serum capped opening for sample removal, and water-cooled condenser. A Vycor immersion well–condenser combination (available from Hanovia), in which were placed a Pyrex filter sleeve and light source (a high-pressure Hanovia 450-w, type L lamp), was placed into the solution through which nitrogen was passed for about 30 min before and also during the irradiation. Low temperatures were achieved by pumping ice-cooled water or Dry Ice cooled methanol through the immersion condenser. Solvents were maintained at reflux by alternately passing steam and water through the condenser. The reactions were monitored by examination of infrared spectra. The relative ratio of products was determined by nmr spectroscopy after distillation in a sublimation apparatus at 100° (0.05 mm) except in experiments with triphenylene. In these experiments, the bulk of triphenylene was removed by crystallization of the total product from benzene–heptane. The supernatants were concentrated, and nmr spectra were obtained following distillation, as above.

**Separation of the Isomers of 2-Phenyl-3-hydroxyl-3-carboxymethyl-2,3-dihydrobenzofuran (IIa and IIb).**—A 2:1 mixture (500 mg) of the isomers IIa and IIb, dissolved in a 1:1 benzene–hexane solution, was applied to a column wet packed with 25 g of neutral alumina (Woelm activity 1). The dimensions of the packed portion were 1.5 × 13.5 cm. Solvent mixtures employed consecutively were hexane–benzene, benzene, benzene–ether, ether, and ether–ethyl acetate. IIa (pure by nmr) was obtained on elution with an ether solution containing 1% ethyl acetate, and was followed by mixtures of IIa and IIb. After the amount of additional eluted material had become negligible, the polarity of eluting solvent was increased and IIb (pure by nmr) was obtained. The nmr spectrum of IIa exhibited carboxymethyl and benzylic hydrogen resonances at 3.73 and 5.75 ppm, respectively; for IIb the corresponding resonances appeared at 3.03 and 5.54 ppm. The isomers exhibited similar infrared and ultraviolet spectra: infrared (chloroform), 2.78 and 5.76 $\mu$ (hydroxyl and ester carbonyl bands, respectively); ultraviolet, $\lambda_{max}^{ether}$ 288 ($\epsilon$ 3.3 × $10^3$) and 280 m$\mu$ ($\epsilon$ 3.6 × $10^3$).

**2-Phenyl-3-carboxymethylbenzofuran (III).**—To a solution of IIa, 70 mg, in 5 ml of ether were added thionyl chloride (0.1 ml) followed by pyridine (0.2 ml). After standing at room temperature for three days, the mixture was poured onto ice–water, which was subsequently extracted with ether. The ether layer was washed, in turn, with dilute aqueous solutions of sodium bicarbonate and hydrochloric acid, dried and concentrated. Crystalline product was obtained directly which, after recrystallization from hexane, provided III in near-quantitative yield: mp and mmp (with product obtained similarly from IIb) 80–81° (lit.[4] mp 80°); infrared spectrum (chloroform), 5.81 $\mu$ (ester carbonyl band); ultraviolet spectrum, $\lambda_{max}^{methanol}$ 302 m$\mu$ ($\epsilon$ 1.6 × $10^4$); nmr spectrum, $\delta$ 3.88 (carboxymethyl hydrogens).

*Anal.* Calcd for $C_{16}H_{12}O_3$: C, 76.2; H, 4.8. Found: C, 76.1; H, 4.9.

***cis*-2-Phenyl-3-hydroxyl-3-carboxymethyl-2,3-dihydrobenzofuran-3,5-Dinitrobenzoate (IIa 3,5-Dinitrobenzoate).**—Solid 3,5-dinitrobenzoyl chloride (one molar excess) was added to an ice-cold solution of IIa in pyridine. After the solution was allowed to warm to room temperature, ice–water was added and the mixture was extracted with benzene. The benzene layer was washed, in turn, with dilute aqueous solutions of sodium bicarbonate and hydrochloric acid, dried and concentrated to an oil which solidified on trituration with ether. Several recrystallizations from ether–hexane resulted in a good yield of pure product: mp 168–169°; nmr spectrum, $\delta$ 3.82 (carboxymethyl hydrogens), 6.04 (benzylic hydrogen), a doublet centered at 8.47 ppm, $J$ = 2 cps (*ortho* aromatic hydrogens on 3,5-dinitrobenzoyl ring), a triplet centered at 8.90 ppm, $J$ = 2 cps (*para* aromatic hydrogen on 3,5-dinitrobenzoyl ring).

*Anal.* Calcd for $C_{23}H_{16}N_2O_9$: C, 59.5; H, 3.5; N, 6.0. Found: C, 59.9; H, 3.6; N, 5.9.

***trans*-2-Phenyl-3-hydroxyl-3-carboxymethyl-2,3-dihydrobenzofuran *p*-Nitrobenzoate (IIb *p*-Nitrobenzoate).**—Treatment of IIb with *p*-nitrobenzoyl chloride and work-up, as above, resulted in a good yield of this compound: mp 153° dec; nmr spectrum, $\delta$ 3.13 (carboxymethyl hydrogens), 5.95 (benzylic hyrogen), 8.07 (aromatic hydrogens on *p*-nitrobenzoyl ring).

*Anal.* Calcd for $C_{23}H_{17}NO_7$: C, 65.9; H, 4.1; N, 3.3. Found: C, 65.7; H, 4.2; N, 3.3.

**Registry No.**—I, 13448-92-5; IIa, 13448-93-6; IIa 3,5-dinitrobenzoate, 13448-94-7; IIb, 13448-95-8; IIb *p*-nitrobenzoate, 13448-96-9; III, 13448-97-0.

