2-Amino-2-oxazolin-4-ones. II. Tautomerism

CHARLES F. HOWELL, Nicanor Q. Quinones, and Robert A. Hardy, Jr.

Organic Chemical Research Section, Ledlele Laboratories Division, American Cyanamid Co., Pearl River, N. Y.

Received November 6, 1961

Comparison of the physical and chemical properties of 2-amino-5-phenyl-2-oxazolin-4-one (VI) with mono- and dimethyl homologs of known tautomeric structure has shown that the 2-amino-2-oxazolin-4-one structure (II) is indicated rather than the 2-imino-4-oxazolidinone structure (I) previously formulated. The latter form, however, prevails in the conjugated 5-phenyl-2-phenylimino-4-oxazolidinone (XIV).

Condensation products of α-hydroxy esters with guanidine have been formulated as 2-imino-4-oxazolidinones (I) since Traube and Ascher first recognized that these compounds were heterocycles and not α-hydroxyacylamidamides. Subsequent workers have accepted the 2-imino structure (I), apparently without consideration of the other possible tautomers (II-V).

Najer has recently examined the complex infrared spectra (solid state) of 5-aryl-2-imino-4-oxazolidinones and the corresponding 2-substituted imino derivatives. These authors concluded that the spectra could be interpreted on the basis of mixtures of tautomers I and III. The complexity of these spectra, particularly in the double bond region, make definitive interpretation difficult and even misleading in the absence of supporting data such as the spectra of model compounds of unequivocal tautomeric structure. A few N,N'-disubstituted derivatives which must have structure I (or IV) have been prepared but have not been utilized in this or other studies of tautomerism. Investigations of tautomerism in the related thiazole or imidazole (glycocyamidine) series have not been reported, although both of these systems have been formulated as the 2-imino tautomers. Our interest in 2-dialkylamino-5-phenyl-2-oxazolin-4-ones which must be derived from structure II (or V) led us to compare their properties with those of the reported derivatives of I. In pursuing this study, the preparation of 3-methyl-2-imino-4-oxazolidinone which must be derived from structure I (or IV) was particularly desirable.

A variety of alkylation techniques provided data on tautomeric behavior and model compounds for ultraviolet and infrared spectral studies. Treatment of 2-amino-5-phenyl-2-oxazolin-4-one (VI) with methyl iodide in dimethylformamide (neutral conditions) yielded 2-imino-3-methyl-5-phenyl-4-oxazolidinone (VII, 55%). Compound VII was a sublimable solid, m.p. 101°C, insoluble in sodium hydroxide and susceptible to hydrolysis even in boiling water. In all of these properties it differs from VI which is soluble in sodium hydroxide and requires acid for hydrolysis. Acidic hydrolysis of VII yielded 3-methyl-5-phenyl-2,4-oxazolidinedione (89%) thus demonstrating the position of the methyl group. Treatment of VII with sodium methoxide gave a rearranged product, 2-methylamino-5-phenyl-2-oxazolin-4-one (IX, 80%) which yielded 5-phenyl-2,4-oxazolidinedione (84%) upon acid hydrolysis. The formation of two different hydrolysis products in good yields indicated that acid-catalyzed rearrangement had not occurred, in contrast to rearrangements reported in the thiazole series. The rearranged product IX was identical with a sample prepared from methylurea and

(1) Presented in part before the Division of Medicinal Chemistry at the 141st Meeting of the American Chemical Society, Washington, D. C., March 26, 1962.

(2) (a) W. Traube and R. Ascher, Ber., 46, 2077 (1913); (b) E. Clemmensen and A. H. C. Hattman, Am. Chem. J., 40, 290 (1908); 42, 310 (1909). Unaccountably, D. T. Elmore and J. R. Ogilvie, Tetrahedron, 3, 310 (1958) also use the acyclic formulation.


