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McMASTER Jr., Marvin Clayton, 1938-
EFFECT OF SUBSTITUTION IN THE VINYL GROUP
ON REACTIONS OF BROMO DERIVATIVES OF
 α, β -UNSATURATED KETONES.

The University of Nebraska, Ph.D., 1966
Chemistry, organic

University Microfilms, Inc., Ann Arbor, Michigan

EFFECT OF SUBSTITUTION IN THE VINYL
GROUP ON REACTIONS OF BROMO DERIVATIVES
OF α,β -UNSATURATED KETONES

by

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A THESIS

Presented to the Faculty of
The Graduate College in the University of Nebraska
In Partial Fulfillment of Requirements
For the Degree of Doctor of Philosophy
Department of Chemistry

Under the Supervision of Dr. N. H. Cromwell

Lincoln, Nebraska

November 19, 1965

TITLE

EFFECT OF SUBSTITUTION IN THE VINYL GROUP ON THE
REACTIONS OF BROMO DERIVATIVES OF α,β -UNSATURATED KETONES

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MARVIN C. McMASTER, JR.

APPROVED

DATE

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The author wishes to express his sincere appreciation to Dr. Norman H. Cromwell for the suggestion of the research problem, and for guidance and encouragement in completing this investigation.

To Dr. A. E. Pohland, the author would like to extend appreciation for his cooperation when our independent investigations converged and for his suggestions in general.

Finally, to the author's wife, Eunice, a special note of appreciation is made for her consideration, understanding, and help.

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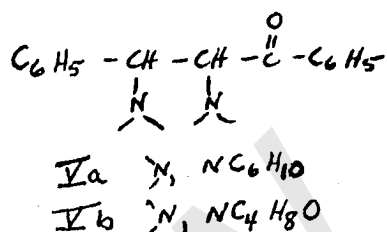
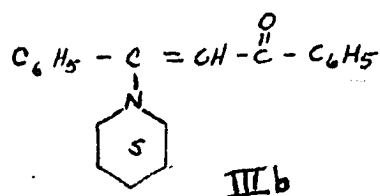
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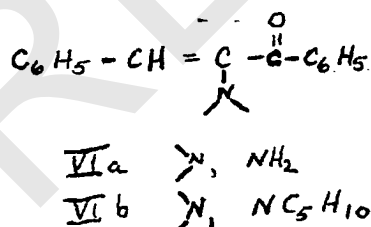
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with a secondary amine. Piperidine in alcohol reacted with 2-bromochalcone to yield two products; a red compound, m.p. 100° , assigned IIIb and a yellow compound, m.p. 157° assigned Va.



Reaction Products with Secondary Amines

In 1927, Dufraisse and Moureu⁵ repeated Watson's work and prepared IIIa (IV) and IIIb. These workers felt that if the compounds were β -amino- α,β -unsaturated ketones, they should produce 1,3-diketones on acid hydrolysis. Since the product formed in both cases was benzyl phenyl diketone, a 1,2-diketone, Dufraisse and Moureu changed the structures to α -amino- α,β -unsaturated ketones VIa and VIb.



The evidence for VIa proved to be misleading as will be explained in the next section, but acid hydrolysis of α -amino- α,β -unsaturated ketones to 1,2-diketones has been used extensively as proof of structure. Reduction of VIb to the known 2-piperidino-3-phenylpropio-phenone by Kohler and Bruce⁶ lent further strength to Dufraisse and Moureu's

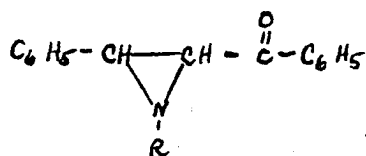
proposed structure.

The structures of the dipiperidino ketone Va and the dimorpholino analog Vb synthesized by Cromwell⁷ were established by hydrolysis also. The investigators obtained some benzyl phenyl diketone but the main products were benzaldehyde and ω -aminoacetophenone which favored the α,β -diamino-ketone structure rather than the alternate α,α -diaminoketone.

Reaction Products With Primary Amines

Structures IIIa and VIa, assigned by Watson and Ruhemann³ and by Dufraisse and Moureu⁵ to the white product from the reaction of bromochalcones with ammonia, did not appear to agree with experimental observations. As mentioned previously, Dufraisse and Moureu eliminated IIIa from consideration by hydrolyzing the product to a 1,2-diketone. Structure VIa appeared to be incorrect since all the known α -sec-amino- α,β -unsaturated ketones were highly colored solids while VIa was colorless.

