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3-Diazo-1,4-Diphenyl-4-Hydroxy-2-Butanone: Preparation and Reactions

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3-DIAZO-1,4-DIPHENYL-4-HYDROXY-2-BUTANONE:
PREPARATION AND REACTIONS

by
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Bachelor of Science, University of Karachi 1963

A Thesis

Submitted to the Faculty

of the

University of North Dakota

in partial fulfillment of the requirements

for the degree of

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August
1971

This Thesis submitted by Mohammed H. Khalil in partial fulfillment of the requirements for the Degree of Master of Science from the University of North Dakota is hereby approved by the Faculty Advisory Committee under whom the work has been done.

Neil F. Woolsey
(Chairman)

Virgil L. Stenberg

Edward J. O'Reilly

A William Johnson
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Title 3-DIAZO-1,4-DIPHENYL-4-HYDROXY-2-BUTANONE: PREPARATION AND REACTIONS

Department Chemistry

Degree Master of Science

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Date July 28, 1971

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ABSTRACT

The recent reports of intramolecular Aldol, Dieckman and alkylation reactions of diazomethyl ketones by Burkoth[16] and Woolsey[21] have demonstrated that under proper conditions diazomethyl ketones will undergo normal base-catalyzed reactions. Similar intermolecular condensation reactions of diazomethyl ketones, however, have apparently not been investigated.

The purpose of the present work was to investigate the possibility of intermolecular base-catalyzed alkylation and aldol-type condensations of diazomethyl ketones of the type RCH_2COCHN_2. The reactions of the hydroxydiazo ketone adducts resulting from aldol condensation and which are generally not available, would also be of interest.

The initial work with 1-diazo-2-butanone (35) and benzaldehyde revealed that condensation took place preferentially at the diazo carbon to give 2-diazo-1-hydroxy-1-phenyl-3-pentanone (41) as a viscous liquid. However, further work on this compound was abandoned in favor of 1-diazo-3-phenyl-2-propanone (36).

When diazo ketone 36 was treated with benzaldehyde, the condensation once again occurred at the diazo carbon and resulted in the formation of 3-diazo-1,4-diphenyl-4-hydroxy-2-butanone (42).

Irradiation of the hydroxydiazo ketone 42 in benzene or methanol below 50° gave 1,4-diphenyl-1,3-butanedione (43). The dione 43 was

also the only product isolated from the pyrolysis of 42 in refluxing chlorobenzene.

Treatment of the hydroxydiazo ketone 42 with hydrogen chloride gas gave 20% of the dione 43 and 31% of 3-chloro-1, 4-diphenyl-4-hydroxy-2-butanone (44). Similarly when treated with hydrogen bromide gas, 42 gave 10% of the dione 43 and 45% of 3-bromo-1,4-diphenyl-4-hydroxy-2-butanone (45). The structures of 44 and 45 rests on the physical data and the reduction of 45 to 2-bromo-1,4-diphenyl-1,3-butanediol (49). The nmr spectrum of the diol 49 unequivocally determined the point of attachment of the halogen.

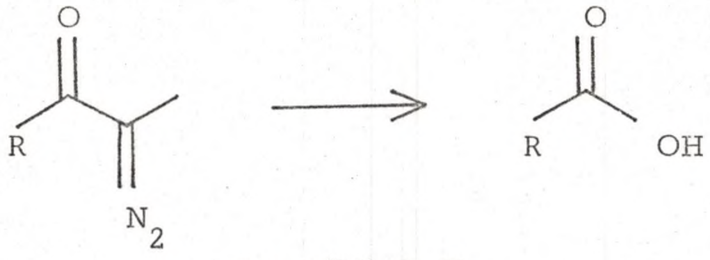
INTRODUCTION

Since Wolff discovered diazo ketones ($RCOCR'N_2$) at the beginning of this century, these compounds have assumed an increasingly important role in the realm of synthetic organic chemistry. Application of diazo ketones to the preparation of homologous carboxylic acids via the Wolff rearrangement by the method of Arndt and Eistert is well known. Apart from making available products from the Wolff rearrangement, diazo ketones have gained preparative significance in other directions also.[1]

However, the reactions of diazo ketones with bases, except under the special conditions of the Wolff rearrangement, remained least studied and understood until recently. Most of the early fragmentary accounts concerning such reactions showed that, whereas diazo ketones were fairly stable to mild basic conditions at low temperatures,[2,3] treatment with strong base or dilute base at elevated temperatures gave rise to a red color and resulted in the formation of much tarry material.[4]

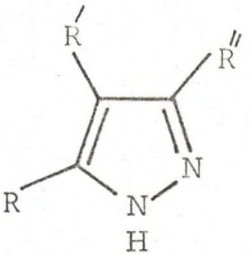
Arndt and co-workers[5] observed that α-diazo-o-nitroacetophenone on treatment with aqueous alkali gave a red solution which on acidification yielded hydrogen cyanide and an amorphous unidentified solid.

Wilds and Meader[6] reported that alkali could cleave a diazo ketone derived from diazoethane. Thus, p-chloro-α-diazoacetophenone on warming with aqueous methanolic potassium hydroxide evolved a gas and gave a 35% yield of p-chlorobenzoic acid along with much tarry material (Equation 1).



$R = p(Cl)\text{-}C_6H_4$ (Eq. 1)

These initial accounts of the instability of the diazo ketones towards strong base or dilute base at elevated temperatures prompted Yates and co-workers[7-9] to investigate such reactions in detail. They studied the decomposition products of a number of diazo ketones under a variety of basic conditions. Azibenzil $PhCOCPhN_2$ (1) and α-diazoacetophenone $PhCOCHN_2$ (2), for example, when treated at elevated temperatures in homogenous solution with dilute sodium hydroxide in aquous dioxane or ethanol and also under anhydrous conditions gave similar major products. Thus, the diazo ketone 2 yielded benzoic acid, acetophenone, hydrogen cyanide, hydroxylamine, ammonia, pyrazole 3 and its hydroxy derivative 4. Treatment of a concentrated solution of the diazo ketone 2 with concentrated sodium methoxide led to a violent exothermic reaction which resulted in the formation of the pyrazole 5, the tetrazole 6 and the triazolotriazine 7 besides the products observed under mild conditions.



3, $R = H$; $R' = Ph$

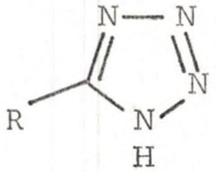
$R'' = COPh$

4, $R = OH$, $R' = Ph$

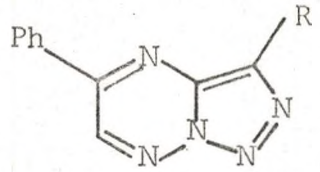
$R'' = COPh$

5, $R = Ph$; $R' = OH$

$R'' = COPh$



6, $R = COPh$



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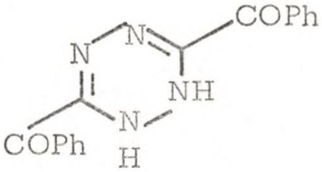
However, the reaction of the diazo ketone 2 with powdered potassium hydroxide or the methylsulfinyl carbanion in dimethyl sulfoxide gave the tetrazine 8 in 60% yield. When treated with potassium t-butoxide under heterogenous conditions using ether as a diluent, 2 gave sodium benzoate and the tetrazoles 9 and 10. However, when t-butyl alcohol was used as a solvent giving a homogenous solution, the tetrazoles 11 and 12 were the main products.



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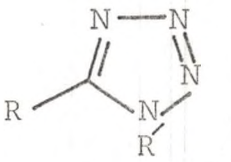
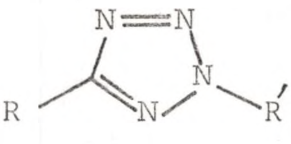


9, $R = H$

$R' = CH_2COPh$

11, $R = COPh$

$R' = CH_2COPh$



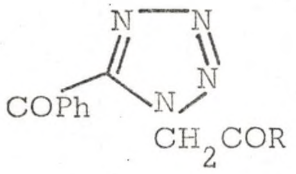
10, $R = H$

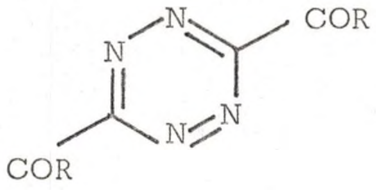
$R' = CH_2COPh$

12, $R = COPh$

$R' = CH_2COPh$

Analogous reactions were observed in the case of 2-diazo-2,4,6-trimethylacetophenone (13) and 1-diazo-3,3-dimethyl-2-butanone resulting in the formation of the tetrazoles 14 and 15, respectively. However, when 13 was treated with concentrated methanolic sodium methoxide at 0°, the tetrazine 16 was obtained in good yield.



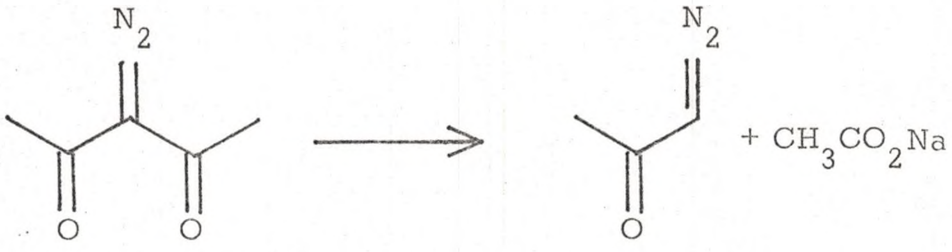


14, R = 2,4,6-$(CH_3)_3C_6H_2$ 16, R = 2,4,6-$(CH_3)_3C_6H_2$

15, R = C $(CH_3)_3$

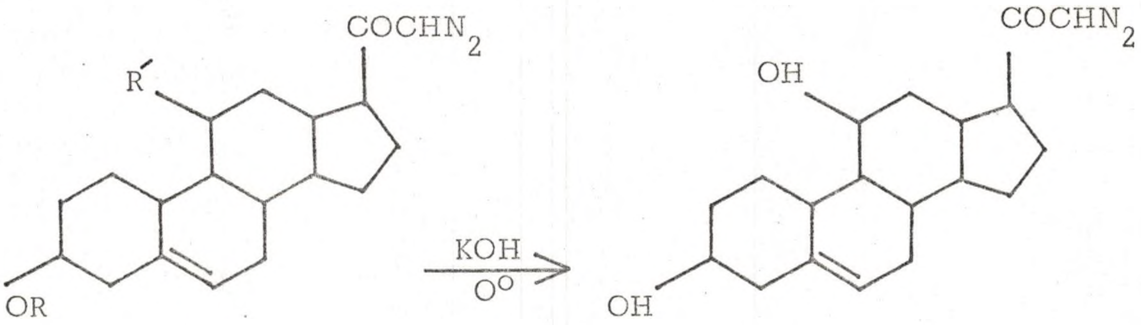
To account for the diversity of paths in the reactions of diazo ketones with bases, Yates and co-workers postulated the formation of four nitrogen atom intermediate by initial terminal attack by the base on the diazo nitrogen and subsequent condensation with another molecule of diazo ketone followed by cleavage, reduction and further condensation to give various products.