(14) Nomenclature is consistent with the structural studies reported herein and with current Chem. Abstr. practice.

dimethylamino derivative (X) to 3-methyl-2-methylamino isomer (XI) parallels the behavior observed in the reaction of ethyl iodide with sodium salt of 2-arylino-4-thiazolines.17

On the basis of their study of infrared spectra, Najer and Giudicelli18 expressed the opinion that 5-phenyl-2-phenylimino-4-oxazolidinone (XII)1b,11 was more completely tautomerized to III (i.e., 4-hydroxy-2-imino-5-phenyl-3-oxazoline) than derivatives with alkyl substituents attached to the exocyclic nitrogen atom. Apparently no other tautomers were considered. We prepared 3-methyl-5-phenyl-2-phenylimino-4-oxazolidinone (XIV, which must correspond to tautomer I) by Aspelund’s procedure16 from 1-methyl-3-phenylurea and α-chlorophenylacetyl chloride. Hydrolysis of XIV gave the 3-methylidione as reported.25 The isomeric derivative related to tautomer II was prepared by treatment of the anion of XII with dimethyl sulfate. Hydrolysis of this compound, 2-N-methylalanino-5-phenyl-2-oxazolin-4-one (XIII), yielded both 5-phenyl-2,4-oxazolidinedione and N-methylalanine (as the p-toluenesulfonamide).

The rearrangement of VII, the position of monomethylation of VI under neutral conditions and the position of dialkylation under basic conditions all suggest that the structure of VI is better represented by tautomer II than by I. Spectral evidence (Table I) confirms this and precludes serious consideration of structures III, IV, and V. The rearrangement of 3-methyl-2-imino-5-phenyl-4-oxazolidinone (VII) to the isomer IX indicates the greater stability of the conjugated endocyclic double bond in IX, since only one-tenth equivalent of methoxide was required for 80% rearrangement. The rearrangement probably involves an acyclic pseudourea intermediate VIII analogous to that postulated by Brown19a in the rearrangement of 1,2-dihydro-2-imino-1-methylpyrimidine. The cleavage of 3-acetyl-2-methyl-3-phenyl-pseudourea to yield methyl acetate and 2-methyl-3-phenyl-pseudourea has been described.19 Base-catalyzed rearrangements of this type are known with thiazole18 and imidazole20 but apparently not with oxazole derivatives. Nuclear alkylation of VI under neutral conditions to give VII is understandable on the basis of structure II where resonance should contribute to the relatively greater nucleophilicity of N-3.20 Addition of the second methyl group to the anion IXa to give predominately the dimethylamino-2-oxazoline compound X appears to parallel the addition of a proton to IXa.

(17) Ref. 11, p. 619.
regenerating IX.\(^3\) 2-Aminopyridine, whose tautomeric structure is well established,\(^5\) undergoes analogous reactions.\(^2\)

Ultraviolet spectral data (Table I) confirm structure II when substituents on the exocyclic nitrogen atom are hydrogen, methyl or benzyl. Substitution of methyl groups on the exocyclic nitrogen atom are hydrogen, methyl or benzyl. Substitution of a methyl group on the nuclear nitrogen atom to give VI\(_1\) causes a hypsochromic shift of 10 mp from VI or 14 mp from the isomer IX. Similar effects are to be expected if VI and IX have the 2-amino structure II (or IV).

In sodium methoxide the maximum is shifted 264 mp but the intensity is diminished. In sodium hydroxide have maxima in similar positions but the intensities were diminished. The spectrum in 0.1 N hydrochloric acid has a maximum at 233 mp but the intensity is diminished. In sodium methoxide the maximum is shifted to 264 mp and the intensity is reduced.\(^4\) The diminished intensity of this band may be due to steric inhibition of coplanarity at the exocyclic double bond and phenyl moiety by the N-3 methyl group in one of the two syn-anti forms.