In 1943, Cromwell, Babson and Harris⁸ reported the reaction of the primary amines, benzylamine and cyclohexylamine, with 2-bromochalcone and with chalcone dibromide to produce VIIa and VIIb respectively.



VII a R, CH₂ C₆H₅

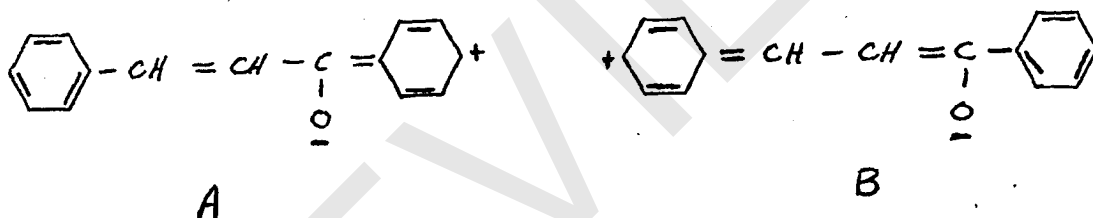
VII b R, C₆H₅

The assignment of the ethylenimine structure was based on the

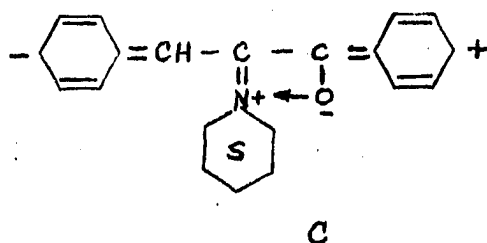
failure of either compound to decolorize a chloroform solution of bromine or to be reduced by Raney nickel catalyst using hydrogen at 50 p.s.i. at room temperature.

More evidence was supplied by ultraviolet spectra. Cromwell and Johnson⁹ showed that compounds of type VI had maxima at nearly the same position as the parent unsaturated ketone, chalcone, while compounds of type VII had spectra more closely resembling the saturated ketone 3-phenylpropiophenone.

Further work by Cromwell and Watson¹⁰ and Black and Lutz¹¹ suggested possible resonance forms responsible for the observed spectra.



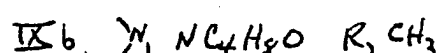
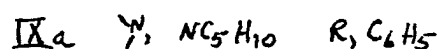
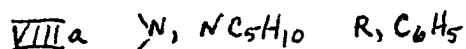
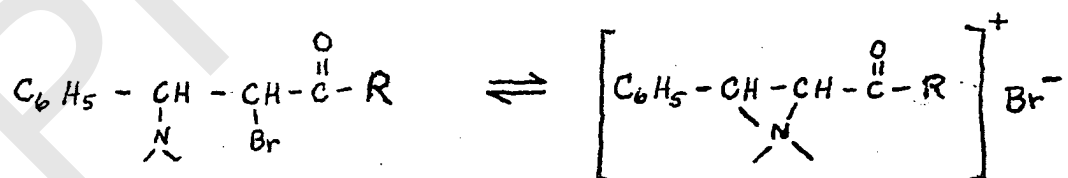
Chalcone in heptane shows two maxima. The first λ_{max} at 226m μ (ϵ 12,100) was attributed to a benzoyl $\pi \rightarrow \pi^*$ transition represented by resonance structure (A); the second λ_{max} at 299m μ (ϵ 23,900) was assigned to the cinnamoyl resonance form (B) and also probably contained a weak benzoyl resonance band. 2-Morpholinochalcone in heptane had three maxima; λ_{max} at 249m μ (ϵ 16,700) (benzoyl), at 278m μ (ϵ 15,700) (cinnamoyl) and at 365m μ (ϵ 1,480). The latter band was extended into the visible region and was thought to be due to the resonance form (C). This absorption probably is responsible for the red color of the compound.



3-Phenylpropionophenone and compounds of type VII exhibit only two maxima; a relatively strong intensity peak at 230-40mμ (benzoyl $\pi \rightarrow \pi^*$) and a weaker peak at 280-300mμ (benzoyl $n \rightarrow \pi^*$).

