2-Amino-2-oxazolin-4-ones. II. Tautomerism[1]

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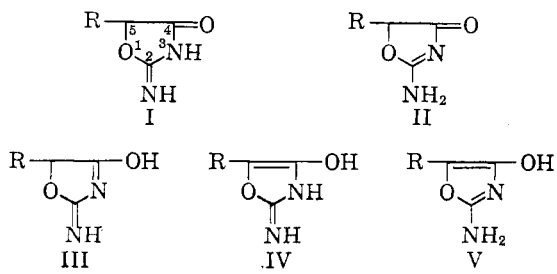
Comparison of the physical and chemical properties of 2-amino-5-phenyl-2-oxazolin-4-one (VI) with mono- and dimethyl homologs of known tautomeric structure has shown that the 2-amino-2-oxazolin-4-one structure (II) is indicated rather than the 2-imino-4-oxazolidinone structure (I) previously formulated. 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[2a] first recognized that these compounds were heterocycles and not α-hydroxyacylcyanamides.[2b] Subsequent workers[3-6] 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[5a] and the corresponding 2-substituted imino derivatives.[5b] These authors concluded that the spectra could be interpreted on the basis of mixtures of tautomers I and III.[5b] 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.[7] A few *N,N'*-disubstituted derivatives which must have structure I (or IV) have been prepared[3b,3c,8,9] but have not been utilized in this[5b] or other studies of tautomerism.[10] Investigations of tautomerism in the related thiazole[11] or imidazole (glycocyamidine)[12] 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[13,14] which must be related to 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)[1,14] with methyl iodide in dimethyl-formamide (neutral conditions) yielded 2-imino-3-methyl-5-phenyl-4-oxazolidinone (VII, 55%). Compound VII was a sublimable solid, m.p. 98–101°, 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.[1] 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.[15] 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. Heitman, *Am. Chem. J.*, **40**, 280 (1908); **42**, 319 (1909). Unaccountably, D. T. Elmore and J. R. Ogle, *Tetrahedron*, **3**, 310 (1958) also use the acyclic formulation.

(3) (a) H. Aspelund, *Acta Acad. Aboensis, Math. et Phys.* **11** (14), 1 (1938); *Chem. Zentr.*, **110** (II), 3092 (1939); (b) H. Aspelund, *Acta Acad. Aboensis, Math. et Phys.* **12**, (5), 1 (1939); *Chem. Abstr.*, **41**, 2413 (1947); (c) H. Aspelund, *Finska Kemistsamfundets Medd.*, **49**, 49 (1940); *Chem. Abstr.*, **35**, 2143 (1941).

(4) J. W. Clark-Lewis, *Chem. Revs.*, **58**, 63 (1958).

(5) (a) H. Najer, R. Giudicelli, E. Joannic-Voisinet, and M. Joannic, *Bull. soc. chim. France*, 1226 (1961); (b) H. Najer and R. Giudicelli, *Bull. soc. chim. France*, 1231 (1961).

(6) J. S. H. Davies, W. H. Hook, and F. Long, *J. Chem. Soc.*, 36 (1950).

(7) Difficulties in the application of chemical evidence to questions of tautomerism are discussed by S. J. Angyal and C. L. Angyal, *J. Chem. Soc.* 1461 (1952) with particular reference to 2-aminopyridine.

(8) G. A. Holmberg, *Acta Chem. Scand.*, **6**, 502 (1952).

(9) E. Schmidt and W. Carl, *Ann.*, **639**, 24 (1961).

(10) J. W. Cornforth, in "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, ed., John Wiley and Sons, Inc., New York, 1957, p. 298.