Although it is quite evident from the above examples that diazo ketones in warm and concentrated basic solutions undergo a variety of reactions resulting in the destruction of $-COCN_2-$ moeity, there are a number of instances in early literature which show that such destructive reactions could be averted if cold and basic solutions were used. As early as 1912, for example, Wolff[10] prepared diazoacetone by the base catalyzed cleavage of 3-diazo-2,4-pentane dione (17) and isolated it from the reaction mixture in good yield.



17

A number of workers have taken advantage of this base stability of diazo ketones to hydrolyze a variety of functional groups in diazo ketones without affecting the diazo ketone moeity. In steroid synthesis, for example, the 3-acetoxy or trifluoroacetoxy groups in the steroids 18, 19, 20 and 21 have been selectively hydrolyzed with cold methanolic potassium hydroxide.[11-13]



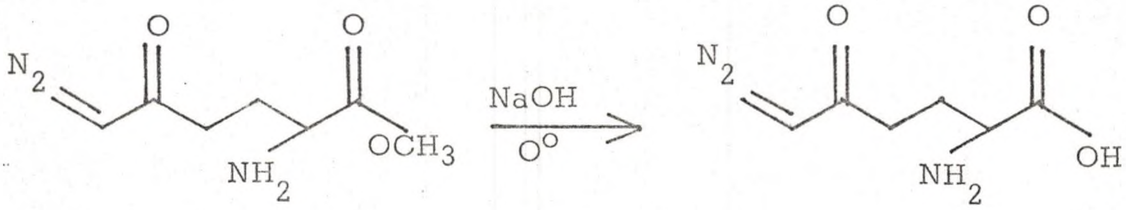
18, R = OAc; R′ = H

19, R = CF_3COO; R′ = H

20, R = H, R′ = OAc

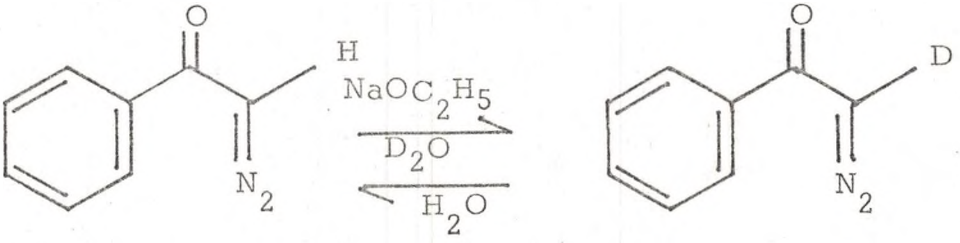
21, R = H, R′ = CF_3COO

Dewald and Moore[14] were able to hydrolyze the methyl ester of 6-diazo-5-oxo-L-norleucine selectively at the ester function to give the corresponding amino acid (Equation 2).



(Eq. 2)

In the last few years a series of papers have been published which deal with the ability of diazomethyl ketones to form an anion at the diazo carbon and undergo reactions characteristic of such species without destroying the $-COCN_2$-moeity. Diazoacetic esters, which are similar to diazomethyl ketones in possessing the $-COCHN_2$-functional group, were also shown to undergo similar reactions. Earlier in 1962 Morrison and Yates[15] had demonstrated the acidity of the azomethine proton of a diazomethyl ketone by the following nmr experiment:

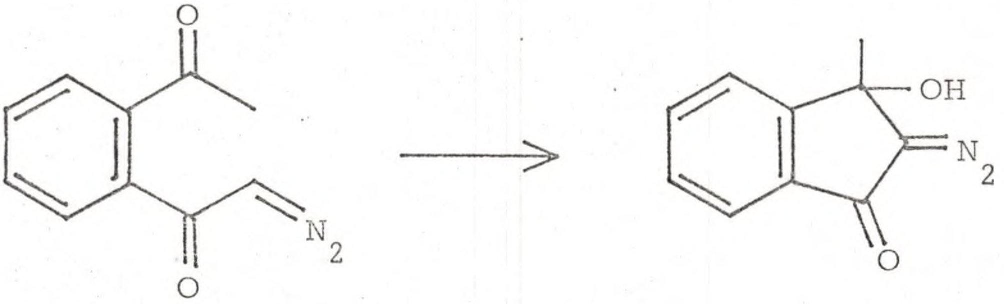


22

23

Addition of $NaOC_2H_5$-D_2O to diazo ketone 22 instantly removed the azomethine peak from the nmr spectrum whereas the addition of water to 23 had the immediate reverse effect.

Burkoth[16] attested to the nucleophilicity of diazomethyl ketones by a similar nmr experiment and also investigated a number of cyclizable diazo ketones systems in terms of their ability to undergo base catalyzed intramolecular aldol and Dieckman type condensations at the diazo carbon. Thus, diazo ketones 24, 25 and 26 were successfully cyclized,



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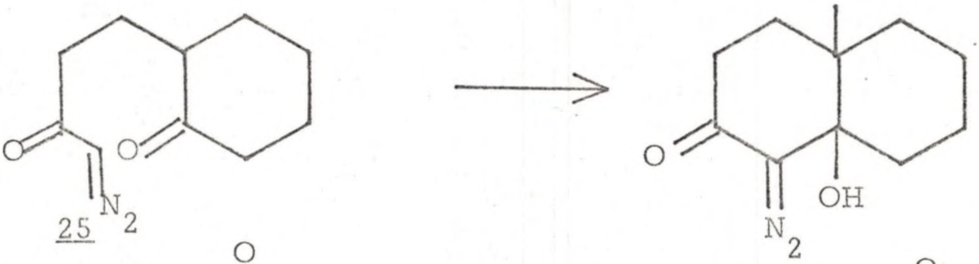

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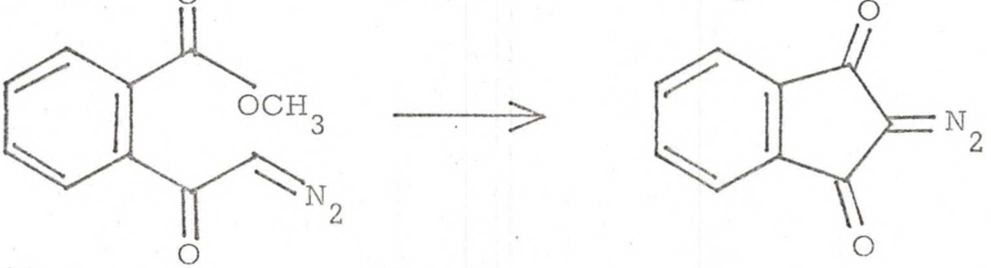

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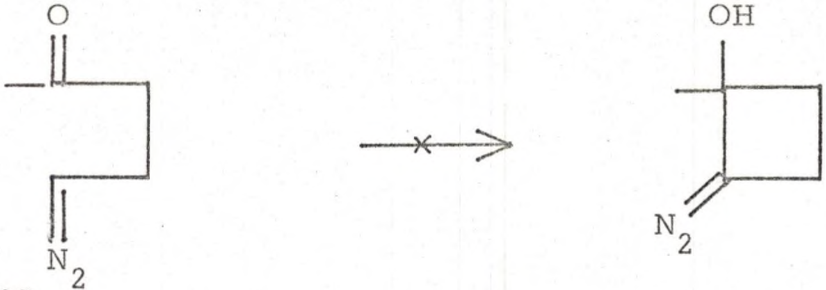
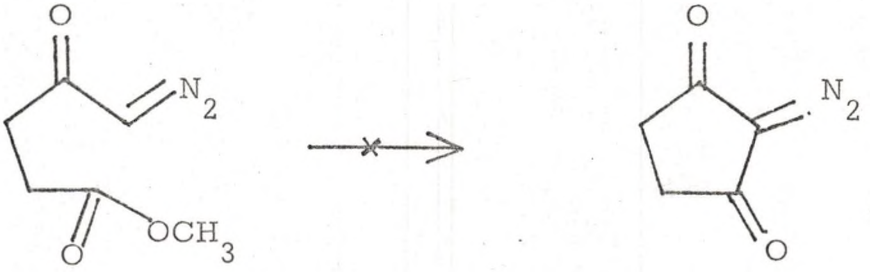
but attempts to apply this kind of reaction to simple acyclic systems derived from levulinic 27 and succinic 28 acids failed.

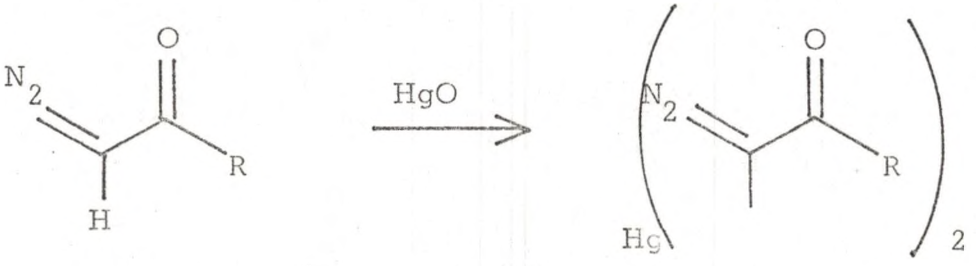


27



28

Although the mercury derivative of diazoacetic ester was made by Buchner as early as the last century,[17] similar derivatives of a number of diazomethyl ketones were reported only recently by Yates and Garneau[18] (Equation 3).

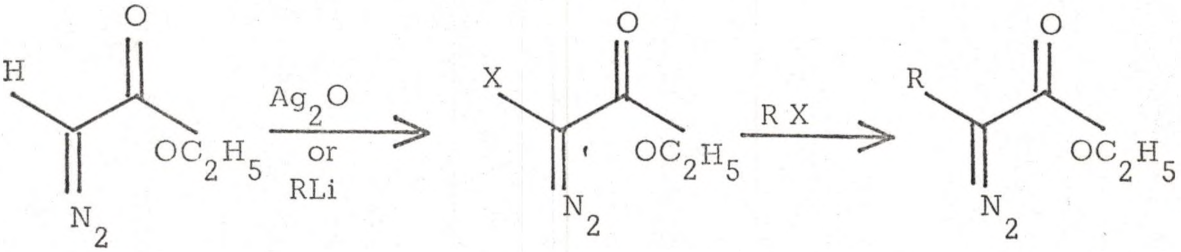


(Eq. 3)

$R = 2,4,6\text{-}(CH_3)_3\ C_6H_2,\ (CH_3)_3$

C_6H_5 or $C_6H_5CH_2$

Schollkopf and co-workers[19-20] have prepared and intercepted the silver 30 and lithium 31 derivatives of ethyl diazoacetate 29 with a variety of halides and carbonyl compounds.