Mechanism of Formation of Reaction Products.

A very important intermediate in the reaction of amines with 2-bromochalcone was reported by Dufraisse and Moureu.⁵ When molar equivalents of piperidine and 2-bromochalcone were reacted at -10° in ether, a white solid VIIIa, m.p. 164, was obtained which contains both the bromo and the piperidino groups. This compound reacted with sodium ethoxide to form the α -piperidinoketone VIb and with excess piperidine to form VIb and the diaminoketone V.

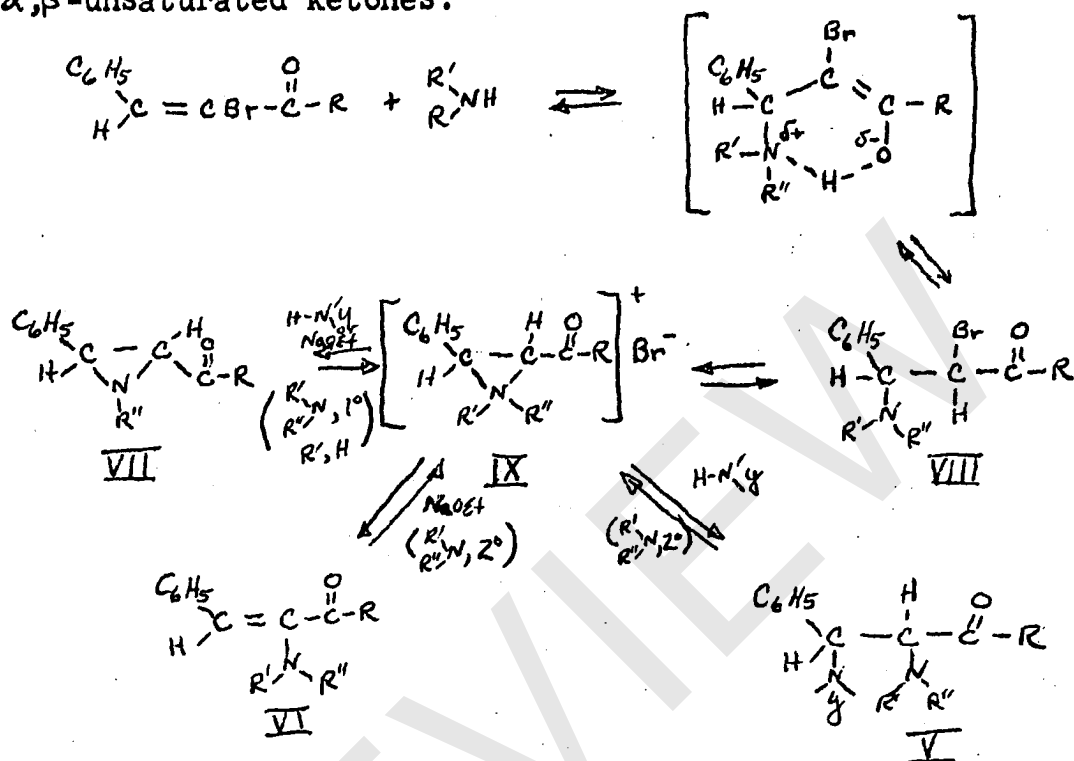


The α -bromo- α -aminoketone structure was preferred by Dufraisse and Moureu but, in 1943, Cromwell and Witt¹² synthesized the morpholino compound VIIIb and showed by its reactions that both compounds have the indicated structures. A solution of VIIIb in water conducted an electric current and, if an aqueous alcohol solution of the compound was allowed to stand for a few minutes, the bromine could be precipitated by silver nitrate addition due to the formation of the ethylenimmonium ion IXb. However, if dilute nitric acid was used as the solvent and alcoholic silver nitrate was added to the solution, protonation of the amine group of VIIIb inhibited ionization and silver bromide precipitation occurred very slowly.

As in the case of VIIa, alcoholic VIIIb reacted with sodium ethoxide to form the α -morpholino- α,β -unsaturated ketone and reacted with excess morpholine to form the dimorpholinoketone. Formation of IXb explained how the α,β -diaminoketones were produced since they were not products of the reactions of α -amino- α,β -unsaturated ketones and excess amine.