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# Aziridines. XVI. Isomerization of Some 1-Aroylaziridines

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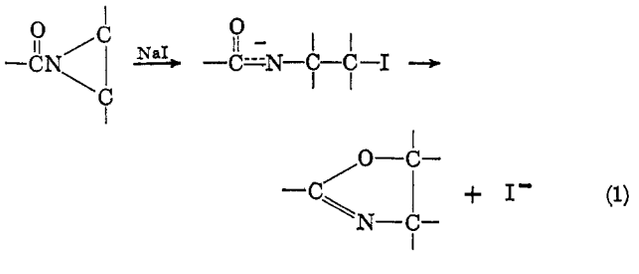
The iodide ion catalyzed isomerizations of 1-*p*-nitrobenzoyl-2-phenylaziridine and 1,3-diaroyl-2-arylaziridines are described. The thermolyses of *cis*- and *trans*-1-*p*-nitrobenzoyl-2,3-diphenylaziridines and 1,3-diaroyl-2-arylaziridines are also reported. The latter reaction represents a novel pyrolytic rearrangement of 1-aroylaziridines to $\alpha$-benzamidobenzalacetophenones.

The isomerization of 1-acylaziridines into 2-aryl- or 2-alkyl-2-oxazolines by various nucleophiles has been investigated extensively in recent years.[1-9] The mechanism[10] proposed for the isomerization involves as a first step an attack by the nucleophile, such as iodide ion, on an aziridinyl carbon to form an N-$\beta$-iodoethylbenzamido ion. In a subsequent step the ion cyclizes to the oxazoline and regenerates the iodide ion (eq 1).




(1)

(1) H. W. Heine, M. E. Fetter, and E. M. Nicholsen, *J. Am. Chem. Soc.*, **81**, 2202 (1959).
(2) H. W. Heine, W. G. Kenyon, and E. M. Johnson, *ibid.*, **83**, 2570 (1961).
(3) M. Lidaks and S. Hillers, *Latvijas PSR Zinatnu Akad. Vestis*, No. 2, 211 (1961); *Chem. Abstr.*, **58**, 4530 (1963).
(4) S. Hillers and M. Lidaks, *Puti Sinteza i Izyskaniya Protivoopukholevykh Preparatov, Tr. Simpoziuma po Khim. Protivoopukholevykh Veshchestv, Moscow*, 193 (1960); *Chem. Abstr.*, **58**, 4531 (1963).
(5) P. Thyrum and A. R. Day, *J. Med. Chem.*, **8**, 107 (1965).
(6) R. D. Guthrie and D. Murphy, *J. Chem. Soc.*, 3828 (1965).
(7) P. E. Fanta and E. N. Walsh, *J. Org. Chem.*, **30**, 3574 (1965).
(8) P. E. Fanta and E. N. Walsh, *ibid.*, **31**, 59 (1966).
(9) H. W. Heine, D. C. King, and L. A. Portland, *ibid.*, **31**, 2662 (1966).
(10) H. W. Heine, *Angew. Chem. Intern. Ed. Engl.*, **1**, 528 (1962).

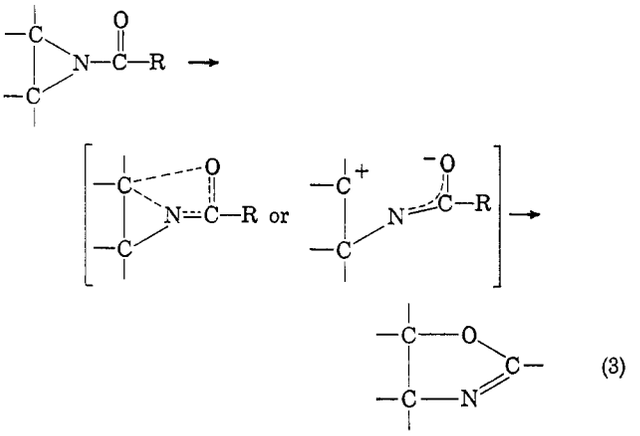
This mechanism predicts that the isomerization should occur with retention of configuration since an inversion of configuration takes place when the aziridine ring is opened by the nucleophile and another inversion takes place when the intermediate N-2-iodoethylbenzamido ion cyclizes. Thus, *trans*-1-aroyl-2,3-disubstituted aziridines should yield *trans*-2-aryl-4,5-disubstituted 2-oxazolines and *cis*-1-aroyl-2,3-disubstituted aziridines should yield *cis*-2-aryl-4,5-disubstituted 2-oxazolines. With one striking and easily understood exception these stereochemical expectations have been found to occur.[9]

Another inference to be drawn from the proposed mechanism is that the nucleophile would attack the more positive carbon atom of the aziridine ring. However, the extent of such a preference might be tempered by steric factors. The selective rearrangement of 1-aroyl-2-alkylaziridines by iodide ion into 2-aryl-4-alkyl-2-oxazolines[1,2] does not give a clear-cut answer to the problem since steric factors as well as electronic effects would prompt attack of the iodide ion at the methylene carbon of the aziridine ring.

The results reported here for 1-*p*-nitrobenzoyl-2-phenylaziridine and 1,3-diaroyl-2-arylaziridines suggest that the electronic factors are the more important. The isomerization of the 1,3-diaroyl-2-arylaziridines is also of interest because the products of rearrangement, the 2-aryl-5-aroyl-2-oxazolines, have not been characterized previously.