The spectra of VI, IX, and X in either 0.1 N hydrochloric acid or 0.1 N sodium hydroxide have maxima in similar positions but the intensities were diminished.\(^5\) The spectrum in 0.1 N hydrochloric acid has a maximum at 233 mp but the intensity is diminished. In sodium methoxide the maximum is shifted to 264 mp and the intensity is reduced.\(^4\) The diminished intensity of this band may be due to steric inhibition of coplanarity at the exocyclic double bond and phenyl moiety by the N-3 methyl group in one of the two syn-anti forms.

Table I

<table>
<thead>
<tr>
<th>Number</th>
<th>Type</th>
<th>Structure</th>
<th>(\text{R}^1)</th>
<th>(\text{R}^2)</th>
<th>(\text{R}^3)</th>
<th>(\text{R}^4)</th>
<th>(\text{(\lambda_{max})(nm)})</th>
</tr>
</thead>
<tbody>
<tr>
<td>VI(_1)</td>
<td>II</td>
<td>II</td>
<td>H</td>
<td>H</td>
<td>(\text{C}_6\text{H}_5)</td>
<td>H</td>
<td>217</td>
</tr>
<tr>
<td>IX(_{1b})</td>
<td>II</td>
<td>II</td>
<td>(\text{CH}_3)</td>
<td>(\text{CH}_3)</td>
<td>(\text{C}_6\text{H}_5)</td>
<td>H</td>
<td>221</td>
</tr>
<tr>
<td>XIV(_{1b})</td>
<td>II</td>
<td>(\text{CH}_3)</td>
<td>(\text{CH}_3)</td>
<td>(\text{C}_6\text{H}_5)</td>
<td>H</td>
<td>227</td>
<td>27,300</td>
</tr>
<tr>
<td>VI(_{1b})</td>
<td>II</td>
<td>(\text{CH}_3)</td>
<td>(\text{CH}_3)</td>
<td>(\text{C}_6\text{H}_5)</td>
<td>H</td>
<td>226</td>
<td>30,700</td>
</tr>
<tr>
<td>XII(_{1b,13})</td>
<td>II</td>
<td>H</td>
<td>(\text{CH}_3)</td>
<td>(\text{C}_6\text{H}_5)</td>
<td>H</td>
<td>254</td>
<td>24,100(^b)</td>
</tr>
<tr>
<td>XVII(_{16,13})</td>
<td>II</td>
<td>(\text{CH}_3)</td>
<td>(\text{CH}_3)</td>
<td>(\text{C}_6\text{H}_5)</td>
<td>H</td>
<td>254</td>
<td>12,800(^b)</td>
</tr>
<tr>
<td>XIX(_{1b})</td>
<td>II</td>
<td>(\text{CH}_3)</td>
<td>(\text{CH}_3)</td>
<td>(\text{C}_6\text{H}_5)</td>
<td>H</td>
<td>233</td>
<td>22,600</td>
</tr>
</tbody>
</table>

\(^a\) The spectra of VI, IX, and X in either 0.1 N hydrochloric acid or 0.1 N sodium hydroxide have maxima in similar positions but the intensities were diminished.\(^5\) The spectrum in 0.1 N hydrochloric acid has a maximum at 233 mp but the intensity is diminished. In sodium methoxide the maximum is shifted to 264 mp and the intensity is reduced.\(^4\) The diminished intensity of this band may be due to steric inhibition of coplanarity at the exocyclic double bond and phenyl moiety by the N-3 methyl group in one of the two syn-anti forms.

The spectrum of an equimolar mixture of XVII and toluene is superimposable on that of X. These data conclusively eliminate tautomer V and, together with the bathochromic and hypsochromic shifts observed in the various methylation products, preclude consideration of tautomer IV. Structure III cannot be excluded quite so conclusively by these facts. Should VI and IX conform to tautomer III, than that conjugated chromophore would have to absorb with remarkable similarity to tautomer II as exemplified by X. The fact that O-methylated products were not found also tends to cast doubt on structure III. 2-Benzylamino-5-phenyl-2-oxazolin-4-one (XVIII)\(_{16,13}\) absorbs at 226 mp and is clearly derived from tautomer II. Thus, the conjugated system of tautomer II and its resonance forms appears to be responsible for the absorption of 2-amino-, 2-alkylamino-, and 2-arylalkylamino-2-oxazolin-4-ones and establishes, at least in methanol, the 2-amino structure for these compounds.

