[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLLEGE OF PHARMACY, UNIVERSITY OF ILLINOIS]

Infrared Spectra and Structure of Aminoisoxazolones[1]

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From their infrared spectra, structures are assigned to the isomeric aminoisoxazolones obtained from the reaction of hydroxylamine with α-cyano esters,[2] as well as their corresponding acyl- and arenesulfonyl derivatives.

Under different experimental conditions, the reaction of an α-cyano ester, $RCH(CN)CO_2C_2H_5$, with hydroxylamine afforded three different crystalline solids: two isomers, arbitrarily referred to as A and B, and the α-amidoxime hydroxamic acid.[2] Although A and B had the correct analysis for an α-cyano hydroxamic acid, RCH(CN)CO—NHOH or $RCH(CN)CO—ONH_2$, these structures could not accommodate their chemical behavior[2] or their infrared spectra. This was most apparent when comparing the carbonyl region (1650–1800 cm.$^{-1}$) of the infrared spectra of isomers A and B with those of simple hydroxamic acids. Characteristic carbonyl stretching frequencies of *O*- and *N*-acyl as well as *O*,*N*-diacylhydroxylamines have been reported[3–8] and these data are used in our study.[9] The carbonyl stretching frequencies of hydroxamic acids are all marked by one intense band, the one for RCONHOH appearing near 1660, for $RCO—ONH_2$ near 1740 cm.$^{-1}$ For example, $CH_3CONHOH$ and $C_6H_5CONHOH$ absorb at 1680 and 1663, $CH_3CO—ONH_2$ and $C_6H_5CO—ONH_2$ at 1757 and 1730 cm.$^{-1}$, respectively. Thus, aliphatic α-cyano hydroxamic acids, RCH(CN)CONHOH or $RCH(CN)CO—ONH_2$, would be expected to exhibit one *strong* carbonyl absorption band near either 1660 or 1760 cm.$^{-1}$ But examination of their infrared spectra, particularly in the 1500–1800- and 3000–3500-cm.$^{-1}$ regions, led us to postulate the aminoisoxazolone structures for isomers A and B and their derivatives. We were further aided in this study by the publication of spectral data of a number of isoxazoles and isoxazolones.[10–15]

Tables I and II record the bands of isomers A and B and their derivatives in the crystalline state, while Table III lists the frequencies only in the 3000–3500- and 1600–1800-cm.$^{-1}$ regions in the crystalline state and chloroform solution. Since only a few of the compounds were soluble in the conventional spectroscopic solvents, all of the compounds were originally examined in the crystalline state in potassium bromide discs. Each set of related compounds presented a very characteristic pattern of absorption bands in the 1500–1800- as well as the 3000–3500-cm.$^{-1}$ regions. However, whenever possible, the infrared spectra of representative members of each set were also examined in chloroform solution to augment the data obtained in the crystalline state. This was particularly helpful in determining the nature of NH and NH_2 group; the nature of hydrogen bonding in the molecule and these complementary studies allowed us to determine the nature of the favored molecular species. Remarkably enough, the over-all pattern of absorption in the 1500–1800-cm.$^{-1}$ region was the same in the solution and crystalline state spectra except for the expected frequency shifts due to hydrogen bonding. This has led us to conclude that each set of these compounds exists primarily as one molecular species in chloroform solution and in the solid state. This postulate was essential as each isomer and its derivatives (acetyl, benzoyl, and arenesulfonyl) can be considered in a large number of tautomeric and resonance forms. Structure determination of the derivatives was further complicated as the attachment of the acyl or arenesulfonyl groups to the parent isomer introduces additional problems of position or functional isomerism.

In the ensuing discussion, the series of compounds derived from isomer B is presented first, as their

(1) This investigation was carried out under the auspices of Grant CY-4661 from the National Cancer Institute of the National Institute of Health, United States Public Health Service.

(2) L. Bauer and C. N. V. Nambury, *J. Org. Chem.*, **26**, 4917 (1961).

(3) F. Mathis, *Compt. rend.*, **232**, 505 (1951); *Bull. soc. chim. France*, **5**, 9D (1953).

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(6) L. A. Carpino, C. A. Giza, and B. A. Carpino, *J. Am. Chem. Soc.*, **81**, 955 (1959).

(7) G. Zinner, *Arch. Pharm.*, **293**, 657 (1960).

(8) O. Exner and M. Horák, *Collection Czechoslov. Chem. Communs.*, **24**, 2992 (1959); O. Exner and B. Kakáč, *Collection Czechoslov. Chem. Communs.*, **25**, 2530 (1960).