The acid-catalyzed rearrangement of 1-*p*-nitrobenzoyl-2-phenylaziridine has also been studied. The same oxazoline is obtained as for the iodide ion catalyzed rearrangement; this is in contrast to the results obtained for the iodide ion and acid-catalyzed rearrangements of 1-aroyl-2-alkylaziridines.[1,2]

Pyrolytic isomerizations of 1-acylaziridines have previously been reported to form either N-allylamides or 2-oxazolines.[10,11] The comprehensive work of Fanta, *et al.*, has shown that 1-acyl-2-alkylaziridines invariably rearrange into N-allylamides.[11] Stereochemical and kinetic studies[11,12] suggest that the rearrangement is an intramolecular, concerted *cis* elimination involving transfer of a proton from the alkyl group to the amido oxygen (eq 2). This transition state is not possible, of course, in the absence of alkyl groups on the aziridinyl carbons of 1-aroylaziridines nor can the transition state form readily with compounds such as 6-benzoyl-3-oxa-6-azabicyclo[3.1.0]-hexane where steric factors prevent bond making between the amido oxygen and the proton. In these instances oxazolines have been observed as the products of pyrolysis.[8,13,14] It has been proposed that the formation of the oxazoline involves either a four-center transition state[10] or possibly an intermediate tight ion pair[8] (eq 3).



(3)

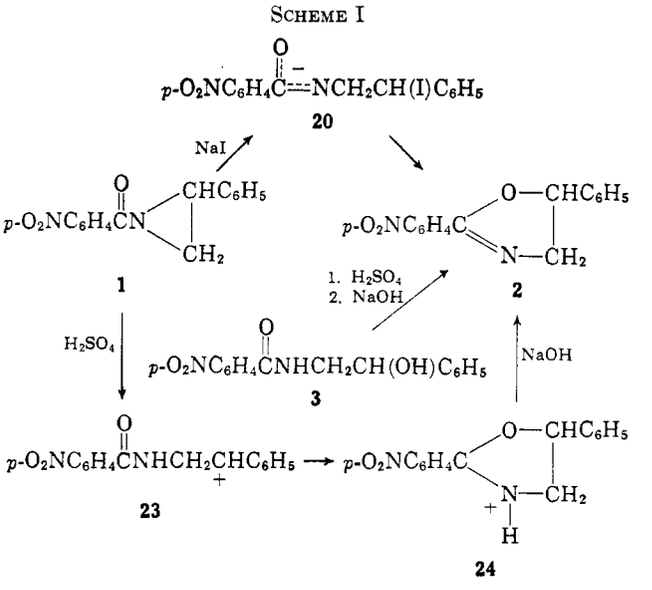
We now present evidence that the pyrolytic isomerization of *cis*- and *trans*-1-*p*-nitrobenzoyl-2,3-diphenylaziridines into 2-*p*-nitrophenyl-4,5-diphenyl-2-oxazolines is a stereospecific process.

We have also observed two examples of the isomerization of 1,3-diaroyl-2-arylaziridines in refluxing xylene to give α-benzamidobenzalacetophenones; this isomerization represents a new pyrolytic rearrangement of 1-aroylaziridines.

## Results

Reaction of 1-*p*-nitrobenzoyl-2-phenylaziridine (**1**) with sodium iodide in acetone gives 2-*p*-nitrophenyl-5-phenyl-2-oxazoline (**2**) in high yield (Scheme I).

SCHEME I



The same product results when **1** is dissolved in concentrated sulfuric acid and the acid subsequently neutralized with sodium hydroxide. The structure of **2** was confirmed by an alternate synthesis involving the reaction of N-2-hydroxy-2-phenylethyl-*p*-nitrobenzamide (**3**) with sulfuric acid.

*trans*-1-*p*-Nitrobenzoyl-2-*p*-nitrophenyl-3-benzoylaziridine (**4**) and *trans*-1,3-dibenzoyl-2-*p*-nitrophenylaziri-

(11) P. E. Fanta, "Heterocyclic Compounds with Three and Four-Membered Rings," Part I, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, pp 524–575.

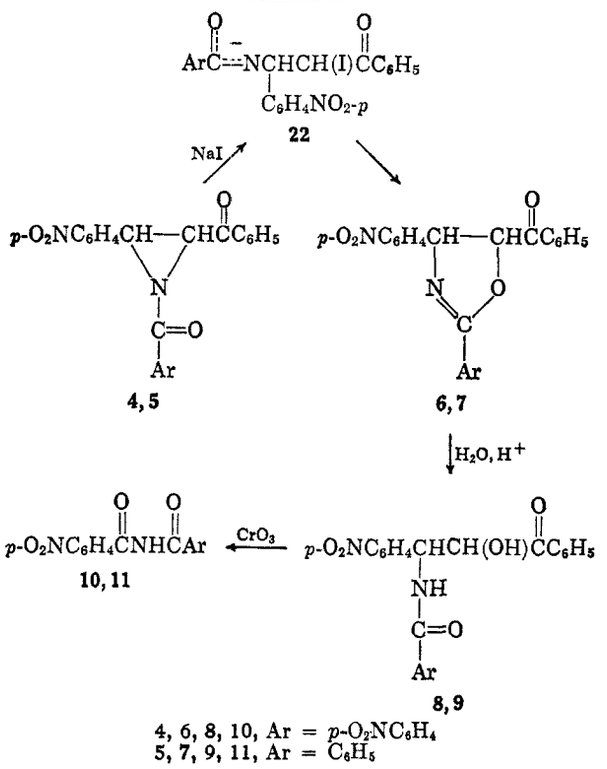
(12) P. E. Fanta and M. K. Kathan, *J. Heterocyclic Chem.*, **1**, 293 (1964).

(13) A. A. Goldberg and W. Kelley, *J. Chem. Soc.*, 1919 (1948).