The absorption of 5-phenyl-2-phenylimino-4-oxazolidinone (XII) at 254 mp is essentially identical with that of the 3-methyl homolog (XIV) and establishes the imino structure for XII, indicating the importance of conjugation with the phenyl group. These observations also conclusively eliminate consideration of tautomer III suggested by Najer and Giudicelli\(^b\) which must have a markedly different chromophore. The isomeric 2-N-methylanilino compound (XIII), in which the anil chromophore is destroyed, absorbs at 233 mp.

The complex bands in the double bond region of the infrared spectra of compounds uniquely derived...
from tautomers I and II are very similar and somewhat unpredictable. Assignment of tautomers from these data can be misleading as seen above. Similarly, the interpretation of the 3-μ region in the spectra of VI and IX is difficult because either or both N—H and O—H stretching is possible. However, the improbable enolic structures IV and V are excluded by the transparency of the 3-μ region in the spectra of X, XI, XIII, and XIV, compounds in which N—H stretching is not possible.

Kokko, Goldstein, and Mandell have examined the tautomerism of pyrimidines derived from nucleic acids by NMR. Unfortunately, the protons attached to nitrogen could not be detected reliably by NMR in compounds VI, VII, IX, XV, and 5-phenyl-2,4-oxazolidinedione (10% solutions in dimethyl sulfoxide).

Thus, the present results of methylation, the rearrangement of an exocyclic to an endocyclic double bond (VII to IX), and ultraviolet spectra are all in harmony with the 2-amino-2-oxazolin-4-one structure II when the substituents on the 2-amino group are hydrogen, alkyl and benzyl, and exclude tautomers I, III, IV, and V. These conclusions are consistent with recent results which show that 2-amino-4-phenyl-2-oxazoline is more stable than the 2-imino tautomer and with the equilibrium between methylene cyclopentane and 1-methylcyclopentene. This one series provides both examples of and exceptions to the principle of parallelism of nucleophilicity and basicity frequently observed in heterocyclic systems. The apparent similarity of the reactions of the anions of 2-amino-5-phenyl-2-oxazolin-4-one (VI) and the 2-methylamino homolog with dimethyl sulfate and with protons is both understandable and expected.

On the other hand, the reactions of the closely analogous anion derived from 5-phenyl-2-phenylimino-4-oxazolidinone (XII) with dimethyl sulfate and with protons indicate that nucleophilicity and basicity of these two nitrogen atoms are apparently reversed. A possible explanation of these divergent results lies in a facile tautomer equilibration to the more stable tautomer. This equilibration could occur rapidly following the initial protonation of the ambident anion of XII in which nucleophilicity and basicity of the two nitrogen atoms are actually more nearly similar than the ultimate results indicate. Ridd and Smith have recently discussed analogous problems in studying imidazole and benzimidazole derivatives. Their observations as well as ours emphasize the problems of interpretation of nucleophilicity and basicity in tautomeric heterocyclic systems.

(24) Our spectra and the published examples are substantially identical.
(28) Melting points are corrected.

Experimental

2-Imino-3-methyl-5-phenyl-4-oxazolidinone (VII).—A mixture of 8.8 g. of 2-amino-5-phenyl-2-oxazolin-4-one (VI), 3.4 ml. of methyl iodide, and 50 ml. of freshly opened dimethylformamide (Eastman White Label) was stored in the dark for 65 hr. with occasional shaking. The dark solution was neutralized with 4.2 g. of sodium bicarbonate and concentrated to dryness. The residue was treated with three 50-ml. portions of hot methylene chloride followed by 50 ml. of water. The remaining solid (2.6 g.) was identified as starting material (VI) by its infrared spectrum. The aqueous and methylene chloride extracts were combined and filtered to remove an additional 0.2 g. of VI (total recovery 32%). The aqueous layer was separated from the methylene chloride solution which was washed with 50 ml. of 0.1-N sodium thiosulfate and dried over sodium sulfate. The solution was concentrated to dryness and the residue was recrystallized from 15 ml. of 1:2 ethyl acetate-cyclohexane and then sublimed (90°, 0.05 mm.). 2-Imino-3-methyl-5-phenyl-4-oxazolidinone (VII, 5.2 g., 55%), m.p. 98–101°, was obtained as colorless needles.