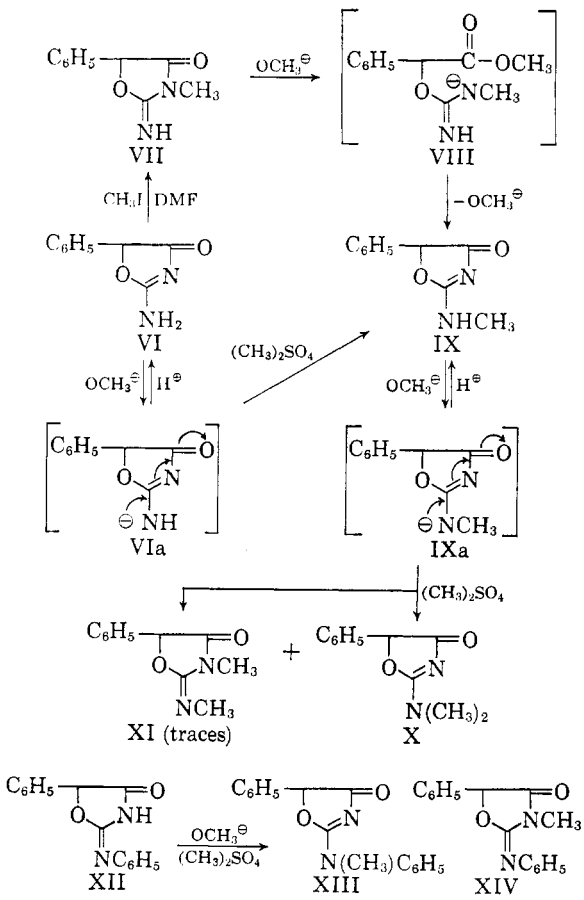
(11) J. M. Sprague and A. H. Land, in "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, ed., John Wiley and Sons, Inc., New York, 1957, p. 615.

(12) C. Lempert, *Chem. Revs.*, **59**, 667 (1959).

(13) C. F. Howell, N. Q. Quinones, and R. A. Hardy, Jr., *J. Org. Chem.*, **27**, 1679 (1962).

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

(15) E. C. Taylor, Jr., J. Wolinsky, and H. H. Lee, *J. Am. Chem. Soc.*, **76**, 1866 (1954) and references cited therein.



phenylchloroacetyl chloride under basic conditions as reported by Aspelund.[3b]

In contrast, methylation of the anion VIa with one equivalent of dimethyl sulfate gave a mixture of recovered VI (30%), the 2-monomethylamino compound IX (20%) and 2-dimethylamino-5-phenyl-2-oxazoline-4-one (X, 16%). Use of two equivalents of dimethyl sulfate in this reaction gave 29% of recovered VI, 9% of IX and 32% of X. The dimethylamino compound X was also prepared in 48% yield from the monomethyl compound *via* the anion IXa and was identical with samples prepared from dimethylcyanamide and ethyl mandelate or from VI and dimethylamine.[13] Traces of 3-methyl derivatives were obtained in the initial basic alkylation. 3-Methyl-2-methylimino-5-phenyl-4-oxazolidinone (XI, 1.4%) and 3-methyl-5-phenyl-2,4-oxazolidinedione (0.4%) were isolated chromatographically. The structure of XI was established by its preparation from ethyl mandelate and *N,N'*-dimethylcarbodiimide[16] (prepared *in situ*) and by acid hydrolysis. The 10:1 ratio of 2-dimethylamino derivative (X) to 3-methyl-2-methylimino isomer (XI) parallels the behavior observed in the reaction of ethyl iodide with sodium salt of 2-arylimino-4-thiazolidinones.[17]

On the basis of their study of infrared spectra, Najer and Giudicelli[5b] expressed the opinion that 5-phenyl-2-phenylimino-4-oxazolidinone (XII)[5b,18] 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 procedure[3c] from 1-methyl-3-phenylurea and α-chlorophenylacetyl chloride. Hydrolysis of XIV gave the 3-methyldione as reported.[3c] 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*-methylanilino-5-phenyl-2-oxazolin-4-one (XIII), yielded both 5-phenyl-2,4-oxazolidinedione and *N*-methylaniline (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 Brown[18a] 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 thiazole[15] and imidazole[18d] 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 predominantly the dimethylamino-2-oxazoline compound X appears to parallel the addition of a proton to IXa

(16) The preparation of 2-alkylimino-3-alkyl-4-oxazolidinones from *N,N'*-dialkylcarbodiimides and α-hydroxy esters in the presence of cuprous (ic) chloride has been described.[9] Our work, using sodium hydride as the condensing agent, was performed before we knew of these results. The reaction of *N,N'*-dimethylcarbodiimide with hydrazoic acid is described by D. F. Percival and R. M. Herbst, *J. Org. Chem.*, **22**, 925 (1957).