(9) In referring to these and other data, due cognizance is taken of the state of the compound when its spectrum was recorded (solution, mull, film, or potassium bromide disc). Furthermore a C=O group attached to an aromatic nucleus shifts this absorption to a lower frequency by about 10–20 wave numbers.

(10) A. R. Katritzky and A. J. Boulton, *Spectrochim. Acta*, **17**, 238 (1961).

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(12) A. J. Boulton and A. R. Katritzky, *Tetrahedron*, **12**, 51(1961).

(13) P. Bravo, G. Gaudiano, A. Quilico, and A. Ricca, *Gazz. chim. ital.*, **91**, 47 (1961).

(14) L. Almirante, A. Bianchi, and V. Zamboni, *Ann. di chimica*, **46**, 623 (1956).

(15) S. V. Sokolov and I. Ya. Postovskii, *J. Gen. Chem. USSR, Eng. Transl.*, **30**, 621 (1960).

TABLE I

INFRARED ABSORPTION BANDS (CM.$^{-1}$) OF 5-AMINO-3-ISOXAZOLONES, ISOMER A, AND DERIVATIVES

	Parent Compounds, VII				Acetyl Derivatives, X			Benzoyl Derivatives, XI				Arenesulfonyl Derivatives, XII (a) Ar = C_6H_5, (b) Ar = p-$CH_3C_6H_4$			
R	Hydrogen	*sec*-Butyl	Cyclohexyl	Benzyl	*sec*-Butyl	Cyclohexyl	Benzyl	Hydrogen	*sec*-Butyl	Cyclohexyl	Benzyl	Hydrogen (a)	*sec*-Butyl (b)	Cyclohexyl (a)	Benzyl (b)
	3430 m	3440 m	3470 m	3455 m								3450 m	3450 sh	3450 sh	3440 m
	3300 sh	3340 m			3380 m	3360 m-b	3350 m-b	3360 m-b	3350 sh	3330 m	3330 m	3390 m	3380 m-b	3360 m-b	3360 sh
			3280 m	3255 m	3290 m				3290 m-b						
	3130 vs	3180 m	3150 m	3100 s	3180 m	3180 m	3150 m	3150 m	3175 m	3180 m	3150 m	3160 m	3170 m	3160 m	3150 m
		2970 m	2920 m		2970 m	2930 m			2970 m	2930 m			2970 m	2930 m	
		2880 sh	2850 m		2880 sh	2850 m			2880 vvw	2850 m			2880 sh	2850 m	
	2800 sh	2800 vvw	2800 sh	2800 vvw											
								1736 m-w	1731 m-w	1727 m-w	1729 m-w	1739 m	1733 m	1737 m-b	1736 m-b
					1718 s	1713 m-b	1713 m								
		1675 w	1668 sh	1671 sh						1666 sh	1675 sh				
	1636 vs-b	1618 s	1621 vs-b	1633 vs-b	1628 vs-b	1634 vs-b	1648 vs-b	1658 vs-b	1636 vs-b	1638 vs-b	1647 vs-b	1656 vs-b	1636 vs-b	1638 vs-b	1636 vs-b
	1574 vs-b	1584 vs-b	1572 vs-b	1576 vs-b	1596 m	1598 m	1594 m	1601 m	1591 m	1593 s	1590 s	1590 m	1589 s	1591 s	1589 s
		1482 w	1511 w								1497 vvw				1496 vvw
			1472 sh	1471 m			1471 m-b				1464 m		1460 sh		1464 m
	1450 m	1452 m	1454 m		1451 m	1451 m		1453 w	1448 m	1450 m	1449 sh	1453 vw	1442 m	1450 m	
	1402 vw-b			1418 vvw				1423 m			1423 vvw	1415 sh			
					1377 m	1377 m	1376 m		1378 vvw			1395 m-b	1381 m	1384 m	1387 m
			1309 vvw		1309 m-b	1304 m-b	1308 sh	1317 m-b	1319 m	1305 m-b	1316 sh		1300 vvw	1317 vvw	1304 vw-b
							1278 m-b		1291 m		1278 sh				
					1274 sh	1261 sh		1265 vw	1286 m	1276 sh	1267 m				
									1271 sh						
	1231 m	1250 vw	1234 w	1234 w-b					1249 sh	1247 sh	1243 sh				
		1222 vw													
			1195 vvw	1200 sh	1185 vvw			1186 m-b	1185 w	1184 w-b		1199 m	1192 m	1192 s	1194 m
		1174 vvw				1172 vvw					1159 m-b	1173 m	1179 m	1181 sh	1181 s
	1096 vw			1115 vvw	1098 vw	1095 vw	1089 vvw	1082 w-b	1110 w	1115 w-b	1095 vvw	1093 w	1088 w	1090 vw	1089 w-b
	1044 m	1043 w	1052 w-b	1059 m	1037 m	1041 vw-b	1025 m-b	1031 vvw	1039 m	1043 vw	1037 m		1037 vw	1052 w-b	1042 m-b
									1021 m						
	996 m		1015 vvw		994 m	998 m		1001 m	1004 m	1006 m	999 vvw	1012 vvw			
			974 w	967 m								989 vvw	985 w	980 m-b	