Anal. Calcd. for C$_{10}$H$_{11}$N$_2$O: C, 69.2; H, 5.31; N, 14.73. Found: C, 63.18; H, 5.35; N, 14.51.

A methylene chloride solution of VII was stable to washing with 1 N sodium hydroxide solution but the compound could not be crystallized from water without extensive hydrolysis (infrared spectrum). An impure sample (8.8 g., m.p. 85–90°) which resisted purification by recrystallization or sublimation was dissolved in 90 ml. of benzene. The imino compound was extracted with 180 ml. of cold 10% hydrochloric acid and neutralized at once with 25 g. of potassium carbonate. The resulting solid was filtered and sublimed to give 5 g. of pure 2-imino-3-methyl-5-phenyl-4-oxazolidinone, m.p. 100.3–101.8°.

3-Methyl-5-phenyl-2,4-oxazolidinedione (A).—From 5-Phenyl-2,4-oxazolidinedione.—To a solution of sodium methoxide prepared from 0.14 g. of sodium in 11 ml. of methanol was added 1.0 g. of 5-phenyl-2,4-oxazolidinedione followed by 0.58 ml. of dimethyl sulfate. The solution was refluxed for 2 hr. and concentrated to dryness. The residue was dissolved in 75 ml. of ether, washed twice with water, and dried over sodium sulfate. Filtration and concentration yielded a solid which was recrystallized from ligroin twice to give 0.73 g. (68%) of 3-methyl-5-phenyl-2,4-oxazolidinedione, m.p. 110–111° (lit., 14.5°, m.p. 111–111.5° for a sample prepared with diazomethane). The infrared spectrum was clearly distinguishable from that of the unsubstituted derivative especially by the lack of a band at 2.9 μ in the spectrum of the latter.

B. From 2-Imino-3-methyl-5-phenyl-4-oxazolidinone (VII).—Hydrolysis of 0.81 g. of VII in 12.5 ml. of 10% hydrochloric acid at 90–100° for 10 min. gave 0.72 g. (89%) of 3-methyl-5-phenyl-2,4-oxazolidinedione, m.p. 112–113°. The infrared spectrum was identical with that of the authentic sample just described (A).

C. From 3-Methyl-2-methylaminio-5-phenyl-4-oxazolidinone (XI).—Similar hydrolysis of 0.4 g. of XI (see below) yielded 0.52 g. (84%) of the 3-methyl dione, m.p. 112–113°, and its infrared spectrum was also identical with that of the authentic sample (A).

Rearrangement of 2-Imino-3-methyl-5-phenyl-4-oxazolidinone (VII) to 2-Methylamino-5-phenyl-2-oxazolin-4-one (IX).—To a solution of 1 mmole of sodium methoxide prepared from 50 mg. of 51% sodium hydride dispersion in 10 ml. of absolute methanol was added 1.9 g. (10 mmole) of 2-imino-3-methyl-5-phenyl-4-oxazolidinone (VII). The solution was heated under reflux for 2 hr., treated with 0.4 ml. of 1 N hydrochloric acid and concentrated to dryness. The residue was recrystallized from reagent grade ethyl acetate
to give 1.5 g. (80%) of 2-methy lamino-5-phenyl-2-oxazolin-4-one (IX), m.p. 121-123°, identical in all respects with a sample isolated chromatographically from the base-catalyzed alkylation of 2-amino-5-phenyl-2-oxazoline 4-one (see below). Anal. Caled. for C_{12}H_{10}N_2O_4: C, 63.19; H, 5.45; N, 13.52.

