## Chemistry of Lactones. VI. Reaction of Unsaturated Azlactones under Friedel-Crafts Conditions<sup>1,2</sup>

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The behavior of unsaturated azlactones under Friedel-Crafts conditions has been studied in detail. The course of the reaction is dependent on a variety of factors, including reaction conditions, solvent, and the nature of substituents on the arylidene ring. Four different products have been isolated: saturated azlactones,  $\omega$ -benzamidoacetophenone, 2-benzamidoindenone, and 1-phenylisoquinoline-3-carboxylic acids.

A recent article by Awad and Hafez,<sup>4</sup> in which they reported results substantially different from those we reported earlier<sup>5</sup> for the reaction of unsaturated azlactones under Friedel-Crafts conditions, prompts us to report our observations in a detailed study of the nature of this reaction.

Despite Awad's unequivocal statement to the contrary, the reaction of 2-phenyl-4-benzylidene-5(4H)-oxazolone(I) does give the saturated azlactone, 2-phenyl-4-benzhydryl-5-oxazolone(II) in 70-75% yield, when compound I reacts with specially dried benzene in a nitrogen atmosphere in the presence of anhydrous aluminum chloride.6 Moreover, a number of analogs of II, substituted on the arylidene ring, have also been prepared in this manner and have been converted to  $\alpha$ -amino acids, such as  $\beta$ , $\beta$ -diphenylalanine. In addition, Mustafa and Sallam' have recently prepared  $\beta$ , $\beta$ -diphenylalanine by a different route and cyclized its Nbenzoyl derivative to II, identical with our compound. They have also successfully repeated our experiments.8

ArCH=C II

The behavior of highly conjugated azlactones under Friedel-Crafts conditions is very complex and the course of the reaction is strongly dependent on the conditions employed, the purity and quantity of anhydrous aluminum chloride, the type of substituents on the arylidene ring, and the nature of the reaction medium. We have studied these factors systematically with the following observations:

- (4) W. I. Awad and M. S. Hafez, J. Org. Chem., 26, 2055 (1961). (5) R. Filler and L. M. Hebron, *ibid.*, 23, 1815 (1958).

(7) A. Mustafa and M. M. M. Sallam, ibid., 26, 1782 (1961).

(8) A. Mustafa and M. M. M. Sallam, ibid., 27, 2406 (1962).

(1) When the benzene contained traces of moisture, we independently confirmed Awad's observation that arylidene cleavage and acylation occurred to give a 50% yield of  $\omega$ -benzamidoacetophenone (III), the structure of which was proved both by degradation to phenacylamine hydrobromide and benzoic acid and by preparation of an authentic sample. A small amount of red oil was also isolated which was shown by infrared spectral comparison with an authentic sample<sup>4,9</sup> to be 2benzamidoindenone (IV), formed by intramolecular acylation.



The sequence of reactions involved in the formation of III is of particular interest. Awad suggested<sup>4</sup> that arylidene cleavage occurs after ring opening, in the final (acid hydrolysis) step. This hypothesis was tested by a specially designed experiment. If cleavage follows acylation, then 2benzamidobenzalacetophenone<sup>10</sup> (VII), in the presence of benzene and aluminum chloride, should be converted to III.



We have found, in fact, that under anhydrous conditions compound VII remained unchanged and

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Society, Chicago, Illinois, September, 1961. (3) On leave of absence from N.B.S. College, Hyderabad, India.

<sup>(6)</sup> R. Filler and Y. S. Rao, ibid., 26, 1685 (1961).

<sup>(9)</sup> E. Chiorénesku and L. Bukhen-Byrlédryanu, 120. Akad. Nauk SSSR, Otd. Khim. Nauk, 149-51 (1961); Consultant Bureau Enterprises, Inc., New York, pp. 130-131 (1961). These authors have also shown that 2-phenyl-4-benzyl-5-oxazolone gives 2-benzamidoindanone under Friedel-Crafts conditions in carbon disulfide at 50°.

<sup>(10)</sup> R. Filler and J. D. Wismar, J. Org. Chem., 22, 853 (1957).