Primary amines were shown to react with α -bromo- α,β -unsaturated ketones by the same general route. From the reactions of molar equivalents of benzylamine and 2-bromo-chalcone, Cromwell, Babson and Harris⁸ isolated 2-bromo-3-benzylaminopropiophenone (VIIIc) which exhibited the same general reaction properties as the α -bromo- β -sec-aminopropiophene.

This enabled Cromwell and Cram¹³ to write a general reaction mechanism for the reaction of amines and the bromo derivatives of α,β -unsaturated ketones:



The amine undergoes 1,4-addition to the unsaturated ketone via a hydrogen-bonded transition state to the enol which tautomerizes to the keto form, VIII. This compound when dissolved in water forms the ethylenimmonium ion IX. If the amine $\text{R}'\text{R}''\text{NH}$ is primary, base removes the hydrogen from the amino group of IX to form the ethylenimine ketone VII. When $\text{R}'\text{R}''\text{NH}$ is secondary, the most labile hydrogen is on the α -carbon and removal of it by ethoxide ion leads to the α -amino- α,β -unsaturated ketone VI. When IX, formed from a secondary amine, is attacked by another amine, two alternate reaction paths are available. The incoming amine may act simply as a basic group and extract the α -hydrogen to give VI

or the amine nitrogen's free electron pair may attack the β -carbon opening the aziridine ring to give the diamino-ketone V.

α,β -Dibromo ketones, i.e., chalcone dibromide, when reacted with amines are thought to initially dehydrohalogenate to α -bromo- α,β -unsaturated ketones which form the observed reaction product by the mechanism above.

2. Amine Reactions of Bromo Derivatives of Endocyclic α,β -Unsaturated Ketones.

The reaction of amines with α -bromo- α,β -unsaturated ketones was shown to be general by a series of papers published by Cromwell, et al on the reaction of bromo derivatives of endocyclic α,β -unsaturated ketones.