13. Methyl-3-2-methylamino-5-phenyl-2-oxazolin-4-one (VI).—To a solution of 190 mg. of IX in 2.9 ml. of acetic acid was added 0.5 ml. of ethereal diazomethane. The mixture was allowed to stand at room temperature for 1 hr., and then the reaction was quenched by the addition of 100 ml. of water. Filtration of the viscous reaction mixture afforded 3.53 g. (9.3%) of 2-methylamino-5-phenyl-2-oxazolin-4-one (VI), m.p. 133-137°, which had an infrared spectrum identical with that of a sample isolated by chromatography. The methylene chloride solution was concentrated to dryness, and the residue was recrystallized from absolute ethyl alcohol, and then sublimated, to yield 0.85 g. (50%) of 2-methylamino-5-phenyl-2-oxazolin-4-one (VI), m.p. 122-124°, which was identical with an authentic sample.

14. The residue obtained by concentration of the fourth fraction (h.b.v. 6-8) was recrystallized from methyl ethyl ketone and from reagent grade ethyl acetate and yielded 4.2 g. (20%) of 2-methylamino-5-phenyl-2-oxazolin-4-one (IX), m.p. 122-124°, which was identical with an authentic sample.

15. From Isolated Fraction (4.6 g.).—A similar oil (1.3 g.) obtained under identical conditions from the methylation of 1.76 g. of VI was subjected to partition chromatography on Celite 100 (31) using a cyclohexane-dioxane-water system (45:55:8). The oil in 15 ml. of lower phase and 5 ml. of upper phase was mixed with 50 g. of Celite and packed on top of a column containing 300 g. of Celite and 30 ml. of lower phase. The column (430 ml. hold-back volume [h.b.v.]) was eluted with upper phase and 100 ml. of absolute ethyl alcohol and observed with a recording ultraviolet spectrophotometer. Four major bands were eluted during the first nine h.b.v. and were combined with identical fractions from chromatography of the 14.6 g. oil described above. Yields of products isolated refer, therefore, to methylation of 10.6 g. (0.11 mole) of 2-amino-5-phenyl-2-oxazolin-4-one (VI).

The first fraction (middle of first h.b.v.) was concentrated to dryness. The residue, dissolved in a little methylene chloride, was extracted into 10% hydrochloric acid. The solid residue was precipitated by addition of excess solid potassium carbonate and sublimed to yield 0.35 g. (1.4%) of colorless needles, m.p. 76-77°.

The infrared spectrum was identical with that of 3-methyl-2-methylaminio-5-phenyl-4-oxazolidinone (XI, m.p. 89-90°) prepared from ethyl mandelate and dimethylbarbituric acid (see above).

Anal. Caled. for C_{12}H_{10}N_2O_4: C, 63.61; H, 0.62; N, 13.52.

The second fraction (first and second h.b.v.) yielded 3-methyl-5-phenyl-2,4-oxazolidinedione, 80 mg. (0.4%) m.p. 107-112°, which was identified by its infrared spectrum.

16. 2-Ethylmethylamino-5-phenyl-2-oxazolin-4-one.—2-Ethylmethylamino-5-phenyl-2-oxazolin-4-one (3.8 g., 0.02 mole) was treated with sodium ethoxide and diethyl sulfate in the preceding example. After the solution had been refluxed 0.5 hr., the products were separated as in the preceding examples. Acidification of the sodium hydroxide extract yielded 0.31 g. (8%) of recovered IX, m.p. 116-121°.

17. The third fraction (fourth h.b.v.) gave 3.5 g. (16%) of recrystallized 2-methylamino-5-phenyl-2-oxazolin-4-one (X), m.p. 135.6-137.9°, which had an infrared spectrum identical with that of a sample prepared from ethyl mandelate and dimethylylamide.