(17) Ref. 11, p. 619.

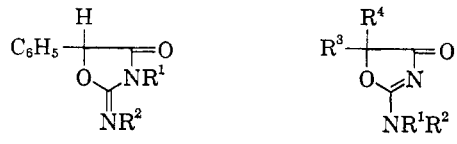
(18) (a) D. J. Brown, *Nature*, **189**, 828 (1961) and references cited therein; for other examples see: (b) E. C. Taylor and P. K. Loeffler, *J. Am. Chem. Soc.*, **82**, 3147 (1960); (c) M. Lempert-Sreter, D. Knausz, and K. Lempert, *Ber.*, **93**, 2290 (1960); (d) K. Lempert and M. Lempert-Sreter, *Ber.*, **94**, 796 (1961).

(19) W. M. Bruce, *J. Am. Chem. Soc.*, **26**, 419 (1904).

(20) R. A. Barnes, in "The Chemistry of Heterocyclic Compounds. Pyridine and Its Derivatives, Part 1," Vol. 1, A. Weissberger and E. Klingsberg, eds., Interscience Publishers, Inc., New York, 1960, p. 70.

TABLE I

ULTRAVIOLET SPECTRA (IN METHANOL, 10γ/ML.)



Type I Type II

Number	Structure: Type	R¹	R²	R³	R⁴	Ultraviolet Spectrum: λmax (mμ)	ε
VI[2a]	II	H	H	C_6H_5	H	217	23,400[a]
IX[3b]	II	CH_3	H	C_6H_5	H	221	27,800[a]
X[13]	II	CH_3	CH_3	C_6H_5	H	227	27,800[a]
VII	I	CH_3	H	...	...	207	20,400
XI	I	CH_3	CH_3	...	...	210	20,600
XV[13]	II	H	H	C_6H_5	CH_3	218	26,800
XVI[2b]	II	H	H	CH_3	CH_3	217	23,400
XVII[13]	II	CH_3	CH_3	CH_3	H	227	27,300
XVIII[5b,13]	II	$C_6H_5CH_2$	H	C_6H_5	H	226	30,700
XII[3b,5b,13]	I	H	C_6H_5	...	...	254	24,100[b]
XIV[3c]	I	CH_3	C_6H_5	...	...	254	12,800[c]
XIII	II	C_6H_5	CH_3	C_6H_5	H	233	22,600

[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. [b] The spectrum in 0.1 *N* hydrochloric acid has a maximum at 253 mμ but the intensity is diminished. In sodium methoxide the maximum is shifted to 264 mμ and the intensity is reduced [c] 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.

regenerating IX.[21] 2-Aminopyridine, whose tautomeric structure is well established,[7,22] undergoes analogous reactions.[20]

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 of 2-amino-5-phenyl-2-oxazolin-4-one (VI) to give IX and then X produces a gradual bathochromic shift from 217 to 227 mμ, an effect also observed in the methylation of aniline or 2-aminopyridine.[22,23] In contrast, methylation on the nuclear nitrogen atom to give VII causes a hypsochromic shift of 10 mμ from VI or 14 mμ from the isomer IX. A similar hypsochromic shift (17 mμ) is observed between X and XI where the position of the double bonds is unequivocal. These effects are to be expected if VI and IX have the 2-amino structure II (or V), but would be difficult to explain if VI and IX have the 2-imino structure I (or IV).

