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The Reaction of *N*-Acylmethylisoquinolinium Betain with Heterocumulens[*1]

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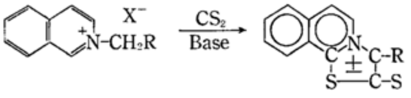
Among the various methods of formation of mesoionic compounds, the 1,3-dipolar cycloaddition method has been widely investigated by Huisgen *et al.*[1,2] In an earlier paper,[3] we reported the preparation of mesoionic triazolone by means of the 1,3-dipolar addition between 3-phenylsydnone and phenyl isocyanate. Kroehnke and his coworkers prepared the mesoionic thiazolo[2,3-*a*]isoquinolinium ring system by treatment of *N*-arylmethyl- and *N*-acylmethylisoquinolinium salts with carbon disulfide and alkali, in which 1,3-dipolar cycloaddition followed by dehydrogenation occurred as shown below.[4,5]

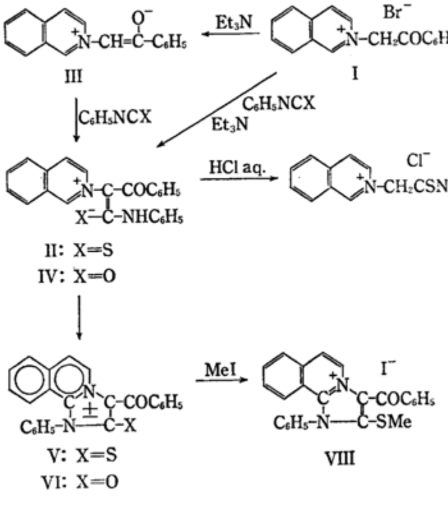


In this paper we wish to report the results of reactions of pyridinium and isoquinolinium betain with heterocumulens.

When triethylamine was added into the solution of *N*-phenacylisoquinolinium bromide (I) and an equimolar amount of phenyl isothiocyanate in dimethylformamide, the yellow precipitates were separated out immediately. The structure of this compound was assinged to be 2-(α-phenylthiocarbamoylphenacyl)isoquinolinium enol betain (II) based on the elementary and spectral analyses. II was obtained directly by the treatment of *N*-phenacyl-isoquinolinium enol betain (III) with phenyl isothiocyanate in quantitative yield. Similarly 2-(α-phenylcarbamoylphenacyl)isoquinolinium enol betain (IV) was obtained by the treatment of III with phenyl isocyanate. However, dicyclohexylcarbodiimide did not react with III.

The hydrolysis of II with hydrochloric acid gave 2-(phenylthiocarbamoyl) isoquinolinium chloride, while II was stable towards the hydrolysis with sodium hydroxide.

The oxidative ring closure of II by air did not occur by passing of air into the solution of II in ethanol for a day. However, II underwent cyclization and dehydrogenation on being heated in toluene for two hours to give anhydro-2-mercapto-3-benzoyl-imidazolo[2,3-*a*]isoquinolinium hydroxide (V) in 40% yield. Furthermore V was obtained by the oxidation of II with potassium ferricyanide



[*1] This paper was presented at the 20th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1967.

1) R. Huisgen, E. Funke, F. C. Schaefer, H. Gotthardt and E. Brunn, *Tetrahedron Letters*, **1967**, 1809.

2) R. Huisgen, R. Grashey and R. Krishke, *ibid.*, **1962**, 387.

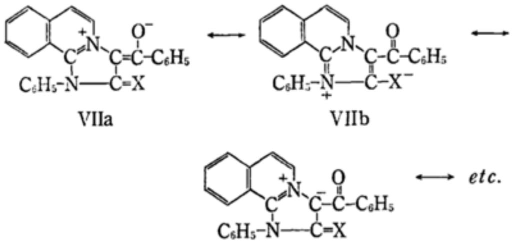
3) S. Sato and M. Ohta, *ibid.*, **1967**, 4261.

4) F. Kroehnke and H. Steuernagel, *Angew. Chem.*, **73**, 36 (1961); *Chem. Ber.*, **97**, 1118 (1964).

5) J. E. Baldwin, M. C. McDaniel, M. Newton and I. C. Paul, *Tetrahedron Letters*, **1966**, 4239.

in 50% yield. A similar treatment of IV with potassium ferricyanide gave anhydro-2-hydroxy-3-benzoyl-imidazolo[2,3-*a*]isoquinolinium hydroxide (VI).