TABLE I (*Continued*)

R	Parent Compounds, VII				Acetyl Derivatives, X			Benzoyl Derivatives, XI				Arenesulfonyl Derivatives, XII (a) Ar = C_6H_5, (b) Ar = p-$CH_3C_6H_4$			
	Hydrogen	*sec*-Butyl	Cyclohexyl	Benzyl	*sec*-Butyl	Cyclohexyl	Benzyl	Hydrogen	*sec*-Butyl	Cyclohexyl	Benzyl	Hydrogen (a)	*sec*-Butyl (b)	Cyclohexyl (a)	Benzyl (b)
	940 m	951 w		922 vvw			936 vw	934 vvw	943 vvw	960 m	924 m	931 m	951 m		927 vvw
			890 vw	876 vw		890 vvw		907 w		893 m	893 vw			894 vw	895 vvw
			856 vvw							866 vvw			854 vw	863 vvw	
			820 vvw	784 vvw	835 vvw 800 vw			792 vw		800 m	792 vvw		812 w	831 vw	819 m
	782 m–b	772 m–b	777 m–b	754 vvw	764 w	760 vw–b		763 m	785 w–b	760 vw		782 m–b	768 w	774 m	762 vvw
	740 m			726 m			730 m		724 m	720 w–b	720 m	730 vw		732 m	714 m

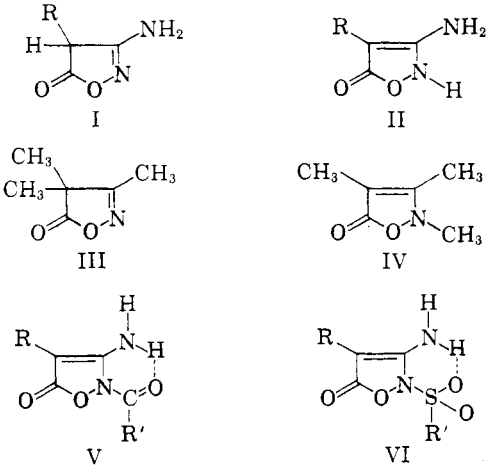
structures are more easily discernible. For each series of compounds there is first a general discussion on structural features embodied by all compounds, followed by a more detailed discussion of the proposed preferred structures of each set of compounds.

Structure of 3-Amino-5-isoxazolones, isomer B, and derivatives (chart I). General structural features. To determine the nature of the amino function at position 3, be it NH_2 or =NH, the 3000–3500-cm.$^{-1}$ region of the spectra of isomer B and its derivatives was examined both in the crystalline state and in chloroform solution. In the solid state, each compound in this series showed two to three medium diffuse bands between 3150–3500 cm.$^{-1}$, a pattern characteristic of hydrogen-bonded NH groups. These bands changed to two *sharp* medium bands near 3400 and 3500 cm.$^{-1}$ in chloroform solution, characteristic of the nonbonded asymmetric and symmetric NH_2 stretching modes, respectively. Furthermore, the positions and relative intensities of these two bands were not altered on dilution of the chloroform solution, thus showing that the bands do not arise from intermolecularly hydrogen-bonded species in solution. Since these two sharp bands and their inherent characteristics were shown by the solution spectra of the parent compound (isomer B) and its acyl and arenesulfonyl derivatives, an NH_2 group was assigned to each of these structures.

In the crystalline state the 1500–1800-cm.$^{-1}$ region presented a number of bands which were common to all of the compounds of this series. The ring carbonyl band appeared as a medium to strong band between 1740–1780 cm.$^{-1}$ Two other notable absorptions were the very strong and broad band between 1616 and 1653 and the medium one between 1573 and 1605 cm.$^{-1}$ These represent the NH_2 scissor deformation and the ring vibrations involving *both* the C=C and C=N vibration of the ring. At present, without deuteration studies it is impossible to divorce the NH_2 scissor deformation from the ring modes.

