a yellow crystalline powder.

Chalkone Ether Derivatives.—The ethers $R_1{\cdot}CO{\cdot}CH{:}C(OAlk)R_2$ referred to in the table were prepared by the action of alkali alkoxide in alcohol on the corresponding chalkone dibromides (see Nadkarni *et al.*, *loc. cit.*, p. 1803). As is usual with this type of compound, the ethers from

(3) and (4) could not be satisfactorily crystallised; the other ethers have previously been described.

iso*Oxazoles*.—The *iso*oxazoles prepared in the present research are indicated in the table by the references to footnotes 3 and 4. The experimental details relating to reactions (*a*), (*b*), and (*d*), which were the methods of preparation employed, are as follows :—*Reaction* (a). The dibenzoylmethane (I) was boiled with hydroxylamine hydrochloride in alcoholic solution with or without addition of alkali (Nadkarni *et al.*, *loc. cit.*, p. 1804). *Reaction* (b). An alcoholic solution of the corresponding chalkone dibromide (IV) containing hydroxylamine hydrochloride (more than 1 mol.) was treated gradually at the b. p. during 30 mins. with aqueous alkali, cooled, and diluted with water (see Weygand and Bauer, *loc. cit.*, p. 138). *Reaction* (d). The chalkone ether (V) was boiled in alcoholic solution with hydroxylamine hydrochloride with addition of aqueous sodium hydroxide to form a neutral or alkaline solution, or of excess of sodium acetate (Weygand and Bauer, *loc. cit.*, p. 134). The methods used for each *iso*oxazole are indicated in the table by the insertion of the m. p. in the appropriate column; as shown at the head of the table, columns 3, 4, and 5 refer respectively to reactions (*b*), (*d*), and (*a*). The similarity or differences of the isomers obtained by the above methods were confirmed by taking mixed m. p.'s. The following new *iso*oxazoles were prepared :—3-p-*anisyl*-5-p-*tolyl*iso*oxazole*, m. p. 148° (Found : C, 76·6; H, 5·8. $C_{17}H_{15}O_2N$ requires C, 76·9; H, 5·7%); 5-p-*anisyl*-3-p-*tolyl*iso*oxazole*, m. p. 130° (Found : C, 76·7; H, 5·8. $C_{17}H_{15}O_2N$ requires C, 76·9; H, 5·7%); 5-*phenyl*-3-o-*hydroxyphenyl*iso*oxazole*, m. p. 231° (Found : C, 75·7; H, 4·8; N, 5·8. $C_{15}H_{11}O_2N$ requires C, 76·0; H, 4·6; N, 5·9%); 3-*phenyl*-5-(3' : 4'-*methylenedioxyphenyl*)iso*oxazole*, m. p. 130° (Found : C, 72·6; H, 4·3. $C_{16}H_{11}O_3N$ requires C, 72·5; H, 4·2%); 3-*phenyl*-5-(6'-*bromo*-3' : 4'-*methylenedioxyphenyl*)iso*oxazole*, m. p. (methyl alcohol) 157° (Found : Br, 23·4. $C_{16}H_{10}O_3NBr$ requires Br, 23·3%); 5-*phenyl*-3-(6'-*bromo*-3' : 4'-*methylenedioxyphenyl*)iso*oxazole*, m. p. (methyl alcohol) 179° (Found : Br, 23·5. $C_{16}H_{10}O_3NBr$ requires Br, 23·3%); 3-*phenyl*-5-β-*naphthyl*iso*oxazole*, m. p. 160° (Found : C, 84·0; H, 4·8. $C_{19}H_{13}ON$ requires C, 84·1; H, 4·8%); 5-*phenyl*-3-β-*naphthyl*iso*oxazole*, m. p. 152° (Found : C, 84·1; H, 4·8; N, 5·2. $C_{19}H_{13}ON$ requires C, 84·1; H, 4·8; N, 5·2%).

Albrecht (*Monatsh.*, 1914, **35**, 1493) described the preparation of " α-naphthyl styryl ketone " (m. p. 105°) and the " dibromide " (m. p. 173°); the m. p.'s agree with those now found for the corresponding β-naphthyl derivatives. Repetition of Albrecht's work with commercial α-acetonaphthone showed that the solid chalkone obtained in poor yield is the β-derivative; the accompanying oil mentioned by Albrecht, which forms the greater part of the product, is probably the α-chalkone. Support is lent to this view by the fact that Albrecht submitted the oxime of his so-called α-chalkone to the Beckmann transformation, but did not obtain the expected " cinnamo-α-naphthylamide." In the preparation from naphthalene and acetyl chloride, a mixture of both α- and β-acetonaphthones is obtained, and the β-compound, being a solid (m. p. 56°), is more readily obtained pure than the liquid α-compound.

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