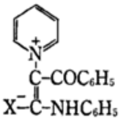
The significant differences of the IR spectra between V and VI were as follows: V has strong absorptions at 1550 cm^{-1} and 1350 cm^{-1}. VI has strong absorptions at 1650 cm^{-1} and 1550 cm^{-1}, but no absorption at 1350 cm^{-1}. These absorptions are attributed as follows: the absorption at 1650 cm^{-1} is due to the ring-carbonyl group, 1350 cm^{-1} to the ring-thiocarbonyl group and 1550 cm^{-1} to the carbonyl group of the benzoyl group. These facts suggest that the carbonyl group of the benzoyl group is fairly polarized, and among the many canonical forms such as VIIa—c which are considered to contribute to the resonance of V and VI, VIIa may be the most important contributor.



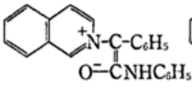
V and VI did not melt at 300°C and did not undergo hydrolysis with hydrochloric acid or sodium hydroxide. V was converted to *S*-methyl derivative (VIII) by treatment with methyl iodide in an almost quantitative yield.

An unidentified resinous oil was obtained by oxidation of 2-(α-phenylcarbamoylphenacyl)- and 2-(α-phenylthiocarbamoylphenacyl)pyridinium enol betain⁶⁾ (IX) with potassium ferricyanide in boiling DMF. It may be produced by the decomposition of the corresponding mesoionic compounds or the starting material under oxidative reaction conditions.

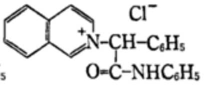
In order to obtain 2-(α-phenylcarbamoylmethyl)-isoquinolinium enol betain (X), 2-benzylisoquinolinium chloride was reacted with phenyl isocyanate in the presence of triethylamine. However, the trimer of phenyl isocyanate was obtained instead of X. The hydrochloride (XI) of X was obtained by the treatment of isoquinoline and phenylchloroacetanilide. However, the treatment of XI with triethylamine gave the tarry substances from which nothing was obtained in pure state.



XI



X



XI

When the benzylpyridinium chloride was reacted with phenyl isothiocyanate or phenyl isocyanate, *N,N'*-diphenylthiourea and carbanilide were obtained respectively.

Experimental⁷⁾

Preparation of 2-(α-Phenylthiocarbamoylphenacyl)isoquinolinium Enol Betain (II). (A) Into a solution of 3.1 g of I and 1.3 g of phenyl isothiocyanate in 10 m*l* of water and 50 m*l* of dimethylformamide (DMF), 1.5 g of triethylamine was added dropwise with stirring. Immediately orange precipitates were separated out. After stirring for half an hour, 50 m*l* of water was added and the precipitates were collected by filtration and recrystallized from ethanol to give 3.5 g of II, yellow needles; mp 175—177°C. Found: C, 75.57; H, 4.34; N, 7.37%. Cacld for $C_{24}H_{18}N_2SO$: C, 75.39; H, 4.71; N, 7.33%.

(B) 0.3 g of phenyl isothiocyanate was added into a suspension of 0.5 g of III in 50 m*l* of DMF, which was stirred for half an hour. After removal of the solvent under reduced pressure, oily residue was crystallized by adding ether. After collecting by filtration, the precipitates were recrystallized from ethanol to give 0.65 g of II; mp 175—176°C.

The Hydrolysis of II with Hydrochloric Acid. A solution of 1 g of II in 80 m*l* of ethanol and 4 m*l* of concentrated hydrochloric acid was refluxed for 2 hr. After removal of the solvent under reduced pressure, the residual precipitates were recrystallized from ethanol to give 0.5 g of 2-(α-phenylthiocarbamoylmethyl)isoquinolinium chloride, pale yellow prisms; mp 230—232°C. Found: C, 64.73; H, 4.52; N, 8.82%. Calcd for $C_{17}H_{15}N_2SCl$: C, 64.86; H, 4.78; N, 8.96%.