CHART I

(Isomer B and Derivatives)



In a thorough and detailed investigation on alkyl and aryl substituted 5-isoxazolones, Boulton and Katritzky[11] assigned the following bands to the ring vibrations of 2*H*-5-isoxazolones (type IV): 1463–1473 m; 1359–1377 m; 1264–1296; m 1140–1197 m; and 1036–1065 m. These authors also suggested that the following bands are due to the 4*H*-5-isoxazolones (type III) ring: 1315–1375 w–m; 1151–1196 m–s; 1001–1050 w–m; 940–952 w; and 872–900 m–s. In all of our 5-isoxazolones we observed at least one band in the following regions, within fifty wave numbers: 1440–1470 m; 1340–1390 w–s; 1145–1190 w–s; 1025–1065 vvw–s; 955–1000 vw–m; and 850–900 vvw–m. Since there is considerable agreement of these regions with those suggested[11] for the 5-isoxazolone ring vibrations, the bands in our compounds may be assigned in that way, with the reservation that our ring substituents are considerably different.

(*a*) *Parent compounds.* Isomer B (R is *sec*-butyl, cyclohexyl, and benzyl) is best represented as an

TABLE II

INFRARED ABSORPTION BANDS (CM.$^{-1}$) OF 3-AMINO-5-ISOXAZOLONES, ISOMER B, AND DERIVATIVES

	Parent Compounds, I			Acetyl Derivatives, V (R′ = CH_3)			Benzoyl Derivatives, V (R′ = C_6H_5)			Arenesulfonyl Derivatives, VI (R′ = p-$CH_3C_6H_4$)		
R	*sec*-Butyl	Cyclohexyl	Benzyl	*sec*-Butyl	Cyclohexyl	Benzyl	*sec*-Butyl	Cyclohexyl	Benzyl	*sec*-Butyl	Cyclohexyl	Benzyl
	3420 s	3430 m	3440 m	3420 m	3440 m	3430 m	3450 m	3450 m	3445 m	3440 m	3465 m	3480 m
											3390 sh	3400 sh
	3335 m	3350 m	3360 m			3320 m	3310 m-b	3330 m	3320 m-b	3340 m	3320 m-b	3310 m-b
		3220 m	3230 m	3280 m	3245 m-b			3240 m		3220 sh		
	3190 m							3180 m			3190 m	3160 m
	2970 m			2970 m			2970 w			2970 m		
		2940 m	2930 vw		2940 m		2940 w	2940 m			2940 m	2930 vvw
	2880 vvw	2870 m		2880 vvw	2870 m		2880 sh	2870 m		2880 vvw	2870 w	
	1768 vs	1769 s	1778 s									
										1758 m-b	1751 m-b	1758 s-b
				1740 m	1742 m	1752 m	1749 m-b	1753 s	1746 m-b	1733 m		
				1707 vs	1706 vs	1695 s						
							1679 s	1675 vs	1685 vs			
	1642 vs-b	1644 vs-b	1653 vs-b	1626 vs-b	1616 vs-b	1622 vs-b	1628 vs-b	1634 vs-b	1627 vs-b	1644 vs-b	1646 vs-b	1646 vs-b
	1595 m	1594 m	1596 m	1575 m	1573 m	1580 m	1581 m	1584 m	1585 m	1603 m	1598 m	1605 m
			1498 vw						1497 vw			1496 m
	1467 m	1471 m	1478 m		1471 m	1470 m				1466 m		
		1453 m	1457 m	1459 m-b	1451 w-b		1453 m	1451 m	1453 m-b	1440 m-b	1446 sh	1454 sh
												1446 m
					1393 m	1423 m			1434 vw		1430 m	1428 m
	1389 vw	1379 vvw		1385 m	1374 vw	1382 s	1381 m-b	1387 s	1376 vs-b	1381 m	1380 m	1379 s
			1343 w-b	1338 m	1349 m	1354 m	1352 m	1362 s				
		1321 w		1298 vvw		1334 m	1301 vvw		1319 vvw	1309 vw		1312 w
		1313 w										
				1280 vvw	1284 m		1283 vvw	1287 m				
		1259 vw	1266 m	1251 vw	1246 m		1249 vvw	1248 vw	1243 w			
	1232 m	1237 vw	1226 m			1232 w						1231 vw
	1191 m	1199 m		1199 vvw			1196 vvw	1189 vw	1189 vvw	1194 m	1193 m	1194 s
			1182 m							1181 m	1177 s	1182 s
	1164 m	1167 w	1121 vw-b	1152 w-b	1156 w	1161 w	1148 vvw	1145 w	1167 vvw			
						1131 vvw						
	1121 w-b	1113 vvw-b	1081 vw	1085 vw-b			1083 vvw		1073 vw	1089 w	1089 w	1088 m