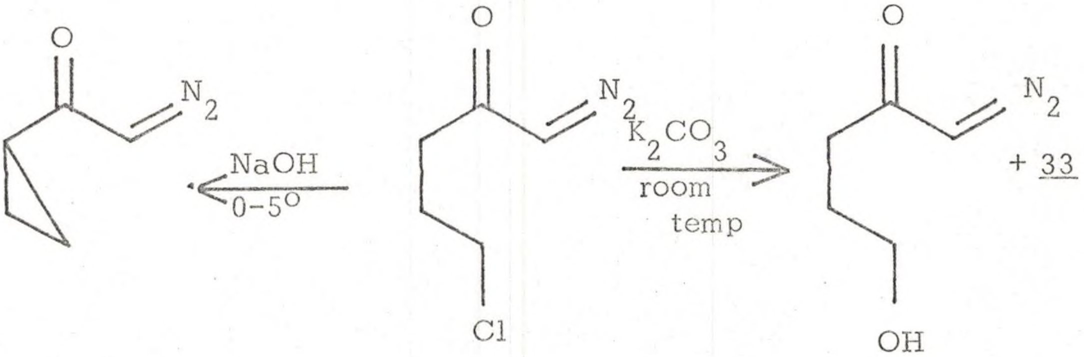
29

30, X = Ag

31, X = Li

R X = Halides
and
Carbonyl
Compounds

Woolsey and Hammargren[21] reported the first example of a normal base catalyzed intramolecular alkylation of an aliphatic diazomethyl ketone at the alpha methylene carbon. They found that 5-chloro-1-diazo-2-pentanone (32) on treatment with sodium hydroxide gave cyclopropyldiazomethyl ketone 33. Treatment of 32 with sodium carbonate solution gave in addition to 33, the corresponding hydroxydiazo ketone 34.



33

32

34

Although, the ability of diazomethyl ketones to form stable anions at the diazo carbon as well as at the alpha methylene carbon have clearly been demonstrated by these recent works, much work remains to be done regarding the synthetic utility of such anions. Thus, for example, use of such anions for intermolecular condensation reactions have not been investigated. Such reactions could lead to the synthesis of a variety of compounds which, ordinarily, would be unavailable.

STATEMENT OF THE PROBLEM

To utilize the low temperature, dilute base stability of diazomethyl ketones for intermolecular condensation reactions, we turned to diazomethyl ketones of the type RCH_2COCHN_2. In diazo ketones of this type there would be two possible sites available for the formation of an anion, i.e., the diazo carbon and the alpha methylene carbon. Thus, for example, if in aldol type of reaction with benzaldehyde, the condensation were to occur at the alpha methylene carbon this would result in a hydroxydiazo ketone which could then eliminate water to give an α,β-unsaturated diazo ketone. Alternately, if the condensation were to occur at the diazo carbon this would lead to the formation of a different hydroxydiazo ketone. Adducts which would result from either mode of condensation have been unavailable from conventional routes. Furthermore, the study of the reactions of the adducts would be an important extension of the current synthetic reactions of diazo ketones.

RESULTS AND DISCUSSION

For the present investigation, two diazomethyl ketones, 1-diazo-2-butanone (35) and 1-diazo-3-phenyl-2-propanone (36), were selected from the list of the diazomethyl ketones of the type RCH_2COCHN_2.

Diazo ketone 35[22] was prepared from the corresponding acid chloride by treatment with excess diazomethane. Initial attempts to condense diazo ketone 35 with benzaldehyde in cold and dilute solution of sodium hydroxide, resulted in a rapid development of a red color which deepened as the reaction progressed, indicating decomposition of diazo ketone. When sodium hydroxide was replaced by a dilute solution of sodium carbonate, the initially light yellow solution became deep yellow in color. Work up of the reaction solution followed by column chromatography gave three main fractions. The benzene and the ether fractions contained unreacted benzaldehyde and diazo ketone 35, respectively. Evaporation of the solvent from the ethanol fraction gave a yellow oil which appeared homogenous on tlc and ultimately proved to be 2-diazo-1-hydroxy-1-phenyl-3-pentanone (41). The structure of the hydroxydiazo ketone 41 rests on the following spectral evidence. The ir spectrum showed absorptions at 2.64, 4.68, and 6.17 μ corresponding to hydroxyl, diazo and carbonyl groups, respectively. The nmr spectrum showed a singlet at δ 7.20 due to five phenyl protons, a singlet at δ 5.85 due to the benzylic methine proton, a singlet near δ 4.6 due to the hydroxyl proton, a quartet at δ 5.85 due to the methylene protons and a triplet at δ 1.08 due to the methyl protons.

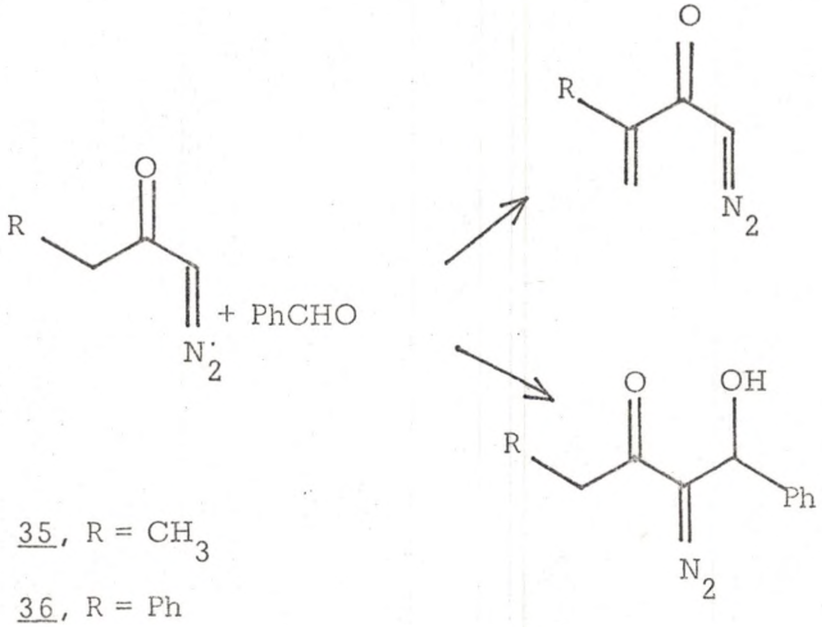
The significant feature of the nmr spectrum of 41 is the loss of the azomethine proton; the appearance of five phenyl protons, a hydroxyl proton and a benzylic methine proton relative to the starting diazo ketone 35. This clearly shows that the condensation had occurred at the diazo-carbon and resulted in the formation of 41 as shown in scheme 1. No evidence could be found for the formation of 37, the product which would have resulted from condensation at the alpha methylene carbon, even on close examination of the nmr spectra of various chromatographic fractions of the reaction mixture.

At this stage further work on 35 was discontinued in favor of 1-diazo-3-phenyl-2-propanone (36) to determine if the substitution of phenyl group for the methyl group would make the methylene proton acidic enough to facilitate condensation at the methylene carbon.

Diazo ketone 36[23] was prepared by reacting phenyl acetyl chloride with excess diazomethane. All efforts to alkylate 36 with methyl iodide failed. A number of base and solvent systems were tried but in each case, the work up of the reaction solution gave resinous mass from which only a small amount of starting diazo ketone could be recovered.

Treatment of a dilute ethanolic solution of the diazo ketone 36 and an excess of benzaldehyde with 2% sodium hydroxide solution resulted in an immediate development of a red color. However, when a similar solution was cooled to 0° and then treated with base, no such color de-

SCHEME 1



35, R = CH_3

36, R = Ph

37, R = CH_3

39, R = Ph

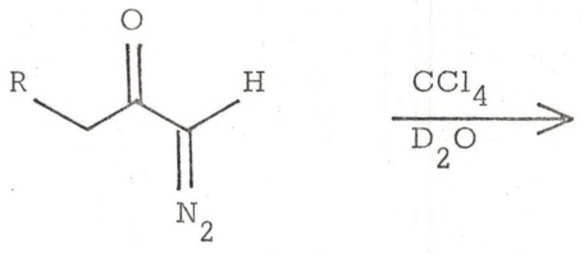
41, R = CH_3

42, R = Ph

veloped. Extraction of the reaction solution with carbon tetrachloride and chromatography of the concentrated extract on alumina gave two main fractions. The carbon tetrachloride fraction contained unreacted benzaldehyde and diazo ketone 36. Evaporation of the solvent from the ethanol fraction gave a deep yellow oil which crystallized in ether-pentane to give yellow crystals of 3-diazo-1,4-diphenyl-4-hydroxy-2-butanone (42) in 63% yield, mp 56-57°. The structure of 42 was established on the basis of following physical data. The element analysis agreed satisfactorily with $C_{16}H_{14}N_2O_2$. The ir spectrum showed absorptions at 2.94, 4.78 and 6.08 μ corresponding to the hydroxyl, diazo and carbonyl groups, respectively. The nmr spectrum of a pure and dry sample in carbon tetrachloride revealed a doublet at δ 7.21 due to ten phenyl protons, a doublet at δ 5.91 due to the benzylic methine proton, a doublet (concentration dependent) near δ 4.3 due to the hydroxyl proton and a singlet at δ 3.68 due to the methylene protons. The assignments to the hydroxyl proton and benzylic methine proton were made on the basis of deuterium oxide decoupling experiment, i.e., on addition of a drop of deuterium oxide, the doublet at δ 4.3 disappeared indicating exchange of hydroxyl proton with deuterium. In addition the doublet at δ 5.91 collapsed to a singlet due to the removal of coupling with hydroxyl proton. Once again the nmr spectrum was unambiguous in proving that condensation had occurred to give hydroxydiazo ketone 42 (scheme 1). This contention was supported by the retention of the methylene protons, disappearance of azomethine proton and appearance of five phenyl protons, one hydroxyl proton and one methine proton in the nmr relative to the starting diazo ketone. In addition, examination of the nmr spectra of various chromatographic fractions revealed no evidence for the formation of alternate condensation product 39. It, therefore, became apparent that under the conditions used for the above reaction either there was no significant formation of the enolate anion at the alpha methylene carbon or whatever enolate anions were formed were rendered unreactive due to solvation. Solvents like dimethyl sulfoxide, dioxane and dimethyl formamide were used to counter the problem of solvation, since these solvents do not solvate the anion and consequently do not diminish its reactivity as a nucleophile. On the contrary, they very effectively solvate the cation, separating it from the cation-enolate anion part thereby leaving a substantially free anion.[24] However, in all cases only 42 could be isolated in varying yields with no evidence that 39 or any other product had been formed.