If the 5-phenyloxazole tautomer (V) were important, addition of a methyl group at C-5 to give 2-amino-5-methyl-5-phenyl-2-oxazolin-4-one (XV) would destroy the conjugated phenyloxazole system and cause a large hypsochromic shift. However, the spectra of XV and XVI are hardly altered from that of VI. Similarly, when the 5-phenyl moiety in X is replaced by a methyl group giving 2-dimethylamino-5-methyl-2-oxazolin-4-one (XVII) the spectrum is essentially unchanged. 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)[5b,13] absorbs at 226 mμ 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-aralkylamino-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 mμ 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[5b] which must have a markedly different chromophore. The isomeric 2-*N*-methylanilino compound (XIII), in which the anil chromophore is destroyed, absorbs at 233 mμ.

The complex bands in the double bond region of the infrared spectra of compounds uniquely derived

(21) For an example of this behavior in the imidazole series, see: (a) A. Grimison, J. H. Ridd, and B. V. Smith, *J. Chem. Soc.*, 1352, 1357 (1960) and (b) J. H. Ridd and B. V. Smith, *J. Chem. Soc.*, 1363 (1960).

(22) L. C. Anderson and N. V. Seeger, *J. Am. Chem. Soc.*, **71**, 340 (1949).

(23) A. Albert, "Heterocyclic Chemistry," Althore Press, London, 1959, pp. 325–327.

from tautomers I and II are very similar and somewhat unpredictable.[24] 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[25] 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[26] and with the equilibrium between methylenecyclopentane and 1-methylcyclopentene.[27] This one series provides both examples of and exceptions to the principle of parallelism of nucleophilicity and basicity[20,21b] 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.[20] 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 tautomeric 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[21b] 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[5] are substantially identical.

(25) J. P. Kokko, J. H. Goldstein, and L. Mandell, *J. Am. Chem. Soc.*, **83**, 2909 (1961).

(26) J. Pitha, J. Jonáš, J. Kovar, and K. Bláha, *Collection Czechoslov. Chem. Communs.* **26**, 834 (1961).

(27) A. C. Cope, D. Ambros, E. Ciganek, C. F. Howell, and Z. Jacura, *J. Am. Chem. Soc.*, **82**, 1750 (1960).

Experimental[28]

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),[1] 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 extracted 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 $C_{10}H_{10}N_2O_2$: C, 63.14; 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[2a] 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.,[29] 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-methylimino-5-phenyl-4-oxazolidinone (XI).—Similar hydrolysis of 0.4 g. of XI (see below) yielded 0.32 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

(28) Melting points are corrected.

(29) K. Iwaya, Y. Namikawa, S. Mitsuhashi, and K. Yoshida, *J. Pharm. Soc., Japan*, **69**, 248 (1949); *Chem. Abstr.*, **44**, 1958 (1950).

to give 1.5 g. (80%) of 2-methylamino-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-oxazolin-4-one (see below).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.14; H, 5.31; N, 14.73. Found: C, 62.82; H, 5.41; N, 14.64.

3-Methyl-2-methylimino-5-phenyl-4-oxazolidinone (XI).—*N,N'*-Dimethylthiourea, m.p. 52–56° (lit.,[30] m.p. 52–53°) was prepared by the method of Hofmann.[30] A mixture of 5 g. of *N,N'*-dimethylthiourea, 100 ml. of ether, 13.5 g. of yellow mercuric oxide, and a little water was stirred vigorously at 0–10° for 1 hr.[16] The ethereal solution was decanted and dried at 0° over calcium chloride for 15 min. This solution was filtered into a second solution, prepared from 0.4 g. of 50% sodium hydride (mineral oil suspension), 9 g. of ethyl mandelate, and 25 ml. of benzene. The mixture was heated under reflux for 1 hr., cooled, and filtered to remove 1.7 g. of sodium mandelate. The ethereal filtrate was extracted with 25 ml. of cold 10% hydrochloric acid and the lower layer was treated with excess potassium carbonate. The precipitated solid was collected and recrystallized from aqueous methanol to give 3.6 g. (35%) of 3-methyl-2-methylimino-5-phenyl-4-oxazolidinone (XI), m.p. 89.4–90.4°.

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.71. Found: C, 64.77; H, 6.24; N, 13.54.