TABLE II (*continued*)

R	Parent Compounds, I			Acetyl Derivatives, V (R′ = CH_3)			Benzoyl Derivatives, V (R′ = C_6H_5)			Arenesulfonyl Derivatives, V (R′ = *p*-$CH_3C_6H_4$)		
	sec-Butyl	Cyclohexyl	Benzyl	*sec*-Butyl	Cyclohexyl	Benzyl	*sec*-Butyl	Cyclohexyl	Benzyl	*sec*-Butyl	Cyclohexyl	Benzyl
	1039 vvw	1064 m–w	1052 m	1027 vvw	1037 w	1034 m	1031 vvw	1048 w 1032 w	1033 m	1025 vw	1043 w–b	1045 sh
	1013 vw	994 w	985 vw	986 w		1018 m	985 vw		999 w	983 m		1020 s
	975 w–b			964 m	964 m	973 m		979 m			978 m	968 vw–b
		926 w	927 vw	948 m		924 m	925 m	936 m 923 m	947 m 919 m	955 m		
	903 m	912 m	904 m									
	881 vw	898 m	883 m		896 m	880 m		892 vw	882 m		895 w	898 vw
		847 vvw		860 vvw			851 vvw	852 vvw		856 vw		
			783 vvw	804 vvw	826 w	828 vw	795 vvw	821 vvw 792 vw	788 vw	815 m	818 m	813 m 792 m
				764 w	760 m	773 w 743 m	762 vw	758 m 750 m	750 m	775 m	775 w	763 s
			715 m			734 m	710 m	707 m	723 m 710 m			720 s

3-amino-5-isoxazolone, I. Since the *sec*-butyl derivative (I; R = *sec*-butyl) was the only one which was sparingly soluble in chloroform, its specific structure will be discussed both in solution and the crystalline state. However, it is evident from the bands in the infrared spectra from Table II that the other parent compounds exist in a similar molecular arrangement. The presence of an amino group in these compounds has been established above. The observed carbonyl frequency at 1793 cm.$^{-1}$ (in chloroform) and at 1768 cm.$^{-1}$ (solid) is consistent with that reported for β,γ-unsaturated γ-lactones (1740–1800 cm.$^{-1}$) in solution.[16] The shift of the carbonyl frequency is explained if one assumes that this compound in the solid state is intermolecularly hydrogen bonded. The carbonyl absorptions of an α,β- and an β,γ-unsaturated isoxazolones have been reported.[11] These are III and IV and they absorb at 1793 and 1725 cm.$^{-1}$ (chloroform), respectively. By comparison with these, isomer B exists as the β,γ-unsaturated structure, I, in preference to the α,β-unsaturated form, II. Furthermore, the effect of substituting an amino for a methyl group at position 3 in structure IV would most certainly shift the carbonyl frequency even further towards 1700 cm.$^{-1}$ Because of the strong absorption in the carbonyl region, tautomeric forms of I bearing an hydroxyl group at position 5 are eliminated.

(16) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," J. Wiley and Sons, Inc., New York, 2nd ed., 1958, p. 186.

(*b*) *Acetyl and benzoyl derivatives.* Structure V is proposed for these compounds, and the following evidence is offered in support for this structure. These substances possess an NH_2 group (*vide supra*), and the carbonyl region of these acyl derivatives V, invariably shows two bands, not appreciably different in the crystalline state or chloroform solution. The band at higher frequency, 1740–1750 cm.$^{-1}$, is assigned to the ring carbonyl vibration. For example, 2-acetyl-3-amino-4-benzyl-5-isoxazolone (V; R = benzyl; R′ = methyl) in the crystalline state or chloroform solution absorbs at 1752 and 1759 cm.$^{-1}$, respectively. The shift of the ring carbonyl frequency from 1770–1780 cm.$^{-1}$ in I to 1740–1750 in V (in the crystalline state) is attributed to the presence of the β,γ-unsaturated C=O in I, the α,β-unsaturated C=O in V.