When a cold and dilute solution of the hydroxydiazo ketone 42 and benzaldehyde was treated with a concentrated solution (20%) of sodium hydroxide, the solution turned red instantly. Work up and column chromatography of the reaction solution yielded only a small amount of the starting diazo ketone with no evidence for the formation of the product of the bis addition.

The results obtained in the present investigation, i.e., the condensation of diazo ketones 35 and 36 with benzaldehyde at the diazo carbon to give hydroxydiazo ketones 41 and 42, are opposite to the one obtained by Woolsey and Hammargren for 5-chloro-1-diazo-2-pentanone (32) where intramolecular condensation occurred at the alpha methylene carbon (cf. p.9). The fact that the formation of anion in diazo ketone 32 and 36 is more fascile at the diazo darbon, was shown by the following nmr experiment. The addition of a drop of deuterium oxide containing a catalytic amount of sodium carbonate to a carbon tetrachloride solution of 32 and 36 instantly and completely removed the azomethine peak from the nmr spectra. The methylene peak remained uneffected. It seems likely, therefore, that on treatment of the diazo ketone 32 with base, the anions are formed at either alpha positions i.e., at the diazo carbon as well as at the methylene carbon with the

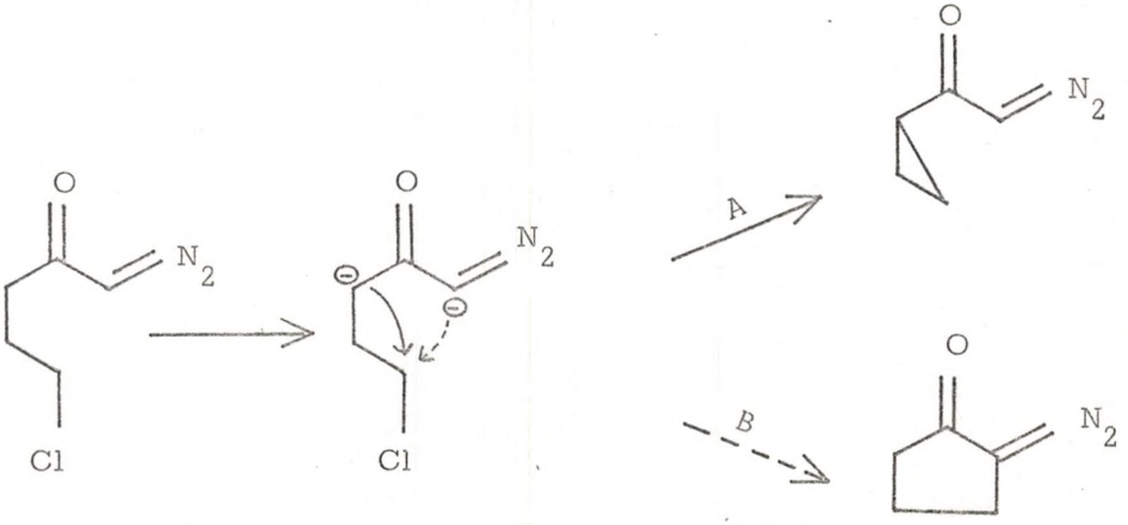


32, R = CH_2CH_2Cl

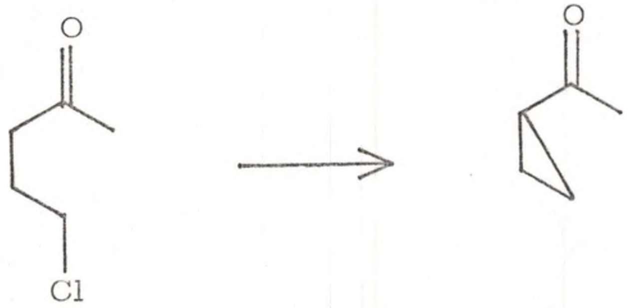
36, R = Ph

former in much greater concentration. The rate determining step, however, could be the cyclization part of the reaction and the product would result *via* the route which would have lower energy of activation. It can be seen from Scheme 2 that entropy of activation would play an important

SCHEME 2



role in determining the total energy of activation for the two paths. The orientation of the reaction sites in the intermediate which would lead to the formation of 3-membered ring (path A, Scheme 2) should have a lower entropy requirement for the elimination of chloride than for formation of the intermediate which would lead to the formation of 5-membered ring (path B, Scheme 2). In other words the entropy of activation would be less negative for the former case, therefore, the total energy of activation would be less and path A would be preferred. A similar example is that of 5-chloro-2-pentanone[25] which also undergoes base-catalyzed intramolecular condensation at the alpha methylene carbon to give cyclopropyl methyl ketone (Equation 4), presumably, controlled by the same entropy factor.



(Eq. 4)

Furthermore, it is interesting to note that efforts by Burkoth to obtain a simple 5-membered cyclic system by the intramolecular condensation at the diazo carbon of the corresponding open chain diazo ketone proved to be unrewarding (cf. p. 8).

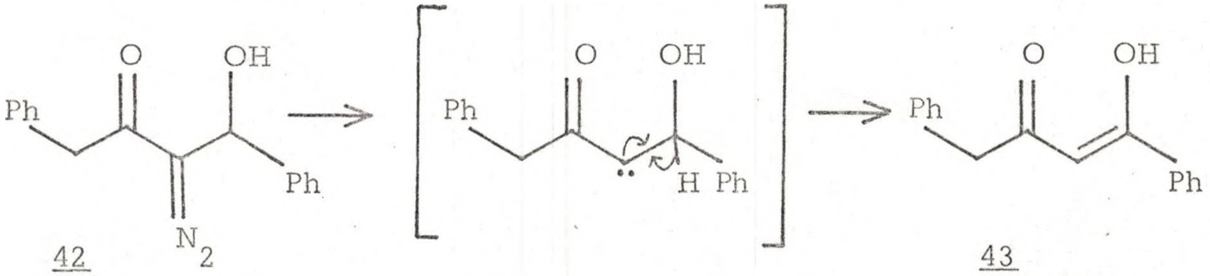
Reactions of 3-Diazo-1,4-diphenyl-4-hydroxy-2-butanone (42)

Three types of reactions of the hydroxydiazo ketone 42 were investigated: pyrolysis, photolysis and reactions with hydrogen halides.

Pyrolysis and Photolysis.--Pyrolysis of 42 in refluxing chlorobenzene and subsequent evaporation of the solvent gave a yellow sticky substance which failed to crystallize on initial attempts. On column chromatography using activated silica gel, the reaction mixture turned red indicating decomposition. However, when the mixture was placed on silica gel deactivated with 20% water and eluted with benzene, decomposition was slow enough to give a small amount of brown eluent which on evaporation of the solvent yielded brown crystals of 1,4-diphenyl-1,3-butanedione (43). Its structure was established by its mp 50° (lit.[26] 51°), elemental analysis which agreed satisfactorily with $C_{16}H_{14}O_2$, molecular weight as determined by mass spectroscopy (parent ion peak at m/e 238), semicarbazone 138-140° (lit.[26] 138-141°), copper salt mp 197-199° (lit.[26] 196-198°) and its ir and nmr spectra. Isolation from the reaction mixture *via* its copper salt gave 43 in 40% yield. The remaining material was an intractable oil from which no further pure material could be obtained.

Photolysis of a benzene solution of 42 with a 550 Watt mercury arc vapor lamp and preparative tlc of the photoproduct eluted with chloroform gave three fractions. The major fraction (60%) with R_f 0.70 was identified from its ir and nmr spectra as dione 43. The second major fraction (25%) with R_f 0.08 had ir spectrum similar to that of diazo ketone 42. The balance was made up by the third fraction with R_f 0.41 which was a red oil and which resisted all attempts at crystallization. From its ir and nmr spectra no definite conclusion could be drawn regarding its structure. A number of efforts were made to obtain this portion of the photoproduct in crystalline form but application of gas chromatography and column chromatography to effect the separation of the mixture proved unrewarding. In order to obtain maximum yield of dione 43, several irradiations of diazo ketone 42 were performed over varying periods of time and the best yield obtained was 49% (isolated via its copper salt).

When irradiation of 42 was performed in methanolic solution under similar conditions as in the previous reaction, preparative tlc eluted with chloroform once again gave three fractions. The two major fractions were identified by their ir and nmr spectra as 42 (15%) and 43 (66%). Once again, the third minor fraction with R_f 0.34 was in the form of red oil and no definite conclusion could be drawn regarding its structure from its ir and nmr spectra. Isolation of the dione 43 from the crude reaction mixture *via* its copper salt gave the former in 52% yield.