18. An authentic sample of IX was prepared in 30% yield (m.p. 117-119°) by the method of Aspelund, which involves cyclization of 1-(4-chlorophenylcetl)-3-methylurea with ethanolic potassium hydroxide. This material was also identical with a sample of IX obtained by rearrangement of VII. Recrystallization of IX from water yielded a product, m.p. 115-118°, with variable amounts of water and different infrared spectra depending upon drying conditions.

Hydrolysis of 190 mg. of IX in 2.9 ml. of 10% hydrochloric acid at 90-100° for 15 min. yielded 130 mg. (84%) of 5-phenyl-2,4-oxazolidinediones, m.p. 107-109° (III, m.p. 111°) after sublimation.

19. From Isolated Fraction (1.5 g.).—A similar oil (1.3 g.) obtained under identical conditions from the methylation of 1.76 g. of VI was subjected to partition chromatography on Celite 100 (31) using a cyclohexane-dioxane-water system (45:55:8). The oil in 15 ml. of lower phase and 5 ml. of upper phase was mixed with 50 g. of Celite and packed on top of a column containing 300 g. of Celite and 30 ml. of lower phase. The column (430 ml. hold-back volume [h.b.v.]) was eluted with upper phase and 100 ml. of absolute ethyl alcohol and observed with a recording ultraviolet spectrophotometer. Four major bands were eluted during the first nine h.b.v. and were combined with identical fractions from chromatography of the 14.6 g. oil described above. Yields of products isolated refer, therefore, to methylation of 10.6 g. (0.11 mole) of 2-amino-5-phenyl-2-oxazolin-4-one (VI).

The first fraction (middle of first h.b.v.) was concentrated to dryness. The residue, dissolved in a little methylene chloride, was extracted into 10% hydrochloric acid. The solid residue was precipitated by addition of excess solid potassium carbonate and sublimed to yield 0.35 g. (1.4%) of colorless needles, m.p. 76-77°. The infrared spectrum was identical with that of 3-methyl-2-methylaminio-5-phenyl-4-oxazolidinone (XI, m.p. 89-90°) prepared from ethyl mandelate and dimethylbarbituric acid (see above).

Anal. Caled. for C_{12}H_{10}N_2O_4: C, 63.61; H, 0.62; N, 13.52.

The second fraction (first and second h.b.v.) yielded 3-methyl-5-phenyl-2,4-oxazolidinedione, 80 mg. (0.4%) m.p. 107-112°, which was identified by its infrared spectrum.


(31) Celite is a trademark of Johns-Manville Corp. for a diamino-}

silsic acid. Before use, it was washed successively with 6 N hydro-}

chloric acid, water, 2% alcohol, and finally was dried in air.
The methylene chloride soluble fraction yielded 2.8 g. (64%) of 2-ethylmethylaminol-5-phenyl-2-oxazolin-4-one, m.p. 90-97°. An analytical sample was recrystallized twice from ethyl acetate, m.p. 104-107°.

Anal. Calcd. for C_{11}H_{13}N_{2}O: C, 71.26; H, 5.10; N, 12.78. Found: C, 71.83; H, 5.32; N, 12.63.

2-N-Methylamino-5-phenyl-2-oxazolin-4-one (XIII).

5-Phenyl-2-phenylimino-4-oxazolidinone (XII, 6.0 g.) was methylated exactly as in the examples above and yielded 8.0 g. of a crystallizable oil. Ordinary recrystallization (from ethyl acetate or methylene chloride-ether) of similar material from other experiments gave samples melting within a 1° range with consistently low (0.6-0.9%) analytical values for carbon. Accordingly, 4.0 g. of this oil was subjected to partition chromatography by the procedure above except that a cyclohexane-dioxane-water system (80:20:8) was used and absorption of the eluate at 235 mp was observed. Concentration of the major fraction (second and third h.b.v.) yielded a solid. Recrystallization from ethyl acetate afforded 1.4 g. (39%) of 2-N-methylamino-5-phenyl-2-oxazolin-4-one (XIII), m.p. 109-109.4°, which, after drying at 65° for 1 hr. in vacuo had m.p. 107-107.5°.