CT \$7: 1.1

		07	of the		Carbon %		Hudrogen %	
Ar	M.p.	Yield	product	Formula	Caled.	Found	Caled.	Found
C <sub>6</sub> H <sub>5</sub>	159°	74	18	$C_{22}H_{17}NO_{2}$	80.71	80.87	5.24	5.23
$C_{e}H_{5}$ (at 80°)			$70^a$					
$4-NO_{\circ}C_{\circ}H_{\circ}$	145°	90		C22H16N2O4	70.95	70.32	4.30	4.17
4-ClC <sub>6</sub> H <sub>4</sub> —	150°	10	60	C <sub>22</sub> H <sub>16</sub> NO <sub>2</sub> Cl	73.02	72.77	4.42	4.46
$4-CH_{3}OC_{6}H_{4}$	149°	4	83	$C_{23}H_{19}NO_3$	77.31	76.95	5.32	5.18
$3,4-(CH_{3}O)_{2}C_{6}H_{3}-$			85					
$4-(CH_3)_2NC_6H_4-$			87			• • •		
$4-CH_3C_6H_4$	145°	14	$57^a$	$C_{23}H_{19}NO_2$	81.15	80.98	5.63	5.43
4-CH <sub>3</sub> COOC <sub>6</sub> H <sub>4</sub>			$35^{b}$					
$CH_{3}$								
4- $CH - C_6H_4 - $	151°	20	40	$\mathrm{C}_{25}\mathrm{H}_{23}\mathrm{NO}_2$	81.30	81.12	6.28	6.17
$CH_{3}$								
$3-NO_2C_6H_4$ —		••	$25^{b}$					
$3-ClC_6H_4$			$62^{b}$					
$3-CH_3OC_6H_4$ —			50					
$3-CH_3C_6H_4$ —			45					
$2-NO_2C_6H_4$ —	137°	80		$C_{22}H_{16}N_2O_4$	70.95	70.62	4.30	4.22
$2-ClC_6H_4$ —	175°	65	5	$C_{22}H_{16}NO_2Cl$	73.02	72.67	4.42	4.42
$2,4-Cl_2C_6H_3-$	115°	60	8	$\mathrm{C}_{22}\mathrm{H}_{15}\mathrm{NO}_{2}\mathrm{Cl}_{2}$	66.67	66.98	3.82	4.01
$2-CH_3OC_6H_4$	144°	15	$40^{a}$	$C_{23}H_{19}NO_3$	77.31	77.20	5.32	5.18
$2-CH_3C_6H_4$	143°	10	40	$C_{23}H_{19}NO_2$	81.15	80.82	5.63	5.52
$2-C_6H_5C_6H_4$	194°	33		$C_{28}H_{21}NO_2$	83.34	83.46	5.25	5.16
$1-C_{10}H_7$			22					
$2-C_{10}H_7$			20			· · •		

 $^{a}$  Together with 1-phenylisoquinoline 3-carboxylic acid derivatives.  $^{b}$  Together with an oily material which did not crystallize. Absolute ethanol was used as the solvent for recrystallization.

only in the presence of traces of moisture was compound III isolated in 27% yield.<sup>11</sup>

Since we also observed that compound III was obtained by the aluminum chloride-catalyzed acylation of benzene by 2-phenyl-5-oxazolone (V),<sup>12</sup> we do not believe that there is, at present, sufficient evidence to rule out the incipient formation of V by a retrograde aldol reaction, *followed* by acylation. The formation of unsaturated azlactones is thought to occur by aldol addition of the active methylene group in V to the aldehyde,<sup>13</sup> followed by dehydra-

(11) The referee has suggested the possibility of the role of specific hydrogen ion catalysis in ring opening, e.g.:

$$H_{2}O + AlCl_{3} \longrightarrow HCl + HOAlCl_{2}$$
$$HCl + AlCl_{3} \longrightarrow HAlCl_{4}$$
$$HAlCl_{4} + I \longrightarrow C_{6}H_{5}CH = C \longrightarrow C^{0} AlCl_{4} \ominus$$
$$NHCOC_{6}H_{5}$$

This intermediate would also be involved in intramolecular acylation. (12) It has recently been observed that compound V reacts with a variety of aromatic hydrocarbons under these conditions to give analogs of III. P. T. Frangopol, A. T. Balaban, L. Bărlădeanu, and E. Ciorănescu, *Tetrahedron*, **16**, 59 (1961). (13) (a) J. W. Cornforth in "Heterocyclic Compounds," Vol. 5,

(13) (a) J. W. Cornforth in "Heterocyclic Compounds," Vol. 5,
R. C. Elderfield, ed., John Wiley and Sons, Inc., New York, 1957, pp. 342-343.
(b) E. Baltazzi, *Quart. Rev.*, **IX**, 150 (1955).

tion, although this occurs in a less acidic medium (sodium acetate-acetic anhydride).

When the thiophene-free benzene was predried and distilled over sodium and the reaction with I conducted in a nitrogen atmosphere, the cleavage reaction was markedly suppressed, although not entirely, and intramolecular acylation was completely avoided. Compound II was isolated in 70-75% yield.