Preparation of 2-(α-Phenylcarbamoylphenacyl)-isoquinolinium Enol Betain (IV). Into a suspension of 3.3 g of I and phenyl isocyanate in 50 m*l* of dry DMF, 2.5 g of triethylamine was added dropwise with stirring. After stirring for 5 hr, the solvent was removed under reduced pressure. The residual precipitate were collected and recrystallized from ethanol to give 4 g of IV; yellow needles, mp 190—192°C. Found: C, 78.28; H, 5.33; N, 7.66%. Calcd for $C_{24}H_{18}N_2O_2$: C, 78.67; H, 4.95; N, 7.65%.

The Oxidative Ring-closure of II and IV. (A) A suspension of 1 g of II and 1 g of potassium ferricyanide in 50 m*l* of DMF and 50 m*l* of water was refluxed for half an hour. After cooling, a large amount of water was added and separated precipitates were collected by filtration. Recrystallization from dimethyl sulfoxide (DMSO) gave 0.5 g of V, pale yellow needles; mp over 300°C. V was insoluble in ethanol, benzene and ether, and soluble in hot DMSO. Found: C, 75.27; H, 4.45; N, 7.51%. Calcd for $C_{24}H_{16}N_2OS$: C, 75.79; H, 4.21; N, 7.38%.

The same treatment of IV with potassium ferricyanide as mentioned above gave VI, pale yellow needles. VI did not melt at 300°C. Found: C, 78.24; H, 4.41; N, 7.89%. Calcd for $C_{24}H_{16}N_2O_2$: C, 79.12; H, 4.39; N, 7.69%.

(B) A suspension of 1.2 g of II in 100 m*l* of toluene

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6) These compounds were prepared by Kroehnke's method: F. Kroehnke and H. Koebler, *Ber.*, **70**, 538 (1937).

7) All melting points were determined on a hot plate and were not corrected.

was refluxed for 2 hr. After removal of the solvent, the residual crystals were recrystallized from DMSO to give 0.3 g of V; mp over 300°C.

The Methyl Derivative of V (VIII). A suspension of 0.5 g of V in 30 m*l* of acetic acid and 0.5 m*l* of methyl iodide was refluxed for a few minutes. After cooling, ether was added into the solution, and the separated precipitates were collected by filtration. The recrystallization from ethanol gave VIII. Yield was almost quantitative. VIII did not melt at 300°C. Found: N, 5.58%. Calcd for $C_{25}H_{19}IN_2OS$: N, 5.47%.

Preparation of 2-(α-Phenylcarbamoylbenzyl)-isoquinolinium Chloride (XI). A mixture of 0.6 g of isoquinoline and 1.2 g of phenylchloroacetanilide was heated at 120—125°C in an oil bath for 5 min. After cooling, the oily reaction mixture was crystallized by the addition of acetone, and was collected by filtration. The recrystallization from ethanol gave 1.4 g of XI, colorless silky needles; mp 245°C. Found: C, 73.33; H, 5.34; N, 7.53%. Calcd for $C_{23}H_{19}ClN_2O$: C, 73.80; H, 5.08; N, 7.49%.

Reaction of *N*-Benzylisoquinolinium Chloride with Phenyl Isocyanate in the Presence of Triethylamine. Into a solution of 5.2 g of *N*-benzylisoquinolinium chloride and 1.5 g of phenyl isocyanate in 100 m*l* of dry DMF, 2.5 m*l* of triethylamine was added dropwise with stirring. The solution was stirred for 5 hr. After removal of the solvent under reduced pressure, 50 m*l* of water and 20 m*l* of alcohol were added into the oily residue, and the separated precipitates were collected by filtration. The recrystallization from ethanol gave 1.2 g of the trimer of phenyl isocyanate; mp 288—289°C.

Reaction of *N*-Benzylpyridinium Chloride with Phenyl Isothiocyanate. Into a solution of 3 g of *N*-benzylpyridinium chloride and 3.7 g of phenyl isothiocyanate in 50 m*l* of acetonitrile, 3.7 g of triethylamine was added dropwise with stirring. After stirring for one hour, the reaction mixture was evaporated to dryness under reduced pressure. Into the residual mixture of triethylamine hydrochloride and oily product, 50 m*l* of water added. The separated precipitates were collected by filtration and recrystallized from ethanol to give 2 g of pale yellow needles; mp 157—158°C. No depression of the melting point on admixture with *N*,*N′*-diphenylthiourea was observed.

Similarly, by the treatment of *N*-benzylpyridinium chloride with phenyl isocyanate, carbanilide was obtained.