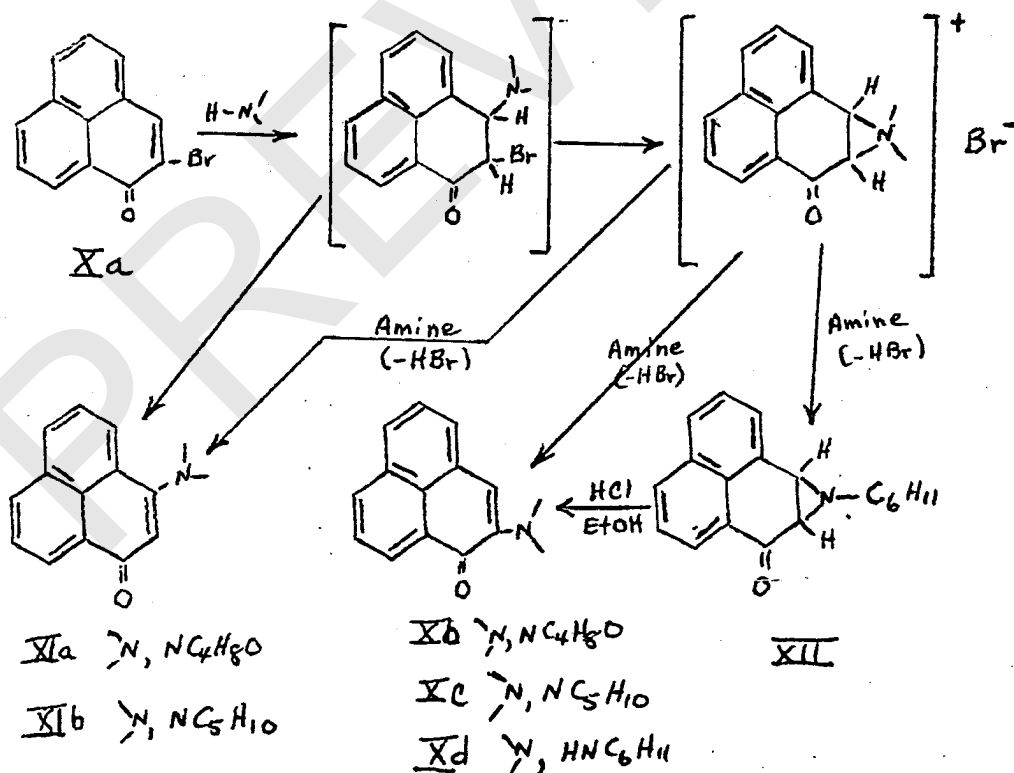
Derivatives of Perinaphthenone-7

Cromwell, Capps, and Palmer¹⁴ heated 8-bromoperinaphthenone-7 (Xa) in an excess of the appropriate amine for 1 hour at 85° and obtained 8-morpholinoperinaphthenone-7 (Xb), red needles, m.p. 144-144.5°, and 8-piperidinoperinaphthenone-7 (Xc), red needles, m.p. 115-116°. They also discovered that allowing Xa to stand in excess amine at room temperature produced yellow crystals of different products; 9-morpholinoperinaphthenone-7 (XIa), m.p. 139-140.5° and 9-piperidinoperinaphthenone-7 (XIb), m.p. 122-123°. In all cases, it was necessary to use excess amine as the solvent; attempts to react Xa with a slight excess of amine in another solvent,

even at elevated temperature, only led to recovery of starting material.

Dissolving compounds Xb or XIa, the 8- and 9-morpholino derivatives, in 10% hydrochloric acid and boiling them for 5 minutes produced the corresponding diketones; perinaphthandione-7,9, yellow crystals, m.p. 262° dec. and perinaphthandione 7,8, orange needles, m.p. $177-181^{\circ}$.

Cyclohexylamine reacted with Xa to produce white crystals, m.p. $147-148^{\circ}$ dec., of the ethylenimine ketone, 8,9-(N-cyclohexyl)iminoperinaphthenone-7 (XII). Product XII was shown to rearrange in dilute ethanolic hydrochloric acid to form 8-cyclohexylaminoperinaphthenone-7 (Xd); fine, purple needles, m.p. $116-118^{\circ}$.

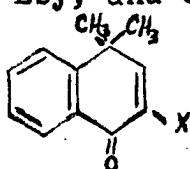


For this series of compounds, a slight change in the mechanism proposed by Cromwell and Cram¹³ was necessary. The

quasi six-membered ring involved in proton transfer from the amine to the ketone oxygen in forming the α -bromo- β -amino-ketone is not possible in the rigid endocyclic ketones. Since higher temperature and larger amine concentrations were necessary for the reaction of Xa, this transition state was suggested as a factor facilitating the reaction of the open-chain analog.

Derivatives of 4,4-Dimethyl-1-keto-1,4-dihydronaphthalene

The reactions of 2-bromo-4,4-dimethyl-1-keto-1,4-dihydronaphthalene (XIIIa) with amines were reported by Cromwell, Eby, and Capps¹⁵ in 1951.

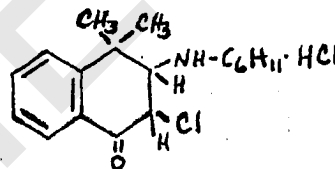


XIIIa X, Br

XIIIb X, NC₄H₈O

XIIIc X, NC₅H₁₀

XIIId X, OH



XIV

Morpholine and piperidine each reacted with XIIIa on standing 2 days at room temperature to give 98% of 4,4-dimethyl-1-keto-2-morpholino-1,4-dihydronaphthalene (XIIIb), colorless crystals, m.p. 124-125° and 99% of 4,4-dimethyl-1-keto-2-piperidino-1,4-dihydronaphthalene (XIIIc). These compounds can be produced in lower yield by heating smaller quantities of amines in other solvents. A benzene solution of XIIIa and 2 molar equivalents of morpholine refluxed 71 hours yielded 68.5% of XIIIb. The aminoketones XIIIb and XIIIc were each

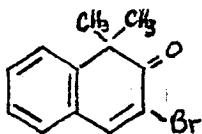
hydrolyzed to colorless crystals of 4,4-dimethyl-2-hydroxy-1-keto-1,4-dihydronaphthalene (XIIIId), the enolic form of the diketone, m.p. $70-71^{\circ}$, by heating them with 30% sulfuric acid on a steam bath for 1.5 hours. The product from the reaction of XIIIa with excess cyclohexylamine on standing 3 days at room temperature was a colorless oil which could not be crystallized. However, treatment with dry hydrochloric acid in ether produced a colorless solid, m.p. $176-177^{\circ}$, identified as the amine hydrochloride XIV. Previous work in open chain series¹ have shown products of this type to result from ethylenimine ketones.