The second carbonyl group is attributed to the acyl side chain. The acetyl derivatives (V; R′ = CH_3) exhibit this band in the crystalline state as a strong band between 1695–1707 cm.$^{-1}$, while that of the benzoyl (V; R′ = C_6H_5) derivatives appears between 1675 and 1685 cm.$^{-1}$ This shift of twenty to thirty wave numbers is expected as R′ in V is changed from methyl to phenyl group.[9] As the frequency of that band is not appreciably altered in

TABLE III

COMPARISON OF FREQUENCIES IN SOLID AND CHLOROFORM SOLUTIONS[a]

Compound	3000–3500 Cm.$^{-1}$ Solid	3000–3500 Cm.$^{-1}$ Solution	1600–1800 Cm.$^{-1}$ Solid	1600–1800 Cm.$^{-1}$ Solution
I (R = *sec*-Butyl)	3420 s 3335 m 3190 m	3510 w 3410 w	1768 vs 1642 vs–b	1793 vs 1631 vs
V (R = Benzyl; R′ = CH_3)	3430 m 3320 m	3490 m 3370 m	1752 m 1695 s 1622 vs–b	1759 m 1703 vs 1643 vs
V (R = *sec*-Butyl; R′ = C_6H_5)	3450 m 3310 m–b	3510 m 3365 m	1749 m–b 1679 s 1628 vs–b	1754 m–b 1671 vs 1635 vs
VI (R = *sec*-Butyl; R′ = *p*-$CH_3C_6H_4$)	3440 m 3340 m 3220 sh	3510 m 3400 m	1758 m–b 1733 m 1644 vs–b	1763 m–b 1650 vs
VI (R = Cyclohexyl; R′ = *p*-$CH_3C_6H_4$)	3465 m 3390 sh 3320 m–b 3190 m	3500 m 3390 m	1751 m–b 1646 vs–b	1760 m–b 1650 vs
X (R = *sec*-Butyl)	3380 m 3290 m 3180 m	3510 w 3410 w 3310 vw 3165 vw	1718 s 1628 vs–b	1718 m–b 1649 s
XI (R = *sec*-Butyl)	3350 sh 3290 m–b 3175 m	3500 w 3400 w 3320 w–b 3170 vw–b	1731 m–w 1636 vs–b	1735 m 1686 sh 1649 vs–b
XII (R = *sec*-Butyl; R′ = *p*-$CH_3C_6H_4$)	3450 sh 3380 m–b 3170 m	3500 w 3410 m 3350 m–b 3300 sh 3150 m	1733 m 1636 vs–b	1735 m 1642 vs–b

[a] The concentration of the solutions are not listed as most of the compounds are so sparingly soluble that they were prepared by filtering a saturated solution.

chloroform solution or the crystalline state, these compounds may exist in the nonbonded or intramolecularly hydrogen-bonded form of V.

(*c*) *Arenesulfonyl derivatives.* These are depicted by structure VI on the following grounds. These derivatives are insoluble in cold 5% aqueous sodium hydroxide solution, thus eliminating possibility of an —$NHSO_2R'$ group in the molecule and the presence of an NH_2 group in these compounds was established above.

The ring carbonyl frequency, 1751 to 1758 cm.$^{-1}$ stands out clearly as a medium band. By comparison, this band in 3-(*p*-aminobenzenesulfonamido)-5-methylisoxazole[17] is conspicuously absent.

Other noteworthy bands for compounds of type VI are those due to sulfonamido[18] and these appear between 1088 and 1091, 1177 to 1182, and 1379 to 1381 cm.$^{-1}$ Similar bands were found in the spectra (potassium bromide) of 3-*p*-aminobenzenesulfonamido-5-methylisoxazole[17] (1093, 1157, and 1367 cm.$^{-1}$) and 3,4-dimethyl-5-*p*-aminobenzenesulfonamidoisoxazole[17] (1093, 1164, and 1345 cm.$^{-1}$).

Structure of 5-Amino-3-isoxazolones, isomer A, and derivatives (Chart II). General structural features. These sets of compounds presented a more difficult problem in structure assignment than isomer B. In general, the parent compounds were not sufficiently soluble in chloroform to examine the solution spectra, particularly the NH stretching region. Three derivatives of the *sec*-butyl series, *viz.*, the acetyl, benzoyl, and *p*-toluenesulfonyl derivatives lent themselves for a study of their solution spectra. In each case the NH region presented the two sharp bands near 3500 and 3400 cm.$^{-1}$ so characteristic of the NH_2 asymmetric and symmetric stretching modes; but there were also always present at least two medium diffuse bands near 3320 and 3150 cm.$^{-1}$ On successive dilutions of the chloroform solutions, the relative intensities of the bands between 3350 and 3150 diminished with respect to the other bands in the spectrum, and hence we concluded that these bands resulted from intermolecular-bonded species in solution. Unlike the corresponding derivatives of isomer B, V and VI, intramolecular hydrogen bonding in the acyl and arenesulfonyl derivatives of A is not possible. Furthermore, since aminoisoxazoles prefer to be in the amino, rather than the imino form,[12] all compounds in this series were assigned an NH_2 group.