(14) C. W. Woods, A. B. Borkovec, and F. M. Hart, *J. Med. Chem.*, **7**, 371 (1964).

dine (**5**) are isomerized by sodium iodide in acetone into 2,4-di-*p*-nitrophenyl-5-benzoyl-2-oxazoline (**6**) and 2-phenyl-4-*p*-nitrophenyl-5-benzoyl-2-oxazoline (**7**), respectively. The structures of the oxazolines were assigned by hydrolysis of **6** and **7** to the corresponding N-1-aryl-2-benzoyl-2-hydroxybenzamides **8** and **9** followed by the chromic acid oxidation of **8** and **9** to the dibenzamides **10** and **11**, respectively (Scheme II). Com-

SCHEME II



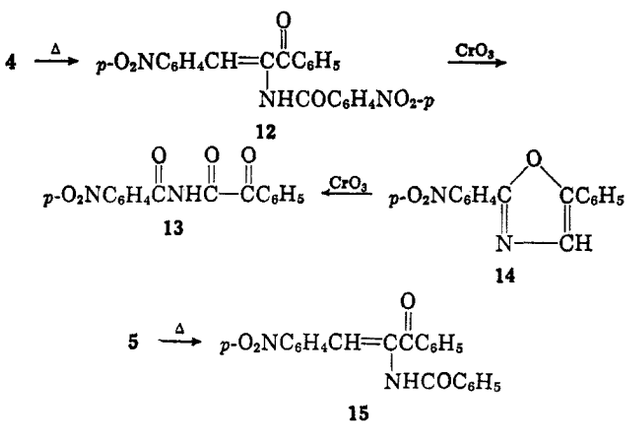

pound **11** had been prepared previously[15] and the melting point and infrared spectra were the same as those observed for **11** obtained by the oxidation of **9**. The infrared spectrum of **10** was virtually the same as that of **11**; the elemental analyses were consistent for 4,4′-dinitrodibenzamide. The isolation of the products **10** and **11** eliminates the possibility that the isomeric 2,5-diaryl-4-aroyl-2-oxazolines are formed by the iodide ion catalyzed reaction.

When a solution of **4** in *p*-xylene was heated, the isomeric α-*p*-nitrobenzamido-*p*-nitrobenzalacetophenone (**12**) was isolated in excellent yield (Scheme III). The structure of **12** was confirmed by elemental analyses and by the oxidation of **12** to N-phenylglyoxyl-*p*-nitrobenzamide (**13**). Compound **13** was also prepared by the oxidation of 2-*p*-nitrophenyl-5-phenyloxazole (**14**). The oxidation of oxazoles is known to form N-phenylglyoxylbenzamides.[16]

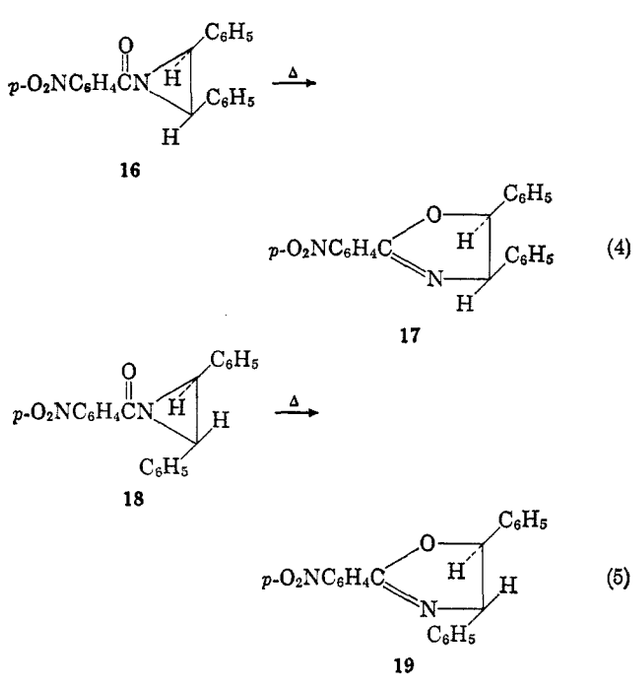
An identical reaction course was observed when a solution of **5** was refluxed in *p*-xylene. That α-benzamido-*p*-nitrobenzalacetophenone (**15**) was obtained as the product was established by analysis and the similarity of the infrared spectra of **12** and **15**. All attempts to isolate N-phenylglyoxyl-*p*-nitrobenzamide by the oxidation of **15** failed.

(15) A. H. Lamberton and W. E. Standage, *J. Chem. Soc.*, 2957 (1960).
(16) E. Fischer, *Ber.*, **29**, 209 (1896).

SCHEME III




In contrast to the 1,3-diaroyl-2-arylaziridines, the heating of solutions of 1-aroyl-2,3-diarylaziridines in *p*-xylene formed 2-oxazolines. Significantly, thermolysis of *cis*-1-*p*-nitrobenzoyl-2,3-diphenylaziridine (**16**) gave *cis*-2-*p*-nitrophenyl-4,5-diphenyl-2-oxazoline (**17**) (eq 4) and *trans*-1-*p*-nitrobenzoyl-2,3-diphenylaziridine (**18**) gave *trans*-2-*p*-nitrophenyl-4,5-diphenyl-2-oxazo-

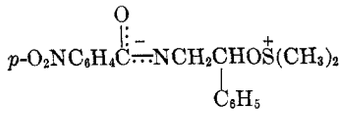



line (**19**) (eq 5). Pyrolysis of *cis*-1-benzoyl-2,3-diphenylaziridine gave a 59% recovery of the aziridine and a gummy residue which could not be characterized.

## Discussion

The formation of 2-*p*-nitrophenyl-5-phenyl-2-oxazoline (**2**) by the iodide ion catalyzed isomerization of 1-*p*-nitrobenzoyl-2-phenylaziridine (**1**) suggests that steric factors do not play a dominant role in the ring-opening step in this instance. The nucleophile attacks the more positive and also more sterically hindered carbon atom of the aziridine ring to form the N-2-iodo-2-phenylethyl-*p*-nitrobenzamido ion (**20**) rather than to form the isomeric N-1-phenyl-2-iodoethyl-*p*-nitrobenzamido ion, the ion to be expected if steric factors prevailed.