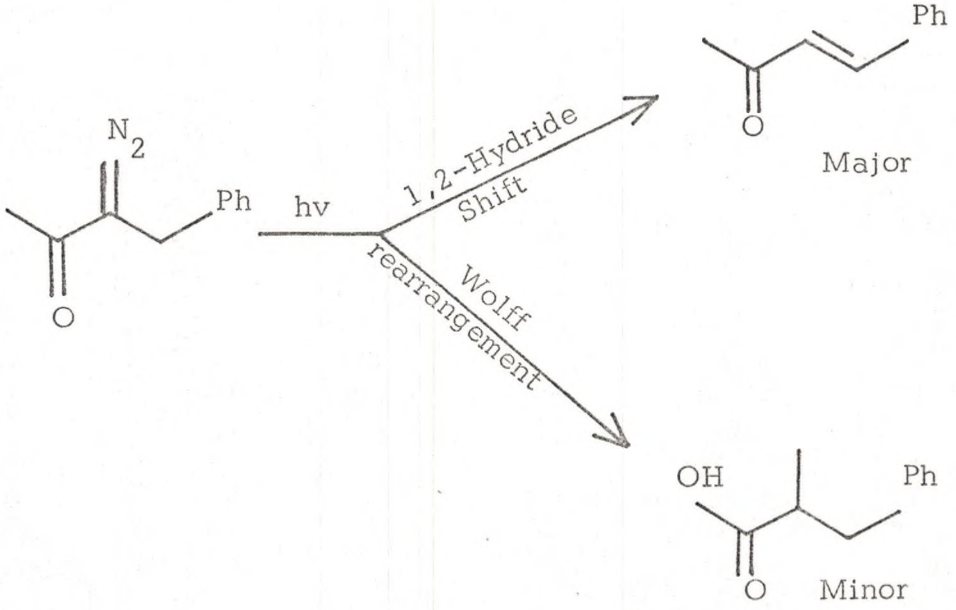


42 43

(Eq. 5)

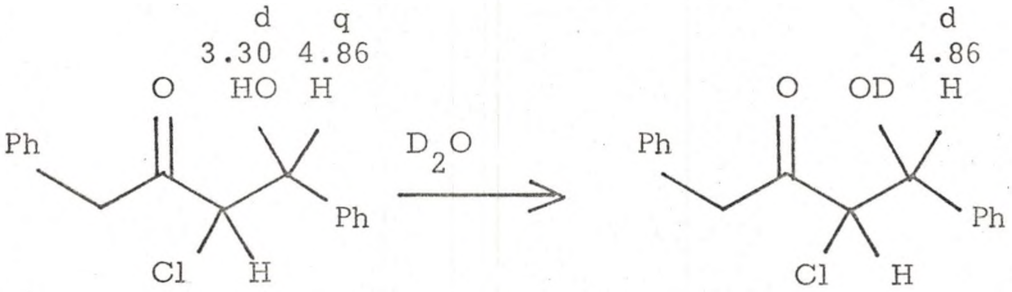
The results of the photolysis and the pyrolysis reactions of the hydroxydiazo ketone 42 show that the major product in these reactions is the dione 43, formed, presumably, via a 1,2-hydride shift in the intermediate keto carbene (Equation 5). Franzen[27] has studied similar reactions of a variety of diazo ketones with carbon-hydrogen bond adjacent to the diazo carbon but lacking the hydroxyl group. His results show that while in a few cases the Wolff product--products formed as a result of the migration of the group alpha to the keto group of the diazo ketone moeity to the divalent carbon in the intermediate keto carbene--were formed in small amount (Scheme 3), in the majority of the cases the products resulted exclusively via a 1,2-hydride shift. He regarded the Wolff rearrangement as a special kind of reaction in the degradation of these type

SCHEME 3



of diazo ketones. The reason, probably, is the lower activation energy required for a 1,2-hydride shift from the adjacent carbon as compared to the migration of a bulkier group from the carbonyl carbon. Furthermore, the formation of the Wolff product seems to be controlled by the steric factors, i.e., such products were not formed at all when the migrating group was bulkier than a methyl group and even then no migration took place if the migrating site was sterically hindered. With both of these factors fairly prominant in the case of the hydroxydiazo ketone 42, the formation of the dione 43 as the major product is comprehendible.

Reaction with Hydrogen Halide.--Treatment of a solution of diazo ketone 42 in ether with dry hydrogen chloride gas and subsequent evaporation of the solvent gave a light yellow oil. The nmr spectrum of the crude reaction mixture showed peaks characteristic of dione 43 plus additional peaks. Preparative tlc eluted with chloroform gave two fractions one of which from its ir and nmr spectra, was identified as dione 43 (20%). The second fraction gave white crystals of 3-chloro-1,4-diphenyl-4-hydroxy-2-butanone (44) in 31% yield, mp 51-52°. The elemental analysis agreed satisfactorily with the molecular formula $C_{16}H_{14}O_2Cl$. The ir spectrum showed absorption at 2.93 and 5.88 μ corresponding to hydroxyl and keto group respectively. The nmr spectrum revealed a multiplet at δ 7.18 due to the ten phenyl protons, a rough quartet at δ 4.86 due to the benzylic methine proton, a doublet at δ 4.24 due to the methine proton alpha to the keto group, a singlet at δ 3.77 due to the benzylic methylene protons and a doublet at δ 3.3 (concentration dependent) due to the hydroxyl proton. The assignment to the hydroxyl and the benzylic methine protons were made on the basis of the following nmr experiment:



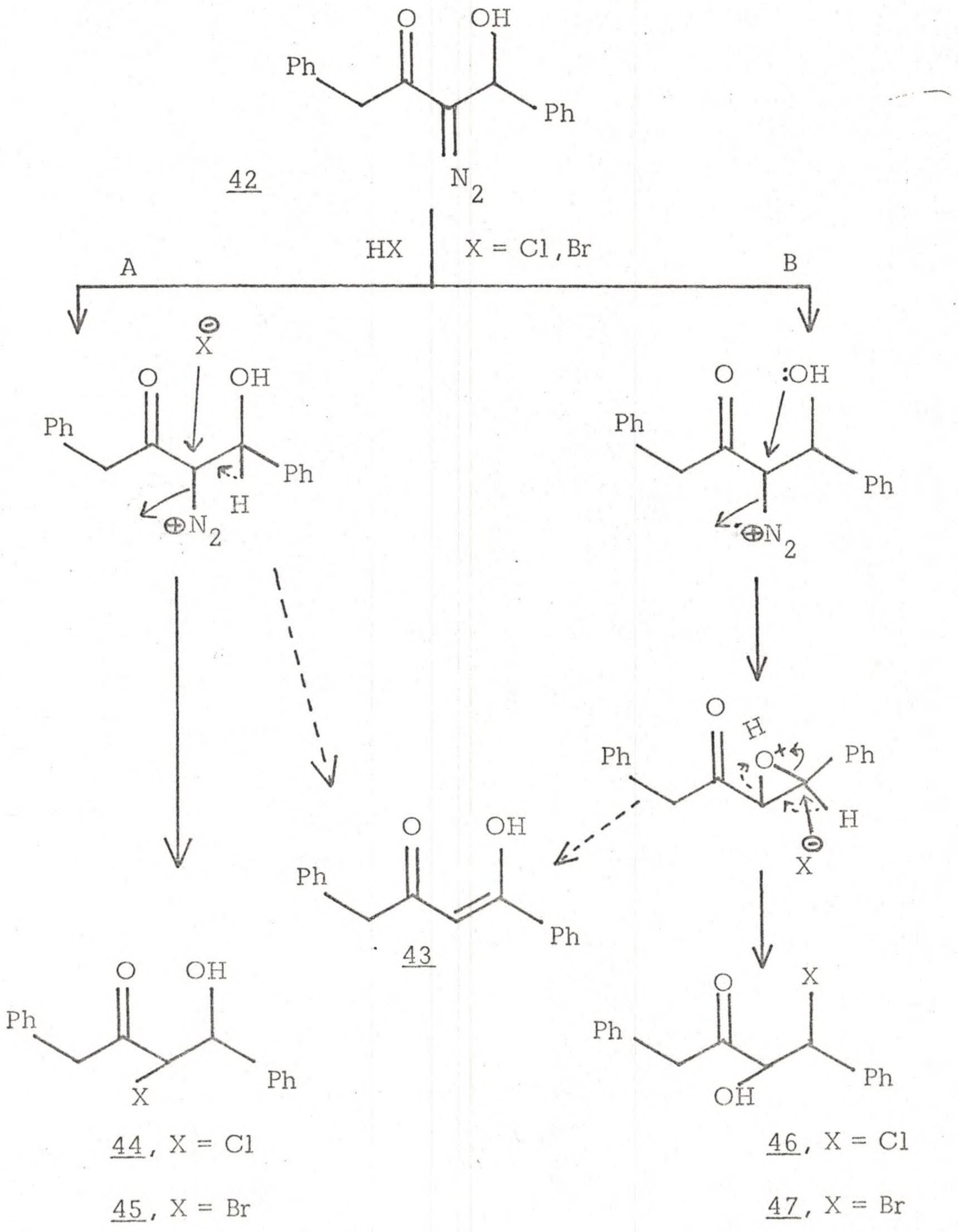
44

The nmr spectrum of 44 in carbon tetrachloride and a drop of deuterium oxide lacked the doublet at δ 3.30 indicating the exchange of hydroxyl proton by deuterium and the quartet at δ 4.86 collapsed to a doublet indicating that this proton was coupled to the hydroxyl proton and, therefore, the hydroxyl group and the proton at 4.86 were at the same carbon.

Treatment of the diazo ketone 42 with hydrogen bromide under conditions similar to those of the previous reaction gave dione 43 (10%) and white crystals of 3-bromo-1,4-diphenyl-4-hydroxy-2-butanone (45) in 45% yield mp 56-57°. The latter analyzed correctly for $C_{16}H_{14}O_2Br$. Its ir and nmr spectra were quite similar to that of chloro compound: the ir showed absorptions at 2.94 and 5.93 μ corresponding to hydroxy and keto groups respectively and the nmr had a multiplet at δ 7.19 due to the ten phenyl protons, a rough quartet at δ 4.95 due to the benzylic methine proton, a doublet at δ 4.32 due to the other methine proton, a singlet at δ 3.85 due to the methylene protons and a doublet at δ 3.4 (concentration dependent) due to the hydroxyl proton. A similar nmr experiment with deuterium oxide as in the previous case resulted in the disappearance of the peak at δ 3.4 and collapse of the quartet at δ 4.95 to a doublet.

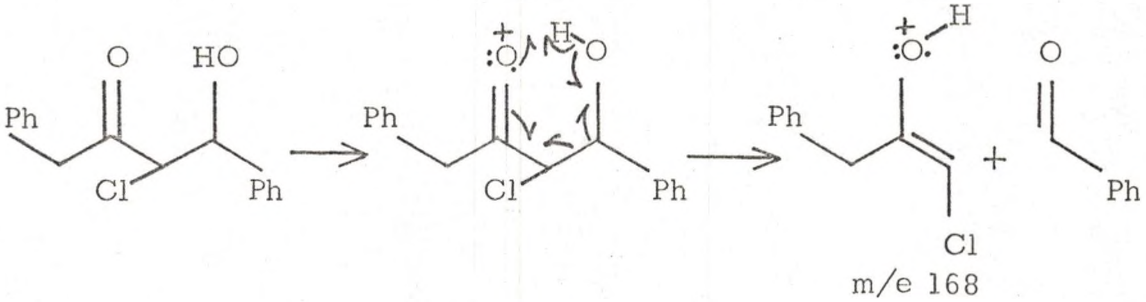
It was not possible to assign structures 44 and 45 to the chloro and bromo compounds exclusively on the basis of ir and nmr data since structure 46 and 47 would also be compatible with this spectral data. Compounds 44 and 45 could, of course be formed as a result of initial protonation of the diazo carbon followed by the nucleophilic displacement of the diazo nitrogen by the halide ion (path A, Scheme 4). Alternately, the diazo nitrogen could also be displaced intramolecularly by the neighboring hydroxyl group to form a protonated epoxide which could then open up as a result of a nucleophilic attack by the halide ion to give 46 or 47 (path B, Scheme 4). Although, the hydroxyl group has very little tendency to participate in the intramolecular displacement type reactions,[28] such a possibility could not be ignored in the light of a few unequivocal examples of such participations.[29] Evidence in favor of structure 44 came from the mass spectrum of the chlorohydroxy ketone which showed an intense peak at m/e 168. An exercise in the fragmentation pattern of structures 44 and 46 revealed that such an ion could only result via McLafferty rearrangement[30] from structure 44 (Scheme 5). The presence of the chlorine atom in the McLafferty ion was supported by a P+2 peak approximately one third the intensity of the former, the two

SCHEME 4



peaks being due, of course, to the ^{35}Cl and ^{37}Cl isotopes.