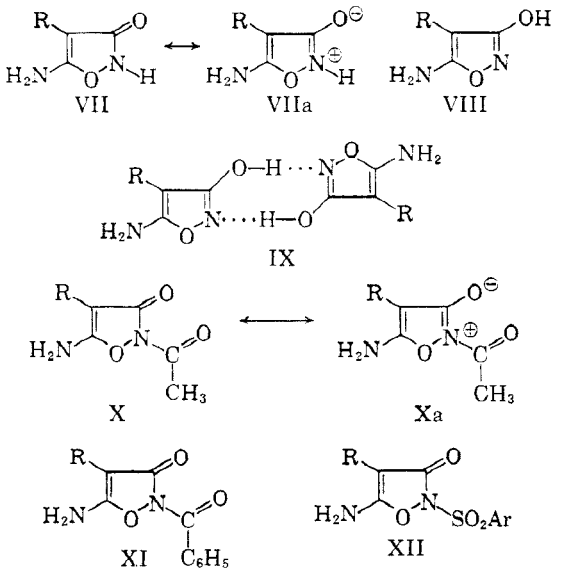
A further anomaly exists in this series; the parent compounds and acetyl derivatives do not show ring carbonyl absorption, (solid or solution), while the benzoyl and arenesulfonyl derivatives exhibit this carbonyl vibration as a medium to weak band in the vicinity of 1727 to 1739 cm.$^{-1}$ A more detailed discussion of these phenomena appears be-

(17) This compound was generously donated by Dr. K. Enoki, Research Lab., Nippon Soda Co., Ltd., Takaoka, Japan, and is described in *J. Pharm. Soc. Japan*, **81**, 120 (1961).

(18) Ref. 16, p. 363.

CHART II

ISOMER A AND DERIVATIVES



low. However the two bands between 1618 to 1656 (very strong and broad) and 1576 and 1601 (medium to very strong) are present in all compounds, quite remarkably in the same range as the two corresponding bands in the isomer B series. These two bands are associated with NH_2 scissor and C=C, C=N ring vibrations. No other bands were found to be present in all of the compounds over a narrow enough range to warrant their inclusion here at this stage.

(*a*) *Parent compounds.* The unique aspect of the structure of the parent compounds (VII; R is hydrogen, *sec*-butyl, cyclohexyl, and benzyl) in the crystalline state is the lack of a ring carbonyl group as evidenced by their infrared spectra. To explain this, it is assumed that VII is better represented by the fully aromatic resonance hybrid, VIIa. Furthermore, in the spectra of these parent compounds, there appear a weak and broad band near 2800 cm.$^{-1}$ which can be assigned to the $=NH^+$ stretching vibration. This band is quite prominent in the spectrum of 5-phenyl-3-isoxazolone[13] which also lacks carbonyl absorption,[19] and has been postulated to exist as a chelate of type IX. In considering the structure of isomer A in the solid state, one can easily consider it as the extreme form of the chelate IX. If one considers form VIIa for the structure of isomer A in the solid state, one can easily see that it represents the chelate in which the proton is more closely associated with the ring nitrogen. This postulate then tends to eliminate the aminoisoxazolol structure VIII which can be regarded as the other extreme form of the chelate IX in which the proton is attached to the oxygen function.

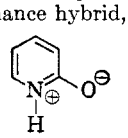
(*b*) *Acetyl and benzoyl derivatives.* The postulate that these substances possess an NH_2 group (*vide supra*) is substantiated by some chemical evidence. The benzoyl derivative of 5-amino-4-benzyl-3-isoxazolone (XI; R = benzyl) when treated with either hot concentrated ammonium hydroxide solution or a hot aqueous solution of benzylamine regenerates the parent compound and benzamide or *N*-benzylbenzamide, respectively. To explain this facile displacement of a benzoyl group, it is postulated that this group is attached to the ring nitrogen atom at position 2 rather than the exocyclic nitrogen atom at position 5. This reaction is also analogous to the ready cleavage of imides by amines to two amides. Hence the acyl derivatives are assigned structures X and XI.