The compound was very soluble in ether, could be sublimed *in vacuo*, and yielded 3-methyl-5-phenyl-2,4-oxazolidinedione upon hydrolysis (see above).

Methylation of 2-Amino-5-phenyl-2-oxazolin-4-one (VI). Basic Conditions.—2-Amino-5-phenyl-2-oxazolin-4-one (VI; 17.6 g., 0.1 mole) dissolved in 100 ml. of methanol containing the sodium methoxide prepared from 2.5 g. (0.11 g.-atom) of sodium was treated during 15 min. with 10 ml. (0.11 mole) of dimethyl sulfate. After 2 hr. of refluxing the solution was cooled and filtered from 4.22 g. of colorless solid (A). The filtrate was concentrated to dryness and distributed between 200 ml. each of methylene chloride and water. Filtration of these two phases gave 1.37 g. of solid (B). Both A and B were identified as starting material (32% recovery) by their infrared spectra. The methylene chloride solution was dried over sodium sulfate, filtered, and concentrated to give 14.6 g. of oil.

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[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 30 g. of Celite and packed on top of a column containing 300 g. of Celite and 150 ml. of lower phase. The column [430 ml. hold-back volume (h.b.v.)] was eluted with upper phase and absorption of the eluate at 222 mμ was 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 19.6 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 was reprecipitated 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-methylimino-5-phenyl-4-oxazolidinone (XI, m.p. 89–90°) prepared from ethyl mandelate and dimethylcarbodiimide (see above).

Anal. Found: C, 64.61; H, 6.23; 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.

(30) A. W. Hofmann, *J. prakt. Chem.*, **104** [I], 81 (1868).

(31) Celite is a trademark of Johns-Manville Corp. for a diatomaceous silica. Before use, it was washed successively with 6 *N* hydrochloric acid, water, 3A alcohol, and finally was dried in air.

The third fraction (fourth h.b.v.) gave 3.5 g. (16%) of recrystallized 2-dimethylamino-5-phenyl-2-oxazolin-4-one (X), m.p. 135.6–137.6°, which had an infrared spectrum identical with that of a sample prepared from ethyl mandelate and dimethylcyanamide.[18]

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. 122.6–124°, which was identical with an authentic sample.

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.14; H, 5.31; N, 14.73. Found: C, 63.19; H, 5.45; N, 14.64.

An authentic sample of IX was prepared in 30% yield (m.p. 117–119°) by the method of Aspelund[3b,3c] which involves cyclization of 1-(α-chlorophenylacetyl)-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 150 mg. (84%) of 5-phenyl-2,4-oxazolidinedione, m.p. 107–109° (lit.,[2a] m.p. 111°) after sublimation.

2-Dimethylamino-5-phenyl-2-oxazolin-4-one (X). A. From 2-Amino-5-phenyl-2-oxazolin-4-one (VI).—The procedure of the preceding experiment was followed except that twice the stated quantities of 2-amino-5-phenyl-2-oxazolin-4-one (VI) and methanol, and four times the amounts of sodium and dimethyl sulfate were used. The solution was heated under reflux 1 hr., cooled, and filtered from 6.73 g. (19.1%) of unchanged VI which was purified by washing with methanol and water and identified by the infrared spectrum. The methanolic filtrate was concentrated to dryness and the residue distributed between 200 ml. of methylene chloride and 200 ml. of 0.5 *M* sodium hydroxide.

The aqueous layer was acidified with 100 ml. of 2 *M* acetic acid, cooled, and filtered. The solid mixture of 2-amino-5-phenyl-2-oxazolin-4-one (VI) and its monomethyl derivative (IX) was separated by dissolving IX first in hot ethyl acetate (80 ml.) and then dissolving the soluble fraction a second time in methylene chloride (58 ml.). The recovery of VI was 3.6 g. (10%). The methylene chloride solution was concentrated and the residue recrystallized from ethyl acetate affording 3.53 g. (9.3%) of 2-methylamino-5-phenyl-2-oxazolin-4-one (IX), m.p. 122–124°, which had an infrared spectrum identical with that of a sample isolated by chromatography.