Anal. Calcd. for C_{11}H_{13}N_{2}O: C, 72.16; H, 5.31; N, 12.64. Found: C, 71.26; H, 5.10.

5-Phenyl-2,4-oxazolidinedione was eluted from similar columns in the same position and may have been a contaminant.

Hydrolysis of 75 mg. in 2 ml. of 10% hydrochloric acid for 0.5 hr. at 90-100° yielded 25 mg. (50%) of 5-phenyl-2,4-oxazolidinedione, m.p. 110-111°, which was identified by its infrared spectrum.

Analysis values for

C, 71.26; H, 5.10. Found: C, 71.83; H, 5.32; N, 12.63.

A solution of 13 g. of a-chlorophenylacetyl chloride and 0.28 g. of sodium hydroxide and 0.11 g. of p-toluenesulfonychloride was heated under reflux for 5 hr. exactly as described by Aspegrenaa and yielded 13.1 g. (71%) of recrystallized 3-methyl-5-phenyl-2-phenylimino-4-oxazolidinone (XIV), m.p. 90-92°.

Anal. Calcd. for C_{11}H_{13}N_{2}O: C, 72.16; H, 5.31; N, 12.64. Found: C, 71.83; N, 5.32; N, 10.63.

Hydrolysis of 0.53 g of XIV in 5.8 ml of 10% hydrochloric acid at 95-100° for 0.5 hr. yielded 0.31 g. (82%) of sublimed 3-methyl-5-phenyl-2,4-oxazolidinedione, m.p. 112-113° as reported. The infrared spectrum of this sample was identical with that of authentic material.

Acknowledgment.—We wish to thank W. B. Fulmor, L. Brancome, and C. Pidacks and their groups for generous assistance with spectral studies, microanalyses, and chromatography, respectively. Our thanks are also extended to Drs. H. G. Arit, Jr., and J. E. Lancaster and their associates for certain preparations and NMR data, respectively. Special appreciation is due to Dr. M. G. Howell for many helpful discussions and assistance with the technical literature.

A Rearrangement of 5-Aryl-1,3-dihydro-2H-1,4-benzodiazepine-2-one 4-Oxides

STANLEY C. BELL AND SCOTT J. CHILDRESS


Received January 15, 1962

5-Aryl-1,3-dihydro-2H-1,4-benzodiazepine-2-one 4-oxides were shown to rearrange to 3-acyloxy-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-ones upon treatment with acylating agents. Hydrolysis of the acyl groups gave 3-hydroxy analogs. Upon treatment with alkali, 7-chloro-3-hydroxy-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-one rearranged to 7-chloro-5-phenyl-4,5-dihydro-2H-1,4-benzodiazepine-2,3(1H)-dione and 6-chloro-4-phenyl-3,4-dihydro-2-quinazolinonecarboxylic acid.

The action of acetic anhydride upon 7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-one 4-oxide has led to the formation of 3-acetoxy-7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-one (II). The course of this rearrangement is similar to that observed upon treatment of an aromatic N-oxide with acetic anhydride. Pyridine 1-oxide, for example, affords 2-acetoxypyridine. In II, however, the acetoxy group is found on a saturated carbon atom. The formation of II would appear, therefore, to be more closely related to the proposed formation of acetylated carbamolines as intermediates in the Polonovski reaction. As an example of this reaction, N,N-dimethylaniline N-oxide is converted by acetic anhydride into N-methylacetanilide with N-acetoxy methyl - N-methyl aniline as the suggested intermediate. In contrast to these proposed intermediates, II appears to be stable.

The acetyl group of II was easily hydrolyzed with one equivalent of sodium hydroxide, affording 7-chloro-3-hydroxy-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-one (III). This product was benzyolated in pyridine solution to afford 3-benzoxy - 7 - chloro - 5 - phenyl - 1,3 - dihydro - 2H-1,4-benzodiazepine-2-one (IV), identical with material prepared by treating I with benzoil.