The reaction of **1** with dimethyl sulfoxide follows a similar pathway.[17] Dimethyl sulfoxide acts as a nucleophile and also attacks the carbon bearing the phenyl group to give the intermediate **21** which subsequently forms N-phenacyl-*p*-nitrobenzamide.



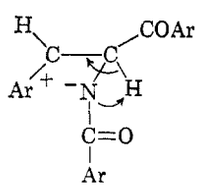
**21**

In the case of the *trans*-1,2-diaroyl-3-arylaziridines as exemplified by compounds **4** and **5**, the iodide ion is again attracted to the more positive atom, that is, the carbon bearing the benzoyl group rather than the carbon bearing the *p*-nitrophenyl group. A N-1-*p*-nitrophenyl-2-benzoyl-2-iodoethylbenzamido ion (**22**) is probably formed which then cyclizes to a 2,4-diaryl-5-aroyl-2-oxazoline such as **6** or **7**. Presumably the oxazolines **6** and **7** are of the *trans* configuration since two inversions of configuration would be expected to occur during the rearrangement.[9]

The conversion of **1** into **2** in concentrated sulfuric acid is best explained by protonation of the aziridine, followed by ring opening to give the more stable of the two possible carbonium ions, namely **23**. The carbonium ion can then cyclize to the oxazolinium ion **24**. The acid-catalyzed isomerization of 1-*p*-nitrobenzoyl-2,2-dimethylaziridine into 2-*p*-nitrophenyl-5,5-dimethyl-2-oxazoline follows a similar reaction pathway[1]. Here the tertiary carbonium ion [$ArCONHCH_2C^+(CH_3)_2$] is the reaction intermediate rather than the unstable isomeric primary carbonium ion [$ArCONHC(CH_3)_2CH_2^+$]. The same tertiary carbonium ion is also formed in the acid-catalyzed conversion of N-(β-methallyl)-*p*-nitrobenzamide into 2-*p*-nitrophenyl-5,5-dimethyl-2-oxazoline.[1]

The acidity of the aziridinyl hydrogen adjacent to the benzoyl group undoubtedly causes the thermal rearrangements of compounds **4** and **5** into **12** and **15**, respectively. The reaction possibly proceeds by a transfer of the aziridinyl hydrogen to the amido oxygen with concurrent breaking of the carbon–nitrogen bond of the ring or in a stepwise fashion in which oxygen–hydrogen bond formation precedes carbon–nitrogen bond fission (Scheme IV).

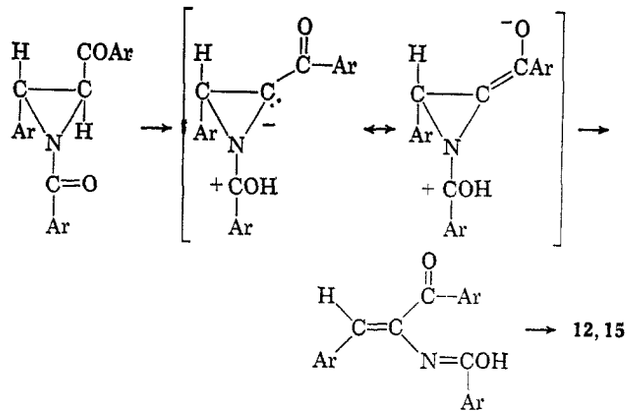
A referee has also suggested the possibility of an ion-pair intermediate which does not involve prior transfer of the hydrogen atom to the amido oxygen. We feel



that this mechanism is not so likely as the transfer of the acidic hydrogen to the amido oxygen. Further work will be necessary with both the *trans*- and the as yet unknown *cis*-1,2-diaroyl-3-arylaziridines to determine whether the rearrangement is stereospecific.

The stereospecific conversion of *cis*- and *trans*-1-*p*-nitrobenzoyl-2,3-diphenylaziridines into *cis*- and *trans*-2-*p*-nitrophenyl-4,5-diphenyl-2-oxazolines, respectively, is consistent with mechanisms that involve either a four-centered transition state or a short-lived tight ion-pair intermediate that collapses to the oxazoline before racemization can occur. In either case, the retention of configuration can be explained by an attack of the amido oxygen on the same face of the carbon at which the carbon–nitrogen bond breaking is taking place. The fact that in the case of the thermolysis of *cis*-1-benzoyl-2,3-diphenylaziridine a 59% recovery of the aziridine occurred while the *cis*-1-*p*-nitrobenzoyl-2,3-diphenylaziridine gave the corresponding *cis*-oxazoline in 80% yield is indicative that carbon–nitrogen bond breaking of the aziridine ring is more important and is preceding carbon–oxygen bond formation.

SCHEME IV



The formation of the *cis*-2-*p*-nitrophenyl-4,5-diphenyl-2-oxazoline by thermolysis of the corresponding *cis*-aziridine (**16**) is of particular interest since the reaction of the *cis*-aziridine (**16**) with iodide ion gives only the *trans*-oxazoline[9]. In the latter case, it has been shown that the iodide ion opens the ring to yield a *threo*-N-1,2-diphenyl-2-iodoethyl-*p*-nitrobenzamido ion which has considerable steric hindrance toward oxazoline formation due to close approach of the two phenyl groups. The *threo* ion is subsequently converted by iodide ion *via* a Finkelstein reaction to the *erythro* ion which can easily undergo ring closure to the *trans*-oxazoline without steric interactions[9].

## Experimental Section

**1-*p*-Nitrobenzoyl-2-phenylaziridine** (**1**).—A solution of 1.85 g (0.01 mole) of *p*-nitrobenzoyl chloride in 17 ml of dry ether was added to a solution of 1.2 g (0.01 mole) of 2-phenylaziridine[18] and 1.01 g (0.01 mole) of triethylamine in 30 ml of dry ether. The mixture was stirred for 0.5 hr and filtered. The precipitate was washed well with water to dissolve the triethylamine hydrochloride. A yield of 2.4 g (89%) of crude **1** was obtained. Three recrystallizations from 95% ethanol gave white needles melting at 127–130°.