The methylene chloride solution from the original distribution was dried over sodium sulfate, filtered, and concentrated. Recrystallization of the residue from 90 ml. of ethyl acetate yielded 13.1 g. (32.3%) of 2-dimethylamino-5-phenyl-2-oxazolin-4-one (X), m.p. 132–137°, which had an infrared spectrum identical with that of the sample isolated by chromatography.

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.71. Found: C, 64.30; H, 6.08; N, 13.81.

B. From Isolated 2-Methylamino-5-phenyl-2-oxazolin-4-one (IX).—To a solution of 0.85 g. (5 mmoles) of 2-methylamino-5-phenyl-2-oxazolin-4-one (IX) in 5 ml. of absolute methanol which had been treated with 0.12 g. (5.5 mg.-atoms) of sodium was added 0.51 ml. (5.5 mmoles) of dimethyl sulfate. After the solution had been refluxed 1 hr., the product, 0.49 g. (48%) of 2-dimethylamino-5-phenyl-2-oxazolin-4-one (X, m.p. 133–137°), was isolated as in the preceding preparation.

2-Ethylmethylamino-5-phenyl-2-oxazolin-4-one.—2-Methylamino-5-phenyl-2-oxazolin-4-one (3.8 g., 0.02 mole) was treated with sodium ethoxide and diethyl sulfate as 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°.

The methylene chloride soluble fraction yielded 2.8 g. (64%) of 2-ethylmethylamino-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 $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.78. Found: C, 65.89, H, 6.62; N, 12.78.

2-*N*-Methylanilino-5-phenyl-2-oxazolin-4-one (XIII).—5-Phenyl-2-phenylimino-4-oxazolidinone (XII, 6.9 g.)[18] 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 mμ 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*-methylanilino-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 $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.31. 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. The acidic mother liquor was treated with 0.28 g. of sodium hydroxide and 0.11 g. of *p*-toluenesulfonyl chloride.[32] The solid obtained (99 mg.) was recrystallized from aqueous ethanol to yield 34 mg. (46%) of *N*-methyl-*p*-toluenesulfonanilide, m.p. 95–97° (lit.,[32] m.p. 94°). The infrared spectrum matched that of the crude material and that of an authentic sample; mixed m.p. 94–96°.

3-Methyl-5-phenyl-2-phenylimino-4-oxazolidinone (XIV).—A solution of 13 g. of α-chlorophenylacetyl chloride and 10.3 g. of 1-methyl-3-phenylurea in 40 ml. of benzene was heated under reflux for 5 hr. exactly as described by Aspelund[36] and yielded 13.1 g. (71%) of recrystallized 3-methyl-5-phenyl-2-phenylimino-4-oxazolidinone (XIV), m.p. 90–92° (lit.,[36] m.p. 90–91°).

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.31; N, 10.52. 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.[36] The infrared spectrum of this sample was identical with that of authentic material.

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

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5-Aryl-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one 4-oxides were shown to rearrange to 3-acyloxy-5-phenyl-1,3-dihydro-2*H*-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-2*H*-1,4-benzodiazepine-2-one rearranged to 7-chloro-5-phenyl-4,5-dihydro-2*H*-1,4-benzodiazepine-2,3(1*H*)-dione and 6-chloro-4-phenyl-3,4-dihydro-2-quinazolinecarboxylic acid.

The action of acetic anhydride upon 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one 4-oxide[2] (I) has led to the formation of 3-acetoxy-7-chloro-5-phenyl-1,3-dihydro-2*H*-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.[3] 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 carbinolamines as intermediates in the Polonovski reaction.[4] As an example of this reaction, *N*,*N*-dimethylaniline *N*-oxide is converted by acetic anhydride into *N*-methylacetanilide with *N*-acetoxymethyl-*N*-methylaniline 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-2*H*-1,4-benzodiazepine-2-one (III). This product was benzoylated in pyridine solution to afford 3-benzoxy-7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one (IV), identical with material prepared by treating I with benzoyl

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