SCHEME 5



Unequivocal evidence in favor of structure 44 was sought through synthesis of chlorohydroxy ketone by an independent route. The simplest route available for such a synthesis was the hydrohalogenation of benzyl styryl ketone 48 (Equation 6). In this type of addition reaction the halogen is placed alpha and hydroxyl group beta to the carbonyl group.[31] However, this approach had one drawback, i.e., compound 44 contains two asymmetric carbon atoms and since the formation of 44 from 48 would lead to the creation of two asymmetric carbons, there was equal probabil-

(Eq.6)

ity of obtaining a different diastereomer of 44 than the one obtained in the reaction of 42 with hydrogen halide. However, since the synthesis itself was fairly simple it was decided to carry it out.

Treatment of a solution of 48 in carbon tetrachloride with hypochlorous acid and subsequent work up and preparative thin layer chromatography gave a white compound with mp 61-62°. The ir spectrum of this compound was quite similar to that of compound 44. The nmr spectrum was also quite similar except that the whole spectrum had shifted upfield.

The difference in the physical data of above compound and that of compound 44, i.e., different R_f value, different mp and different chemical shift of the protons in the nmr spectrum did not allow proof of the structure for 44 but suggested that the two compounds were indeed related as diastereomers.

Structure proof of 44 by dehalogenation *via* hydrazone derivative[32] and by zinc and acetic acid[33] also proved to be unrewarding.

Unambiguous proof for the structure of 44 and 45 was obtained from the lithium aluminum hydride reduction of bromohydroxy ketone to give 3-bromo-1,4-diphenyl-1,3-butanediol (49), a white compound with mp 106-107°. The structure of 49 rests on the following chemical and physical data. The compound analyzed correctly for $C_{16}H_{17}O_2Br$ and gave a negative borax test for 1,2 diol. The ir spectrum showed no carbonyl peak. The nmr spectrum revealed a ten proton multiplet at δ 7.28, a rough one proton multiplet at δ 5.10, a two proton multiplet at δ 4.05, a rough one proton doublet at δ 3.40 and a three proton multiplet at δ 2.85.

On the addition of a drop of deuterium oxide, the multiplet at δ 5.10 became a sharp doublet, the doublet at δ 3.40 disappeared and the multiplet at δ 2.85 integrated for two protons.

The above nmr study of the reduced product established the following three things:

1) the peak at δ 3.40 is due to a hydroxyl proton.

2) the second hydroxyl proton is under the multiplet at δ 2.85.

3) the peak at δ 5.10 is due to a proton which is on a carbon bearing a hydroxyl group.

The last point bears a clue to the structure of compound 49 and, therefore, to the structure of compounds 44 and 45.

45 49

47 50

Structure 50, which would be expected from the reduction of 47, would have two protons on the carbon bearing a hydroxyl group, i.e., protons H_f and H_g. The nmr spectrum of 50 in deuterium oxide would be expected to show multiplet for the proton H_f since it would be coupled to the methylene protons H_{ee} as well as to the methine proton H_g. Similarly H_g would be expected to give a multiplet, a triplet or a quartet since it would be coupled to the two neighboring methine protons H_f ahd H_h. The doublet at δ 5.1 which must be coupled to a hydroxyl group, therefore, could not be due to either H_f or H_g. This excludes the 1,2-diol 50 from consideration as the possible structure for the reduction product and, therefore, eliminates structure 47 as the possible structure for the bromohydroxy ketone.

Structure 49, the product which would be expected from the reduction of 45, would also have two protons on carbons bearing a hydroxyl group, i.e., proton H_b and H_d. Once again, H_b would be expected to give a multiplet since it would be coupled to the methylene protons H_{aa} as well as to the methine proton H_c. H_b must, therefore, absorb near δ 2.85 or δ 4.05 but can not be the cause of the doublet at δ 5.1. However, the proton H_d is coupled only to the methine proton H_c and would be expected to give a doublet after deuteration of the alcohol. The doublet at δ 5.1 must be, therefore, due to the proton H_d. This firmly establishes structure 49 for the reduced product and, therefore, structure 45 for bromo-hydroxyl ketone.

Dahn[34] studied the mechanism and the kinetics of the decomposition of diazo ketones in acidic media. According to his observations, acid-catalyzed hydrolysis of diazo ketones with perchloric acid follow a A-1 path, i.e., pre-equilibrium protonation followed by rate determining unimolecular decomposition of the diazonium ion to give a carbonium ion which then reacts with water to give a ketol. However, he suggested a A-2 path for the formation of alpha chloro ketone from acid catalyzed hydrolysis in the presence of more strongly nucleophilic chloride ions, a behaviour similar to that of diazoacetic esters which were shown by Alberly[35] to follow such a path with hydrogen chloride. It is possible that in the present case the hydroxydiazo ketone 42 follows a similar path with hydrogen halide to give expected α-halohydroxy ketones 44 and 45 (path A, Scheme 4). The yields of the latter compounds are, however, affected due to the formation of dione 43, a side product formed as a result of the elimination of the diazo nitrogen (path A, Scheme 4). Furthermore, the apparent exclusive formation of one diastereomer of 44 and 45 indicates a stereospecific reaction. The source of this stereospecificity is at present unknown but could be due to the intramolecular stereospecific protonation of the diazo carbon.

EXPERIMENTAL

General.--In the preparation of diazomethane ground glass joints were completely avoided, all the connections were made with rubber stoppers and the glass tubes were carefully fire polished. Irradiations were done with a 550 Watt Hanovia high pressure mercury-vapor arc lamp in a small Pyrex reaction vessel equipped with a Pyrex water cooled immersion well. The volume of the reaction vessel, after immersing the inner well, was 150 ml as measured to the level of the side arms. The reaction solution was stirred with a magnetic stirring bar with a slow stream of nitrogen passing through the reaction solution during the irradiation. Small scale tlc was performed on 3 x 1" glass plates coated with silica gel HF-254 (Merck) or alumina oxide H (Merck). Preparative tlc was done on 200 x 200 mm glass plates coated with silica gel HF-254 (Merck) and made by shaking silica gel (25 g) with 50 ml of water in a 125-ml stoppered Erlenmeyer flask to form an even slurry and applying it immediately to the surface of the glass plates. After leaving overnight to air dry, the plates were activated in an oven for 30 minutes before use. Separated materials were detected by uv light or iodine vapor. Solvents used in column chromatography were purified by simple distillation. Evaporation of the solvents was carried out in vacuo with bath temperatures kept below 50^{o}. Melting points (mp) were determined on a Kofler hot stage and are uncorrected. The infrared (ir) spectra were determined on Beckman IR-12 and

Perkin-Elmer Infracord (i) spectrometer. The nuclear magnetic resonance (nmr) spectra were determined on a Varian A-60 spectrometer using carbon tetrachloride (CCl_4) or deuterated chloroform ($CDCl_3$) as the solvent and tetramethylsilane (tms) as an internal reference. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tms, and the signal multiplicities are expressed as singlet (s); doublet (d); triplet (t); quartet (q); and multiplet (m). Values given for coupling constant (J) are in cycles per second (cps). Mass spectra were performed by Mr. V. Fiel of USDA laboratory and Morgan Schaffer, Montreal, Quebec, Canada. Microanalysis were performed by Midwest Microlabs, Inc., Indianapolis, Indiana.

Diazomethane.[36]--To a chilled mixture of 0.6 liter of solvent grade ether, 90 ml of 2-(2-ethoxyethoxy) ethanol and 0.12 liter of 30% sodium hydroxide solution contained in a 1-liter round bottomed flask was added 36 g (0.10 mole) of bis-(N-methyl-N-nitroso) terapthalamide (70% in mineral oil) in one portion. The flask was immediately transferred to an oil bath and connected to a condenser (26 cm long) which was fitted with a long glass tube extending nearly to the bottom of a 500-ml calibrated filtering flask equipped with a magnetic stirrer and a drying tube and containing 100 ml of anhydrous ether in a well mixed ice-salt bath. Diazomethane dissolved in ether started distilling as the mixture was warmed to 30° and about 300 ml of ether was distilled in two hours. At this stage reaction was presumed complete as judged by the disappearance of the yellow color in the reaction vessel. The distillate contained 0.72 mole

(72%) of dizomethane as determined by treating 5-ml aliquot of the ethereal solution of diazomethane with an excess of benzoic acid (1.00 g) dissolved in 5-ml of ethanol and then titrating the unreacted benzoic acid against standard sodium hydroxide solution using phenolpthalein as indicator.

1-Diazo-2-butanone (35).[22]--A solution of 5.4 g (51 mmole) of propionyl chloride[37] (bp 78-80°) in 25 ml of anhydrous ether was added dropwise from a 60 ml separatory funnel to a cold and stirred solution of diazomethane (157 mmole) during a period of 45 min. The solution was then brought to the room temperature and stirred for 2 hr more. Evaporation of the solvent in vacuum 3.8 g (70%) of 1-diazo-2-butanone (35) as a yellow oil, nmr (CCl_4) δ 5.28 (s, 1H, $C\underline{H}N_2$), 2.30 (q, 2H, J = cps, $C\underline{H}_2$), 1.00 ppm (t, 3H, J = 7 cps, $C\underline{H}_3$); ir ($CHCl_3$)$_i$ 4.70 (m, CN_2), 6.20μ (s, $\underline{CO}CHN_2$).