*Anal.* Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.50; N, 10.44. Found: C, 67.43; H, 4.91; N, 10.47.

**The Iodide Ion Catalyzed Isomerization of 1 into 2**.—A mixture of 293 mg of **1** and 390 mg of sodium iodide in 25 ml of acetone was refluxed for 2.5 hr. The solvent was evaporated and the 290 mg (98%) of crude **2** was washed with water and filtered. Three recrystallizations from ethanol gave **2** melting at 148–149°. The crude product and the analytical sample had identical infrared spectra.

*Anal.* Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.50; N, 10.44. Found: C, 67.28; H, 4.13; N, 10.69.

(17) H. W. Heine and T. Newton, *Tetrahedron Letters*, 1859 (1967).

(18) The authors thank Dr. S. Brois for a generous sample of 2-phenylaziridine.

**The Acid-Catalyzed Isomerization of 1 into 2.**—Compound **1** (200 mg) was added slowly and with swirling to 10 ml of concentrated sulfuric acid. The solution was poured into a mixture of 150 g of ice and water containing 20 g of sodium hydroxide. The solution was filtered and the precipitate washed with water. Crude **2**, mp 147–151°, weighed 170 mg (85%).

**The Thermal Isomerization of 1 into 2.**—A mixture of 100 mg of **1** and 15 ml of *p*-xylene was refluxed for 13 hr. The solvent was evaporated to give 98 mg of **2**.

**N-2-Phenyl-2-hydroxyethyl-*p*-nitrobenzamide (3).**—A solution of 1.85 g (0.01 mole) of *p*-nitrobenzoyl chloride in 30 ml of ether was added to a mixture of 1.37 g (0.01 mole) of 1-phenyl-2-aminoethanol and 1.01 g (0.01 mole) of triethylamine in 40 ml of ether. The mixture was stirred for 0.5 hr and filtered. Crude **3** was washed well with water and recrystallized from ethanol to give 2.3 g (80%) of white needles melting at 205–209° (lit.[19] mp 201–202°).

**Conversion of 3 to 2.**—To 10 ml of concentrated sulfuric acid was added 300 mg (1.04 mmoles) of **3**. The mixture was poured into a mixture of 100 g of ice and water and 20 g of potassium hydroxide. The mixture was filtered and the precipitate washed with water. A yield of 250 mg (86%) of **2** was obtained, melting after recrystallization at 149–151°. The infrared spectrum was identical with the spectra obtained in the isomerization reactions.

***trans*-1-*p*-Nitrobenzoyl-2-*p*-nitrophenyl-3-benzoylaziridine (4).**—A solution of 557 mg (3 mmoles) of *p*-nitrobenzoyl chloride in 10 ml of dry benzene was added to a mixture of 804 mg (3 mmoles) of *trans*-2-*p*-nitrophenyl-3-benzoylaziridine[20,21] in 25 ml of dry benzene and 303 mg (3 mmoles) of triethylamine. The reaction mixture was filtered after 12 hr and the precipitate washed with water. The 1-g sample (79%) of crude **4** could not be recrystallized without some isomerization to **12** taking place. An analytical sample of **4** which melted at 178–179° was prepared by washing crude **4** several times with cold 95% ethanol.

*Anal.* Calcd for $C_{22}H_{15}N_3O_6$: C, 63.29; H, 3.62; N, 10.07. Found: C, 63.15; H, 3.27; N, 9.93.

**The Isomerization of 4 into *trans*-2,4-Di-*p*-nitrophenyl-5-benzoyl-2-oxazoline (6).**—A solution of 100 mg of **4** and 200 mg of sodium iodide in 25 ml of acetone was stirred for 5 hr. The solvent was evaporated and a very small quantity of cold methanol was added to the residue. The suspension was immediately filtered and the solid washed with water. A 95-mg sample of crude **6** was recrystallized several times from benzene to give **6**, mp 164–165°.

*Anal.* Calcd for $C_{22}H_{15}N_3O_6$: C, 63.29; H, 3.62; N, 10.07. Found: C, 63.40; H, 3.80; N, 9.76.

***trans*-1,3-Dibenzoyl-2-*p*-nitrophenylaziridine (5)** was synthesized in the same manner as **4** using 2.8 g (0.02 mole) of benzoyl chloride in 15 ml of benzene and a mixture of 5.4 g (0.02 mole) of *trans*-2-*p*-nitrophenyl-3-benzoylaziridine and 2.02 g (0.02 mole) of triethylamine in 50 ml of benzne. A 5.8-g sample (77%) of crude **5** was washed five times with cold ethanol to give an analytical sample melting at 137.5–138.5°.

*Anal.* Calcd for $C_{22}H_{16}N_2O_4$: C, 70.97; H, 4.33; N, 7.52. Found: C, 70.68; H, 4.36; N, 7.55.

**The isomerization of 5 into 2-phenyl-4-*p*-nitrophenyl-5-benzoyl-2-oxazoline (7)** was accomplished in the same manner as the isomerization of **4** into **6** employing 2.0 g of **5** and 4.0 g of sodium iodide in 75 ml of acetone. A crude yield of 1.85 g (92%) of **7** was obtained which melted at 115–117° after several recrystallizations from 95% ethanol.

*Anal.* Calcd for $C_{22}H_{16}N_2O_4$: C, 70.97; H, 4.33; N, 7.52. Found: C, 70.86; H, 4.14; N, 7.56.

**Hydrolysis of 6 to N-1-*p*-Nitrophenyl-2-hydroxy-2-benzoylethyl-*p*-nitrobenzamide (8).**—A mixture of 2.1 g (0.005 mole) of **6**, 20 ml of 95% ethanol, 30 ml of water, and 1.5 ml of concentrated hydrochloric acid was refluxed for 10 hr. The cooled reaction mixture was filtered and 2.0 g (91%) of crude **8** was recrystallized from methanol which afforded a yellow powder melting at 198–199°.