70-75% yield. (2) The purity of aluminum chloride was found to be an important factor. Fresh, anhydrous aluminum chloride gave the 1,4 addition product with compound I and dry benzene, whereas aged aluminum chloride led to III.<sup>14</sup> The quantity of aluminum chloride required varied with the nature of the substituent. Thus, with an azlactone bearing a methoxy group on the arylidene ring, a mole ratio of azlactone-aluminum chloride of 1:4 was required for reaction to occur. With two methoxy groups, a 1:5 mole ratio was necessary. The additional aluminum chloride coordinates with the ether oxygens.

(3) In the case of substituted azlactones, the presence of an electron-withdrawing substituent enhanced the addition reaction, while electrondonating groups gave much lower yields of the

<sup>(14)</sup> This effect of aged aluminum chloride has also been observed by Mustafa and Sallam, ref. 8.

saturated azlactone and a corresponding increase in the amount of III. The yields of saturated azlactones decreased in the following order:

$$4-NO_2 > 4-H > 4-Cl > 4-OCH_3 > 3, 4-(OCH_3)_2 > 4-N(CH_3)_2$$

Azlactones with substituents in the *meta* position of the arylidene moiety gave solely III and no 1,4 addition. With *ortho* substituted azlactones, both compound III and analogs of II were always obtained. Azlactones derived from heterocyclic aldehydes, such as furfural, 2-thenaldehyde, and indole-3-carboxaldehyde, failed to react at all.

The contention<sup>4</sup> that "the presence of two groups  $(>C==O \text{ and } --\mathrm{NHCOC}_6\mathrm{H}_5)$  with a  $-\mathrm{T}$  effect attached to the unsaturated carbon of the benzylidene facilitates hydrolysis of the double bond in the acid medium" is not supported by the data in Table I or by our previously described experiment with compound VII. We believe, rather, that the most important single factor in determining the course of the reaction is the nature and position of substituents on the arylidene ring. While the presence of moisture in the initial reaction mixture is a sufficient condition for >C==C< cleavage, it is apparent that it is not a necessary condition.

(4) While all other reactions were conducted at room temperature, it was found that I reacted with benzene at 80° (reflux) to give, in addition to III, a small amount of a colorless substance whose molecular weight, elemental analysis, and spectral properties supported the structure assignment of the previously unknown 1-phenylisoquinoline 3-carboxylic acid (VI), formed by *intramolecular alkylation*, similar to the formation of 4-phenyl-2-naphthoic acid from  $\alpha$ -benzylidene  $\gamma$ -phenyl $\Delta^{-\beta,\gamma}$ butenolide.<sup>15</sup> The following mechanism is suggested for its formation:



The structure of VI was confirmed by decarboxylation to the known 1-phenylisoquinoline hydrochloride and comparison of the latter with an authentic sample.

When the reaction was conducted in tetrachloroethane as solvent at  $60^{\circ}$ , 2-benzamidoindenone, IV, and compound VI were obtained. Thus, the white compound, claimed<sup>4</sup> to be a polymer of IV is, in fact, 1-phenylisoquinoline-3-carboxylic acid. In a similar fashion, 5-methoxy- and 7-methyl-1phenylisoquinoline 3-carboxylic acids were also prepared.

(5) Solvent participation leading to cleavage products in chlorobenzene, toluene, and m-xylene

(15) R. Filler, L. H. Mark, and E. J. Piasek, J. Org. Chem., 24, 1780 (1959).

has also been reported by Awad.<sup>4</sup> While we have confirmed that such participation is important, we have further observed that cleavage need not necessarily be the only reaction. Thus, in chlorobenzene, both intramolecular alkylation and cleavage occurred, when aged aluminum chloride was used with compound I. With fresh aluminum chloride, a small amount of 1,4-addition product was the only new material isolated. This was identical with a sample obtained from the *p*-chlorobenzylidene azlactone and benzene. Under the latter conditions anisole gave 55% of 1,4-addition product, exclusively, and with toluene, only cleavage product was obtained.

These results indicate the complexity of this reaction and do not support the general statement<sup>4</sup> that the oxazolone ring reacts as a cyclic anhydride under Friedel-Crafts conditions.