1-Diazo-3-phenyl-2-propanone (36).--A solution of 8.1 g (50 mmole) of phenylacetyl chloride[38] (bp 55-57°, 1mm) in 20 ml of anhydrous ether contained in a 60 ml separatory funnel was added dropwise to the cold and stirred ethereal solution of diazomethane (150 mmole) during a period of 30 min. The stirring was continued first at 0° for 1 hr and then at room temperature for 1 hr more. Evaporation of the solvent in vacuo gave a yellow oil which was recrystallized from ether-pentane to give 7.6 g (90%) of 1-diazo-3-phenyl-2-propanone (36) as yellow crystals, mp 40-42° (lit.[23] mp 42°); nmr (CCl_4) δ 7.18 (s, 5H, Ph), 5.10

(s, 1H, C$\underline{H}$N$_2$), 3.46 ppm (s, 2H, C$\underline{H}_2$); ir (CHCl$_3$)$_i$ 4.80 (m, CN$_2$), 6.16 μ (s, CO).

2-Diazo-1-hydroxy-1-phenyl-3-pentanone (41).--A solution of 0.5 g (4.1 mmole) or 1-diazo-2-butanone (35), 0.5 g (4.1 mmole) of sodium carbonate and 2 ml of benzaldehyde in 80 ml of 60% ethanol was stirred in a 250 ml 3-necked flask for 2 hr at room temperature. The solution was then poured into 100 ml of cold water and was extracted with three 50-ml portions of carbon tetrachloride. After the evaporation of most of the solvent, the yellow oil was placed on a column (24 mm by 340 mm) packed with basic alumina (Fisher, 50 g) in benzene and eluted with benzene (100 ml), ether (100 ml), ethyl acetate (100 ml) and finally with ethanol (200 ml). Evaporation of the solvent from the ethanol fraction afforded 0.4 g (38%) of 2-diazo-1-hydroxy-1-phenyl-3-pentanone (41) as a yellow viscous oil, nmr (CCl$_4$) δ 7.20 (s, 5H, Ph), 5.85 (s, 1H, C$\underline{H}$OH), 4.60 (s, 1H, CHO$\underline{H}$), 2.38 (q, 2H, J = 7 cps, C$\underline{H}_2$), 1.08 ppm (t, 3H, J = 7 cps, C$\underline{H}_3$); ir (CHCl$_3$)$_i$ 2.64 (w, OH), 4.68 (m, CHN$_2$), 6.17 μ (s, CO).

3-Diazo-1,4-diphenyl-4-hydroxy-2-butanone (42).--To an ice cold, stirred solution of 1.0 g (6.0 mmole) of 1-diazo-3-phenyl-2-propanone (36) in 60 ml of redistilled ethanol (0.10 M) and 3 ml of benzaldehyde contained in a 150-ml, 3-necked flask was added 5 ml of a 2% (0.2 g in 10 ml of water) sodium hydroxide solution. After 30 min of stirring, during which time the solution acquired a golden yellow color, 5 ml more of the sodium hydroxide solution and 3 ml of benzaldehyde solution were added. The solution was stirred for an additional 2 hr then poured into 150 ml of cold water and finally extracted with three 100 ml portions of carbon tetrachloride. After evaporation of most of the solvent, the yellow extract was placed on a chromatography column (24 mm by 34 cm) packed with basic alumina (Fisher, 100 g) in carbon tetrachloride and eluted with carbon tetrachloride (150 ml), benzene (150 ml) and finally with ethanol (300 ml). Removal of the solvent from the ethanol fraction afforded 1.4 g of yellow oil which was crystallized in cold ether-pentane to give 1.2 g (65%) of 3-diazo-1,4-diphenyl-4-hydroxy-2-butanone (42) as yellow crystals, mp 56-57°; nmr (CCl_4) δ 7.21 (m, 10H, 2Ph), 5.91 (d, 1H, J = 4 cps, C$\underline{H}$OH), 4.20 (d, 1H, J = 4 cps, CHO$\underline{H}$), 3.68 ppm (s, 2H, C$\underline{H}_2$); (CCl_4-D_2O) δ 7.20 (d, 10H, 2Ph), 5.88 (s, 1H, C$\underline{H}$OD), 3.66 ppm (s, 2H, CH_2); ir (KBr) 2.94 (w, OH), 4.78 (s, CHN_2), 6.08 μ (s, CO).

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.20; H, 5.26; N, 10.52.
Found: C, 72.30; H, 5.31; N, 10.40.

In a second run, the same quantities of the reactants were used as in the previous run, but this time the reaction was run at room temperature. After two hr of stirring, the work up of the intensely red solution in a similar fashion as in the initial attempt gave 0.5 g (30%) of diazo ketone 42.

In a third run, a solution of 1.0 g (6 mmoles) of diazo ketone 36, 0.6 g (6 mmoles) of sodium carbonate and 2 ml of benzaldehyde in 80 ml of dimethyl sulfoxide was stirred at room temperature for 2 hr. Work up of the reaction mixture and column chromatography on basic alumina gave 0.5 g (30%) of the diazo ketone 42.

In a fourth run, a solution of 1.0 g (6 mmoles) of diazo ketone 36, 0.25 g (6 mmoles) of sodium hydroxide and 2 ml of benzaldehyde in 80 ml of dioxane was stirred at room temperature for 2 hr. Work up of the reaction solution and column chromatography of the concentrate gave 0.3 g (18%) of the hydroxy diazo ketone 42.

In a fifth run, a solution of 1.0 g (6 mmoles) of diazo ketone 36, 0.5 g (6 mmoles) of sodium carbonate and 4 ml of benzaldehyde in 80 ml of dimethyl formamide was stirred at room temperature for 2 hr. Work up and column chromatography in a similar fashion as in the previous cases gave 0.2 g (13%) of the hydroxy diazo ketone 42.

Irradiation of 3-Diazo-1,4-diphenyl-4-hydroxy-2-butanone (42) in Benzene.--A solution of 500 mg (1.9 mmole) of the hydroxydiazo ketone 42 in 150 ml of benzene contained in a medium size reaction vessel was purged with nitrogen for 30 min and then irradiated (cf. p 31) for 75 min. Removal of the solvent under reduced pressure gave a yellow oil which was dissolved in 4 ml of methanol and poured into 20 ml of hot saturated solution of aqueous copper acetate and left overnight to ensure complete precipitation of the copper salt of 1,4-diphenyl-1,3-butanedione. Filtration gave green flakes of the copper salt of the dione which were washed with cold ether and dried, mp 197-199° (lit.[25] mp 196-198°). The copper salt was placed in a 125 ml separatory funnel together with 10 ml of ether and was shaken with 20 ml portions of 20% sulphuric acid until decomposition was complete and two homogenous phases were present. The ether layer was separated from the aquous layer and dried over Drierite. Filtration and evaporation of the solvent gave 220 mg (49%) of 1,4-diphenyl-1,3-butanedoine (43) as yellow crystals, mp 49-50° (lit.[25] 51°); nmr (CCl_4) δ 15.50 (s, 1H, CHOH), 7.75 and 7.25 (m, 10H, 2Ph), 6.02 (s, 1H, CHOH), 3.59 ppm (s, 2H, CH_2CO); ir ($CHCl_3$) 3.64 (m, b, OH), 6.41μ(s, b, CO).

Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.67; H, 5.92.

Found: C, 80.70; H, 5.95.

In a second run, the same quantities of the reagents and the same irradiation time were employed as in the previous case but this time the dione 43 was isolated *via* thin layer chromatography.. Aliquots from an ether solution of 500 mg of the irradiated diazo ketone 42 were applied by a thin glass capillary about 1.5 cm from the lower edge of 200 x 200 mm glass plates coated with silica gel HF-254 (*cf*. p. 31). The Chromatograms were developed in a glass tank in the ascending direction using doubly distilled chloroform as mobile phase. The plates were taken out after the solvent had travelled about 80 mm from the end and were permitted to air dry. The spot with R_f 0.72 was collected in a beaker and extracted with ether. Evaporation of the solvent from the combined ether extracts gave 280 mg (60%) of the dione 43 in the form of a red oil. The identification was done by comparing the ir and the nmr spectra of the oil with those of the standard sample.

Irradiation of the Diazo Ketone 42 in Methanol.--A solution of of 500 mg (1.9 mmole) of the diazo ketone 42 in 150 ml of methanol was purged with nitrogen for 30 min and then irradiated for 75 min in a small size reaction vessel. Removal of the solvent under reduced pressure gave a yellow oil. Treatment of the oil with hot saturated solution of copper acetate and decomposition of the precipitated copper salt of dione 43 in a similar fashion as in the previous reaction gave 235 mg (52%) of the dione 43, mp 49-50°.

In a second run, the same quantities of the reagents and the same irradiation time was employed as in the above run. Preparative tlc of the photoproduct in a similar fashion as in the previous reaction gave 300 mg (66%) of the dione 43 in the form of red oil. Identification was made by comparing the ir and the nmr spectra of the oil with those of the standard sample.

Pyrolysis of 3-Diazo-1,4-diphenyl-4-hydroxy-2-butanone (42) in Chlorobenzene.--A solution of 500 mg (1.9 mmoles) of the diazo ketone 42 in 20 ml of redistilled chlorobenzene contained in a 50-ml round bottom flask equipped with a magnetic stirring bar and reflux condenser was heated rapidly by immersing the reaction vessel in a pre-heated oil bath maintained at 170°. After an induction period of about 60 sec a vigorous evolution of nitrogen occurred and the reaction was complete in approximately 5 min. Treatment of the yellow oil, which resulted after the evaporation of the solvent, with hot saturated solution of copper acetate and decomposition of the precipated copper salt in a similar fashion as in the photolysis reactions, gave 200 mg (40%) of the dione 43, mp 49-50°.

Reaction of 3-Diazo-1,4-diphenyl-4-hydroxy-2-butanone (42) with Hydrogen Chloride in Ether.--Dry hydrogen chloride gas was bubbled through a stirred solution of 500 mg (1.9 mmoles) of hydroxydiazo ketone 42 in 60 ml of anhydrous ether contained in a 100-ml 3-necked flask equipped with a drying tube. After 10 min, the light yellow reaction solution was transferred to a separatory funnel and washed with three 20-ml portions of 2% sodium bicarbonate solution. Removal of the solvent afforded a light yellow oil which was applied by a thin glass capillary on 200 x 200 glass plates coated with silica gel and developed in a glass tank with chloroform. Plates were removed from the tank after the solvent had traveled 100 mm from the bottom and were permitted to air dry. Removal of the spot with R_f 0.69, extraction with ether and subsequent evaporation of the solvent yielded 220 mg of a light orange liquid which crystallized in ether-pentane to give 90 mg (20%) of brown crystals of dione 43, mp 49-50°. Similar recovery of the spot with R_f 0.45 gave 230 mg of a brown oil which crystallized in ether-pentane to give 160 mg (31%) of 3-chloro-1,4-diphenyl-4-hydroxy-2-butanone (44) as white crystals, mp 51-52°; nmr (CCl_4) δ 7.18 (m, 10H, 2Ph), 4.86 (q, 1H, J = 5 cps, J' = 8 cps, C$\underline{H}$OH), 4.24 (d, 1H, J' = 8 cps, C$\underline{H}$Cl), 3.77 (s, 2H, $C\underline{H}_2$) 3.30 ppm (d, 1H, J = 5 cps, CHO$\underline{H}$); ir (KBr) 2.93 (w, OH), 5.88 μ (s, CO); mass spectrum m/e (rel intensity) 170 (9), 168 (25), 139 (4), 119 (4), 107 (25), 106 (22), 105 (25), 91 (10), 90 (100), 77 (25).