*Anal.* Calcd for $C_{22}H_{17}N_3O_7$: C, 60.69; H, 3.93; N, 9.65. Found: C, 60.59; H, 3.60; N, 9.50.

**Hydrolysis of 7 to N-1-*p*-Nitrophenyl-2-hydroxy-2-benzoylethylbenzamide (9).**—A mixture of 0.80 g (2.1 mmoles) of **7**, 12 ml of 95% ethanol, 12 ml of water, and 1 ml of concentrated hydrochloric acid was refluxed for 17 hr. Filtration of the cooled reaction mixture gave 210 mg (25%) of **9** melting at 205–208° Four recrystallizations from 95% ethanol gave white needles melting at 213–215°.

*Anal.* Calcd for $C_{22}H_{18}N_2O_5$: C, 67.68; H, 4.65; N, 7.17 Found: C, 67.73; H, 4.64; N, 7.37.

**Oxidation of 9 to 4-Nitrodibenzamide (11).**—A mixture of 200 mg (0.51 mmole) of **9** was dissolved in 7 ml of acetic acid. To this mixture was added 10 ml of a hot saturated solution of chromium trioxide in acetic acid. After 15 min the dark green reaction mixture was poured over 100 g of ice. Filtration gave 80 mg (58%) of crude **11**. Three recrystallizations gave **11** melting at 176–178° (lit.[15] mp 174). The infrared spectra of **11** prepared by Lamberton[15] and by the oxidation of **9** were identical.

**Oxidation of 8 to 4,4'-Dinitrodibenzamide (10).**—A mixture of 400 mg (0.92 mmole) of **8** and 15 ml of acetic acid was heated until all of **8** was dissolved. To this mixture was added 20 ml of a hot saturated solution of chromium trioxide in acetic acid. After 10 min the dark green reaction mixture was poured onto 150 g of ice and then filtered. The filtrate was saved and the residue was washed well with water. The filtrate and the washings were partially evaporated and 30 mg (10%) of crude **10** was filtered. Recrystallization from 95% ethanol gave white needles, mp 225–227°. The infrared spectra of **10** and **11** were very similar.

*Anal.* Calcd for $C_{14}H_9N_3O_6$: C, 53.33; H, 2.87; N, 13.33. Found: C, 53.24; H, 2.40; N, 13.25.

**The isomerization of 4 into α-*p*-nitrobenzamide-*p*-nitrobenzacetophenone (12)** was accomplished by refluxing a solution of 1.0 g of **4** in 15 ml of dry xylene for 1 hr. Evaporation of the solvent gave a quantitative yield of **12**. Recrystallization from benzene gave **12** melting at 215–216°.

*Anal.* Calcd for $C_{22}H_{15}N_3O_6$: C, 63.29; H, 3.62; N, 10.07. Found: C, 63.27; H, 3.74; N, 10.06.

**The isomerization of 5 into α-benzamido-*p*-nitrobenzalacetophenone (15)** occurred by refluxing a solution of 2.0 g of **5** in 40 ml of *p*-xylene for 1 hr. Evaporation of the solvent gave 1.9 g (95%) of crude **15**. Recrystallization from 95% ethanol afforded material melting at 148–149.5°.

*Anal.* Calcd for $C_{22}H_{16}N_2O_4$: C, 70.97; H, 4.33; N, 7.52. Found: C, 70.74; H, 4.33; N, 7.41.

**Oxidation of 12 into N-phenylglyoxyl-*p*-nitrobenzamide (13).**—A 0.55-g (1.3 mmoles) sample of **12** was dissolved in 6 ml of hot acetic acid. To this solution was added a hot saturated solution of 1.0 g of chromium trioxide in 10 ml of acetic acid. After 5 min the reaction mixture was poured over 30–40 g of ice. The mixture was filtered and the precipitate of crude **13** washed with water. The 220-mg sample (59%) of crude **13** was recrystallized from chloroform or ethanol to give **13**, mp 199–200°.

*Anal.* Calcd for $C_{15}H_{10}N_2O_5$: C, 60.40; H, 3.37; N, 9.39. Found: C, 60.67; H, 3.65; N, 9.23.

**Alternate Synthesis of 13 by Oxidation of 2-*p*-Nitrophenyl-5-phenyloxazole.**—A sample of 0.67 g (2.5 mmoles) of **14**[22] was dissolved in 8.5 ml of acetic acid and the solution heated. To this solution was added 11 ml of hot acetic acid containing 2 g of chromium trioxide. After 5 min the reaction mixture was poured over ice. Filtration afforded a near quantitative yield of crude **13**. Recrystallization from 95% ethanol gave **13**, mp 199–201°, identical with the product obtained from the oxidation of **12**.

**The isomerization of 16 into 17** was accomplished by refluxing a solution of 344 mg of **16**[9] in 25 ml of dry xylene for 48 hr. The solvent was evaporated and crude **17** mixed with a small quantity of 95% ethanol and filtered. The 275-mg sample (80%) of **17** was recrystallized from methanol to give material melting at 159–161° (lit.[9] mp 162). The infrared spectra of an authentic sample[9] and of the product of pyrolysis were identical.

The ethanolic filtrate was evaporated to give a gummy solid. The infrared spectrum of this material showed peaks characteristic of **16** and **17**. Similar treatment of 300 mg of *cis*-1-benzoyl-2,3-diphenylaziridine (**25**) gave after evaporation of the *p*-xylene and treatment of the gummy residue with 1 ml of methanol a 177-mg recovery (59%) of **25**. Two recrystallizations from petroleum ether gave **25** melting at 140–141°. Crude **25** and recrystallized **25** gave the same infrared spectrum.