## Experimental<sup>16</sup>

Reaction of 2-Phenyl-4-benzylidene-5(4H)-oxazolone under Friedel-Crafts Conditions. (a) With Benzene.-In a 1-l. round-bottomed flask, provided with a mechanical stirrer, dropping funnel, and a condenser connected to a nitrogen supply, were placed 9.6 g. of anhydrous aluminum chloride (0.072 mole) and 125 ml. of dry thiophene-free benzene, freshly distilled over sodium. The flask was cooled in an ice bath and the contents of the flask stirred for 1 hr. at 10°. I (6.0 g., 0.024 mole), dissolved in 125 ml. of dry benzene, was added gradually, care being taken that the temperature did not rise above 10°. After the addition of the azlactone solution, the ice bath was removed and the reaction mixture was stirred at room temperature for 3 hr. Dilute (1:15) hydrochloric acid (250 ml.) was added to decompose the complex. The aqueous layer was washed with benzene. The combined benzene layer was washed with water several times, dried over anhydrous magnesium sulfate and the benzene removed by distillation on a water bath. The residual oil was dissolved in ether and petroleum ether was added. The solid which separated was filtered, dried, and recrystallized from absolute ethanol.  $\omega$ -Benzamidoacetophenone was recovered from the mother liquor, after the saturated azlactone had been removed by filtration.

A similar procedure was used for the substituted azlactones.

(b) With Chlorobenzene.—The reaction was carried out as described above. The chlorobenzene layer was dried over anhydrous magnesium sulfate and excess chlorobenzene was distilled under reduced pressure. The oil which remained was dissolved in ether and petroleum ether was added. The white solid, which separated, was recrystallized from absolute ethanol, m.p. 221° (1 g.). A second compound, melting at 159°, was obtained when the mother liquor was concentrated. The first compound was identical with the 1-phenylisoquinoline-3-carboxylic acid, described below. The second compound was  $\omega$ -benzamido-p-chloroacetophenone. With a fresh sample of anhydrous aluminum chloride, a 20% yield of 1,4-addition product was obtained, m.p. 150° (mixed melting point with authentic sample was not depressed). Starting material was also recovered.

(c) With Anisole.—The reaction was conducted as described in (b) using fresh anhydrous aluminum chloride and 6.0 g. of compound I. A white compound was isolated, m.p. 149° [yield: 3.2 g. Infrared spectrum: 1810 cm.<sup>-1</sup> (>C== O) in saturated azlactones] and 1645 cm.<sup>-1</sup> (-C==N). The compound was identical with the product obtained by the

<sup>(16)</sup> All melting points were determined on a Fisher-Johns block and are uncorrected,

reaction of 2-phenyl-4-(p-anisylidene)-5(4H)-oxazolone with benzene.

(d) With Toluene.—The reaction was run as described in (c). The product obtained (4.8 g.), m.p. 117° (lit.,<sup>4</sup> m.p. 118°), was  $\omega$ -benzamido-*p*-methylacetophenone.

(e) With Benzene at 80°.—The experiment was carried out as described in (a), except that after the addition of the azlactone solution, the reaction mixture was heated under reflux at 80° for 1 hr. The mixture was decomposed with dilute hydrochloric acid. The benzene layer was removed, washed with water, and left overnight. The product which separated was filtered and dissolved in sodium carbonate solution. The alkaline solution was decolorized with compound, m.p. 221°, mol. wt., calcd.: 249, found (neut. equiv.):248. Anal. calcd for  $C_{16}H_{11}NO_2$ : C, 77.11, H, 4.42. Found: C. 76.50, H, 4.59.

The benzene layer gave  $\omega$ -benzamidoacetophenone, m.p. 124°, after removal of benzene and treatment of the residual oil with ether and petroleum ether.

Decarboxylation of 1-Phenylisoquinoline 3-Carboxylic Acid.<sup>17</sup>—The acid (0.8 g.) was mixed with 4 g. of benzophenone and the nixture was heated for 24 hr. at  $155^{\circ}-165^{\circ}$  in a nitrogen atmosphere in a round-bottomed flask, provided with a condenser. The flask was cooled, its contents extracted with ether, and the ether-insoluble portion was removed by filtration. The ether soluble portion was retracted three times with 1:15 hydrochloric acid and the hydrochloric acid extract, saturated with sodium carbonate. The sodium carbonate layer was then extracted with ether. The ether layer was saturated with dy hydrogen chloride gas to give solid 1-phenylisoquinoline hydrochloride, m.p. 234°, lit.<sup>18</sup>(a) m.p. 235-36°; (b) m.p. 237-39°. Preparation of 1-Phenylisoquinoline.<sup>19</sup>—To a solution of

**Preparation of 1-Phenylisoquinoline.**<sup>19</sup>—To a solution of phenylmagnesium bromide, prepared from 0.9 g. of magnesium metal and 5.9 g. of bromobenzene, was added 10 g. of

(17) T. L. Jacobs, S. Winstein, R. B. Henderson, and E. C. Spaeth, J. Am. Chem. Soc., 68, 1310 (1946).