Anal. Calcd for $C_{16}H_{15}ClO_2$: C, 69.96; H, 5.46; Cl, 12.93.

Found: C, 69.76; H, 5.51; Cl, 13.05.

Reaction of the Diazo Ketone 42 with Hydrogen Bromide in Ether.-- Dry hydrogen bromide gas was bubbled through a stirred solution of 500 mg (1.9 mmoles) of hydroxy diazo ketone 42 in 60 ml of anhydrous ether contained in a 100 ml 3-necked flask equipped with a drying tube. After 5 min, the almost colorless reaction solution was transferred to a separatory funnel and washed with three 20-ml portions of 2% sodium bicarbonate solution. The organic layer was separated from the aqueous layer and after drying it over Drierite, the solvent was evaporated in vacuo. The light yellow oil thus obtained, was dissolved in 2 ml of ether and 10 ml of pentane and left in refrigerator for 48 hr. The white crystals which settled during this period were filtered to give 280 mg (45%) of 3-bromo-1,4-diphenyl-4-hydroxy-2-butanone (45) as white crystals, mp 56-57°; nmr (CCl_4) δ 7.19 (m, 10H, 2Ph), 4.95 (q, 1H, J = 5cps, J́ = 8 cps, $\mathrm{C\underline{H}OH}$), 4.32 (d, 1H, J́ = 8 cps, $\mathrm{C\underline{H}Br}$), 3.85 (s, 2H, $\mathrm{C\underline{H}_2}$) 3.40 ppm (d, 1H, J = 5 cps, $\mathrm{CHO\underline{H}}$); ir (KBr) 2.94(w, OH), 5.93 μ (s, CO).

Anal. Calcd for $C_{16}H_{15}BrO_2$: C, 60.23; H, 4.70; Br, 25.04.

Found: C, 60.42; H, 4.51; Br, 25.29.

The rest of the reaction mixture was dissolved in 2 ml of methanol and poured into 10 ml of hot saturated solution of copper acetate and left overnight in a refrigerator. The copper salt of dione 43 which precipitated during this period was filtered and shaken with 15 ml of ether and 20 ml portions of 20% sulphuric acid until the decomposition of the copper salt was complete and two homogenous phases were present. The ether layer was separated from the aqueous layer and dried over Drierite. Filtration and evaporation of the solvent gave 30 mg (10%) of the yellow crystals of the dione 43, mp 50-51°.

Reaction of 1,4-Diphenyl-3-buten-2-one (48) with Hypochlorous Acid.--A solution of 250 mg (1-1 mmole) of 48,[39] mp 72-73°, in 20 ml of carbon tetrachloride and 5 ml of 5% hypochlorous acid contained in a 60 ml separatory funnel was shaken for 15 min. The organic layer was then separated from the aqueous layer and the solvent was evaporated in vacuo. The yellow oil which resulted, was dissolved in a small amount of ether and applied on 200 x 200 glass plates coated with silica gel and then developed with chloroform. Extraction of the spot with R_f 0.35 with ether and evaporation of the solvent gave 120 mg of the starting material identified by its melting point and mixed melting point with an authentic sample. Recovery of the spot with R_f 0.75 with ether pentane gave 40 mg (15%) of 3-chloro-1,4-diphenyl-4-hydroxy-2-butanone as white crystals, mp 61-62°; nmr (CCl_4) δ 7.30 (m, 10H, 2Ph), 5.18 (d, J = 10 cps, 1H, C$\underline{H}$OH), 4.56 (d, J = 10 cps, C$\underline{H}$Cl), 4.08 (s, 1H, CHO$\underline{H}$) 3.88 ppm (s, 2H, C$\underline{H}_2$); (CCl_4-D_2O) δ 7.30 (m, 10H, 2Ph), 5.18 (d, J = 10 cps, 1H, C$\underline{H}$OH), 4.56 (d, J = 10 cps, C$\underline{H}$Cl) 3.88 ppm (s, 2H, C$\underline{H}_2$); ir ($CHCl_3$) 3.13 (w, OH) 5.79 μ (s, CO).

2-Bromo-1,4-diphenyl-1,3-butanediol (49).--To a 50 ml 3-necked flask containing 10 ml of sodium-dried anhydrous ether and equipped with a condenser with a drying tube and a 15-ml addition funnel, was added an excess (40 mg) of powdered lithium aluminum hydride and the resulting slush was stirred for 10 minutes. A solution of 100 mg (0.31 mmole) of bromohydroxy ketone 45 in 5 ml of sodium-dried anhydrous ether was added to the stirred slush at such a rate that ether refluxed gently. After 1 hr of stirring, the excess of lithium aluminum hydride was decomposed with 2 ml of ethyl acetate. Filtration of the reaction mixture and slow evaporation of the solvent from the filtrate gave a white solid. Extraction of the solid with ether and subsequent evaporation of the solvent from the extract gave a colorless viscous residue which crystallized in ether-pentane to give 42 mg (40%) of 2-bromo-1,4-diphenyl-1,3-butanediol (49), mp 106-107°, nmr ($CDCl_3$)δ 7.28 (m, 10H, 2Ph), 5.10 (m, 1H, C$\underline{H}$OHPh), 4.05 (m, 2H), 3.40 (d, 1H, J = 5 cps, O$\underline{H}$), 2.85 ppm (m, 3H); (CCl_4-D_2O) 7.28 (m, 10H, 2Ph), 5.10 (d, 1H, J = 5 cps, C$\underline{H}$OH Ph), 4.05 (m, 2H); ir (KBr) 3.04 μ (m, OH).

Anal. Calcd for $C_{16}H_{17}BrO_2$: C, 59.85; H, 5.29; Br, 24.91.

Found: C, 60.13; H, 5.58; Br, 24.90.

Attempted Alkylation of 1-Diazo-3-phenyl-2-propanone (36) with Methyl Iodide.--To a cold and stirred solution of 1.0 g (3.8 mmole) of diazo ketone 36 in 60 ml of ethanol and an excess of methyl iodide (4 ml) contained in a 150 ml 3-necked flask was added 0.2 g (5 mmole) of sodium hydroxide dissolved in 5 ml of ethanol. The initially yellow solution acquired an orange color immediately on the addition of base and after 1 hr, during which time the solution became deep red, stirring was discontinued. The solution was poured into 100 ml of cold water and extracted with three 100 ml portions of carbon tetrachloride. Removal of the solvent from the combined carbon tetrachloride extracts under reduced pressure yielded a red gummy material which on tlc (a) with benzene-ether (6:14) showed one spot corresponding to the starting diazo ketone and a highly colored major spot at the origin. The nmr spectrum of the extract did not reveal peak in the region of methyl protons.

In a second run using the same quantities of the reactants as in the previous attempt but employing sodium carbonate (0.6 g, 6 mmole) as the base, the solution did not turn red immediately but did so slowly. After 8 hr of stirring the solution was worked up in a similar fashion as in the initial run. Tlc (a) with benzene-ether (6:4) and nmr spectrum revealed the same results as in the previous attempt.

In other attempts, the combination of solvent-base systems tried, were sodium hydroxide-dimethyl sulfoxide, sodium carbonate-dimethyl sulfoxide, sodium hydroxide-dioxane and sodium carbonate-dioxane. In all cases work up of the reaction solution and analysis by tlc with benzene-ether (6:4) showed a faint spot corresponding to the starting diazo ketone and an intensely colored spot at the origin. The nmr spectra of the crude reaction mixtures did not reveal any peak in the region of methyl protons. Column chromatography yielded only small amounts of the starting material in all cases.

Attempted Dehydrohalogenation of 3-Chloro-1,4-diphenyl-4-hydroxy-2-butanone (44) via 2,4-Dinitrophenylhydrazone.--A solution of 100 mg (0.37 mmoles) of chlorohydroxy ketone 44 in 1 ml of methanol was added to 40 mg of 2,4-dinitrophenylhydrazine dissolved in 5 ml of methanol and five drops of concentrated hydrochloric acid contained in a 50-ml Erlenmeyer flask. After 30 min of stirring, during which time the 2,4-dinitrophenylhydrazone (2,4-DNP) of the chlorohydroxy ketone 44 separated as a yellow precipitate, the reaction mixture was filtered and the precipitate was washed several times with water and cold methanol. The precipitate was then transferred to a 50-ml 3-necked flask containing 5 ml of benzene and 5 ml of glacial acetic acid and heated to reflux. Analysis of the reaction misture by tlc (s) ether during reflux showed only one spot corresponding to the starting material. After 6 hr of refluxing 20 ml of water was added to the reaction mixture and the latter left in refrigerator overnight which resulted in the separation of the yellow precipitate of starting 2,4-DNP which was identified by its ir spectra.

In a second run, 2,4-DNP obtained from 100 mg (0.37 mmole) of chlorohydroxy ketone 44 in a similar fashion as in the previous case, was dissolved in 5 ml of benzene and heated to reflux with 10 ml of 5 N sulphuric acid. The solution slowly became red. After 10 hrs, analysis by tlc (s) ether showed a faint spot corresponding to the starting material and a highly colored spot at the origin. No spot corresponding to the dione

43 was noticed. Cooling of the reaction mixture after 5 hr of stirring resulted in the separation of a small amount of yellow precipitate which had ir spectra similar to that of the starting material.

Attempted Dehalogenation of 3-Chloro-1,4-diphenyl-4-hydroxy-2-butanone (44) with Zinc and Acetic acid.--A solution of 100 mg (0.37 mmoles) of chlorohydroxy ketone 44 in 10 ml of anhydrous ether contained in a 50-ml 3-necked flask was heated to reflux with 30 mg of activated zinc dust and 4 drops of glacial acetic acid. After 45 min, heating was discontinued and the reaction mixture was filtered. Evaporation of the solvent from the filtrate gave a brown viscous liquid which crystallized with ether-pentane to give 30 mg of the starting chlorohydroxy ketone, mp 51-52°. The ir spectra of the rest of the material was quite similar to that of benzylstyryl ketone (48), but no purified material could be obtained from it.

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