Derivative of 1,1-Dimethyl-2-keto-1,2-dihydronaphthalene

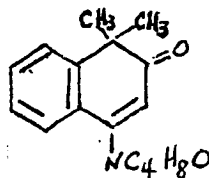
The next endocyclic α,β -unsaturated ketone series studied were the 1,1-dimethyl-2-keto-1,2-dihydronaphthalenes by Cromwell and Campbell¹⁶ in 1957. The dibromide, 3,4-dibromo-1,1-dimethyl-2-tetralone (XV), was reacted with benzylamine in benzene at room temperature for 2 days. The only product was 3-bromo-1,1-dimethyl-2-keto-1,2-dihydro-naphthalene (XVI); none of the expected ethylenimine ketone was found.



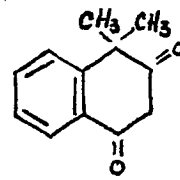
XV



XVI



XVII



XVIII

Both XV and XVI reacted with morpholine when heated to 65° for 24 hours; but the only product of these reactions was

1,1-dimethyl-2-keto-4-morpholino-1,2-dihydronaphthalene (XVII), m.p. 102-103°, yellow needles. The aminoketone (XVII) hydrolyzed on heating in 20% sulfuric acid for 2 hours on a steam bath to form 1,3-diketo-4,4-dimethyltetralin (XVIII). The formation of XVII supported the work of Cromwell, Capps, and Palmer which proved that either α - or β - amino- α,β -unsaturated ketone are possible products of the reactions of α -bromo- α,β -unsaturated ketones. The first intermediate formed, the α -bromo- β -aminoketone, can form products by two routes; direct loss of hydrogen bromide forms β -amino- α,β -unsaturated ketones, while formation of the ethylenimmonium ion followed by loss of hydrogen bromide yields α -amino- α,β -unsaturated ketones and ethylenimine ketones. In the 4,4-dimethyl-2-keto-1,2-dihydronaphthalene series, failure to form the α -amino- α,β -unsaturated ketone may indicate that the ethylenimmonium is not formed at all.

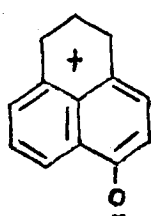
Infrared and ultraviolet spectra of Endocyclic α,β -unsaturated ketones.

The infrared and ultraviolet spectra of the open chain α,β -unsaturated ketones have been studied,^{1,9} as indicated above, and have proven very useful in characterizing the products obtained. The spectra of the three series of endocyclic ketones studied were reported in part in the references given and summarized in detail by Campbell and Cromwell.¹⁷

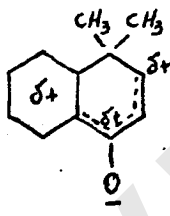
The intense λ_{\max} below 250m μ were assigned to benzoyl ($\pi-\pi^*$) resonance with some contribution in the 230-240m μ region

from vinylketone or acrylophenone chromophones. Weak benzoyl ($n-\pi^*$) resonance bands from 280-300m μ were often not observed due to the intense cinnamoyl chromophore at 280-350m μ .

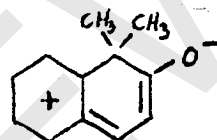
Increasing the length of the resonator, increases the ability of the molecule to stabilize the incipient positive charge and causes the λ_{\max} to fall at higher wavelength (lower energy). The longest resonance system is contained by perinaphthenone-7 as is shown in resonance structure (D),



D



E



F

one of 5 canonical forms which can be written for this molecule. The next longest resonator (F) is in 1,1-dimethyl-2-keto-1,4-dihydronaphthalene; 4,4-dimethyl-1-keto-1,4-dihydronaphthalene with its cross-conjugated system (E) has the shortest. This results in the long wavelength bands of the perinaphthenones-7 falling 50-80m μ nearer the visible region than those of the other compounds. The three colored α -aminoketones XIa, XIc, and XIIIb all contained an additional broad, low intensity band in the visible region at 452m μ (ϵ 5,200), 500m μ (ϵ 5,500), and 325 m μ (ϵ 1,900) respectively. As mentioned previously, this characteristic band was assigned to a dipolar ion similar to C.