(18) (a) E. Bergmann, O. Bergmann, and A. Christiani, Ann., 483, 80 (1930);
(b) M. Whaley and W. Hartung, J. Org. Chem., 14, 650 (1949).

(19) E. Bergmann and W. Rosenthal, J. prakt. Chem., 135, 267 (1932).

isoquinoline. The reaction mixture was heated under reflux for 2 hr. and decomposed with a saturated solution of ammonium chloride. The ethereal extract, on evaporation, gave 1-phenylisoquinoline. Its hydrochloride melted at  $235^{\circ}$ .

Debenzoylation of  $\omega$ -Benzamidoacetophenone.—III (2 g.) was heated under reflux with 50 ml. of a 2:1 mixture of glacial acetic acid-48% hydrobromic acid for 6 hr. The excess of acid mixture was distilled under reduced pressure. The residue was dissolved in water and extracted with ether. The ethereal extract gave benzoic acid on evaporation. The aqueous layer gave, when concentrated, phenacylamine hydrobromide, m.p. 217°, lit.<sup>20</sup> m.p. 217°-218°.

**Preparation of**  $\omega$ -Benzamidoacetophenone.—Phenacylamine hydrochloride (1 g.) (Aldrich Chemical Co.) was benzoylated by the Schotten-Baumann method and the benzoyl derivative was recrystallized from ethanol, m.p. 124°.

All the cleavage products obtained from the various azlactones proved to be identical with this sample (m.p. and mixed m.p.).

**Reaction in Tetrachloroethane Medium.**—Compound I reacted with aluminum chloride in the molar quantities given in (a) in 100 ml. of tetrachloroethane at 60°, following Awad and Hafez's<sup>4</sup> procedure. 2-Benzamidoindenone, m.p. 140°, and 1-phenylisoquinoline-3-carboxylic acid were obtained.

5-Methoxy-1-phenylisoquinoline-3-carboxylic acid, m.p. 213°.

Anal. Calcd. for  $C_{17}H_{13}NO_3$ : C, 73.11; H, 4.69; Found: C, 72.90, H, 4.58) and 7-methyl-1-phenylisoquinoline 3-carboxylic acid, m.p. 227°.

Anal. Calcd. for  $C_{17}H_{13}NO_2$ : C, 77.98; H, 4.99; Found: C, 77.29; H, 5.10), were prepared from 2-phenyl 4-(o-methoxybenzylidene)-5(4H)-oxazolone and 2-phenyl-4-(p-tolylidene)-5(4H)-oxazolone, respectively.

Spectral Measurements and Analyses.—Infrared spectra were obtained on a Perkin-Elmer Infracord. The samples were examined in chloroform or methylene chloride. Microanalyses were conducted by Micro-Tech Laboratories, Skokie, Illinois.

(20) I. M. Heilbron: Dictionary of Organic Compounds, Vol. 3, Oxford University Press, New York, 1938, p. 361.

## Action of Grignard Reagents. XXIII. Action of Organomagnesium Compounds on Saturated and Unsaturated Azlactones. Addition Reactions of Mercaptans and Piperidine with Unsaturated Azlactones

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The reaction between alkyl- and aralkylmagnesium halides on unsaturated azlactones (I) was studied, and was found to give compounds having structure IV, while the reaction between the same reagents and ethyl 2-benzamidocinnamate gave compounds having structure II, which were converted to the corresponding oxazolines (III) by the action of alcoholic potassium hydroxide. The reaction between arylmagnesium halides and 2-benzamidobenzalacetophenone (VII), unsaturated azlactones (I), and saturated azlactones (VIII) was also studied. The Friedel-Crafts reaction on unsaturated azlactones (I) was also discussed. The behavior of unsaturated azlactones toward arylmercaptans was investigated, and products having structure X were obtained. Ic reacted with piperidine to give the ring-opened piperidide.

It had been shown that the oxazolone ring in 2-phenyl-4-methyl-5(4H)-oxazolone,<sup>1</sup> and 2-phenyl-4-

(1) E. Mohr and F. Stroschein, Ber., 42, 2521 (1909); H. T. Clarkes J. R. Johnson, and R. Robinson, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 738.

arylidene-5(4H)-oxazolone (I)<sup>2</sup> was readily cleaved by the action of arylmagnesium halides to give

(2) (a) A. Mustafa and A. H. E. Harhash, J. Org. Chem., 21, 575
(1956); (b) H. Pouratt, Bull. soc. chim. France. 828 (1955); (c) R. Filler and J. D. Wismar, J. Org. Chem., 22, 853 (1957).