**The isomerization of 18 into 19** was carried out analogously to the conversion of **16** into **17**. A 70% yield of **19**, mp 120–122° (lit.[9] mp 122–124), was obtained after recrystallization from 95% ethanol. The **19** obtained from the pyrolysis was identical with an authentic sample[9] in all respects.

(19) E. Takagi and I. Tosaka, Japanese Patent 6470 (Sept 13, 1955); *Chem. Abstr.*, **52**, 1237 (1958).

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*cis*-1-Benzoyl-2,3-diphenylaziridine (25) was prepared in the same manner as 16[9] in 75% yield. Recrystallization from petroleum ether gave 25 melting at 139–141°.

*Anal.* Calcd for $C_{21}H_{17}NO$: C, 84.23; H, 5.72; N, 4.68. Found: C, 84.10; H, 5.53; N, 4.69.

**Registry No.**—1, 13866-50-7; 2, 13866-51-8; 3, 13866-52-9; 4, 13866-53-0; 5, 13866-54-1; 6, 13866-06-3; 7, 13866-07-4; 8, 13866-08-5; 9, 13866-09-6; 10, 13866-10-9; 12, 13866-11-0; 13, 13866-12-1; 15, 13866-13-2; 25, 13866-14-3.

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# A Total Synthesis of 8-Isoestrone *via* Novel Intermediates. The Unique Salt Formation of 2-Methylcyclopentane-1,3-dione with Strong Acids

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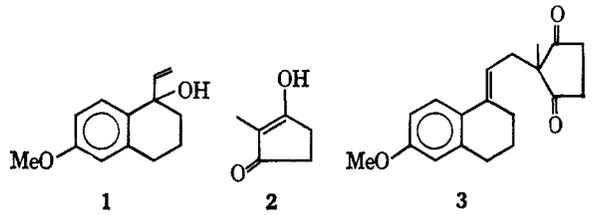
Condensation of 4-acetoxy-2-methylcyclopentane-1,3-dione with the isothiouronium salt derived from 1-vinyl-1-hydroxy-1,2,3,4-tetrahydro-6-methoxynaphthalene yielded the enedione 6. The latter cyclized under acidic conditions to the unstable hexaene 7, which on hydrogenation and demethylation afforded 8-isoestrone 8b. 2-Methylcyclopentane-1,3-dione was observed to yield highly crystalline salts with strong acids, notably hydrogen halides and fluorosulfonic acid.

Since the original discovery by the Russian workers of the unique and facile condensation of cyclic β-diketones with 1-vinyl-1-hydroxy-1,2,3,4-tetrahydro-6-methoxynaphthalene 1 leading to steroid end products,[1] a great deal of activity in this area has resulted relative to the condensation of 1 with 2 to give 3.[2]



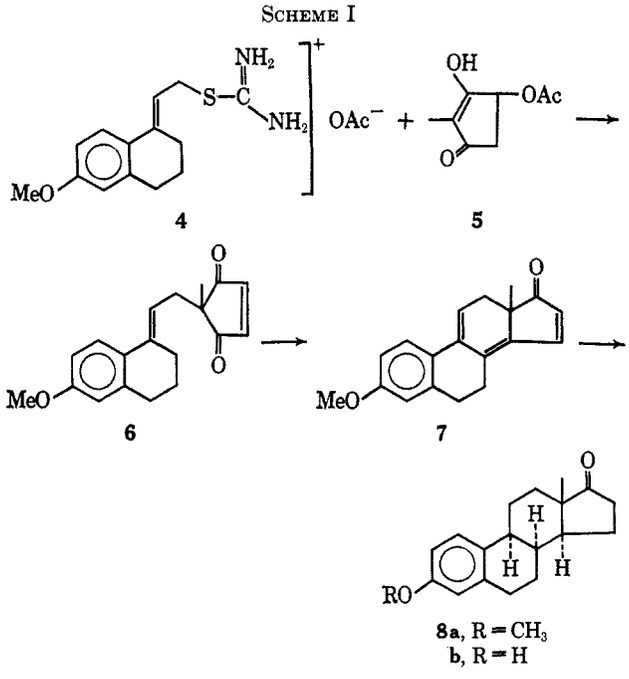

1 2 3

We had observed that 1 can be advantageously as well as nearly quantitatively converted into the crystalline isothiouronium salt 4, which in turn spontaneously couples with 2-methylcyclopentane-1,3-dione (2) in high yield to give the estrone precursor 3.[3] In this connection we were interested in examining other β-dicarbonyl systems insofar as they might provide alternative or superior routes to the steroid skeleton.

2-Methylcyclopentane-1,3-4-trione,[4] the precursor of 2-methylcyclopentane-1,3-dione (2) by the Panouse and Sannié synthesis,[5] had been catalytically reduced to 4-hydroxycyclopentane-1,3-dione by Orchin and Butz.[6] Neither 2-methylcylopentane-1,3,4-trione nor 4-hydroxycyclopentane-1,3-dione gave useful products on reaction with vinyl carbinol 1. However, the corresponding acetate derivative 5, available by controlled acetylation, did undergo condensation (see below).

Condensation of 2-methyl-4-acetoxycyclopentane-1,3-dione (5) with vinyl carbinol 1 under a variety of conditions gave at best 18% of the pentaene 6 after chromatography. However, reaction of 5 with isothiouronium salt 4 in water–ether at room temperature gave by direct crystallization 48% of adduct 6 with substantial additional amounts in the mother liquors (Scheme I). In this condensation, elimination of

SCHEME I




acetic acid appears to occur more or less spontaneously since the reaction conditions are extremely mild. The fact that β elimination does not occur with comparable facility in 5 itself is probably ascribable to the enolic character of 5 and the inherent instability of a resultant cyclopentadienone system.

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