The absence of the ring carbonyl group in the acetyl derivatives, X, suggests that the fully aromatic resonance hybrid Xa may represent these compounds more adequately. However, the more strongly electron-attracting benzoyl group imparts partial double bond character to the ring C=O group and a medium to weak band appears between 1727 and 1736 cm.$^{-1}$. Since the arenesulfonyl derivatives also absorb as a medium band in this frequency range, 1733–1739 cm.$^{-1}$, both series of compounds must possess a ring carbonyl group. This band appears unchanged in the solution spectra (Table III). But since the C=O absorption band is weaker than anticipated, it is therefore assumed that the resonance hybrids of type Xa are really the major contributors to the structure of the acetyl derivatives. In other words, in assigning structure Xa and XI to the acetyl and benzoyl derivatives respectively we recognize that the C—O bond at position 3 possesses more single bond character in Xa, more double bond character in XI.

The side chain C=O band in the acetyl derivatives appears between 1713 and 1718, that of the benzoyl derivatives some 10–20 wave numbers lower,[9] appearing either as a shoulder or hidden by the next very strong broad band at 1636–1658 cm.$^{-1}$

(*c*) *Arenesulfonyl derivatives.* As mentioned in (b), these compounds show ring carbonyl absorption (1733–1739 cm.$^{-1}$) and are therefore best pictured as XII. The bands characteristic of the sulfonamido group are also evident (see corresponding compounds for isomer B). These derivatives readily dissolve in dilute sodium hydroxide solution to form an orange-red solution, but acidification does not regenerate the original compounds. The red solution decolorizes on standing and new products

(19) This problem of —CO—NH— and —C(OH)=N— tautomerism is a common one in aromatic heterocyclic aromatic lactams. The most frequently debated simple example is that of α-pyridone and 2-pyridol. R. M. Acheson in *An Introduction to the Chemistry of Heterocyclic Compounds*, Interscience Publishers Ltd., London, 1960, p. 187, concludes that this compound is best envisioned as the fully aromatic resonance hybrid,



are formed. These reactions are currently being investigated.

EXPERIMENTAL

All spectra were obtained using a Beckman IR-4 spectrophotometer, sodium chloride optics. Band frequencies were checked against known frequencies of polystyrene (film). As solids or saturated solutions of samples were used to obtain the spectra, the bands were classified according to an arbitrary intensity scale (in per cent absorption): 10–15, very, very weak (vvw); 15–20, very weak (vw); 20–80, medium (m); 80–90, strong (s); and above 90, very strong (vs). Spectra of the crystalline solids were obtained using the standard potassium bromide disc techniques using two different concentrations of sample. The above intensities refer to a concentration of about 1 mmole/g. of potassium bromide. The solution spectra were obtained using chloroform as the solvent. Solutions were made at room temperature and excess sample removed by filtration.

Ammonolysis of 2-benzoyl-4-benzyl-5-amino-3-isoxazolone XI; *R = benzyl.* (*a*) *With ammonia.* The benzoyl derivative (1.0 g.) was heated on the steam bath with concentrated ammonium hydroxide solution (10 ml.) until a solution was obtained. Extraction of the hot solution with chloroform (2–15-ml. portions) afforded benzamide, (0.17 g.) which crystallized from water, m.p. and mixed m.p. 127°. Acidification of the aqueous layer with dilute hydrochloric acid yielded the parent compound, (VII; R = benzyl) (0.28 g., 43%), m.p. and mixed m.p. 147°.

(*b*) *With benzylamine.* Similarly, this benzoyl derivative (730 mg.) was heated first at 50° for 20 min., then at 90° for 5 min. with an aqueous solution of benzylamine (0.27 g. in 12 ml.). On cooling a solid separated which was extracted with boiling benzene (25 ml.). The benzene-insoluble material (60 mg.) proved to be starting material. Crystallization of the benzene extract afforded 200 mg. of the parent compound (VII; R = benzyl). Concentration of the benzene filtrate and dilution with petroleum ether, (b.p. 30–60°; 7 ml.) yielded *N*-benzylbenzamide, (325 mg., 67%) m.p. and mixed m.p. 103–105°. Acidification of the aqueous layer with dilute hydrochloric acid afforded an additional 175 mg. of the parent compound (total of 375 mg. represents 87% recovery), m.p. and mixed m.p., 145–147°.

CHICAGO 12, ILL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MIAMI]

Reissert Compound Studies. II. Nature of the Quinoline[1,2]

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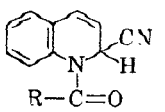
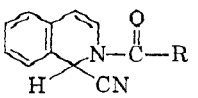
Reaction of a wide variety of 3-, 4-, 5-, 6-, and 7-substituted quinolines with benzoyl chloride and potassium cyanide in methylene chloride–water has resulted in the formation of the appropriate Reissert compounds. The yields of Reissert compounds were largest when the substituents were electron-donating groups. No Reissert compounds could be obtained from 2- and 8-substituted quinolines. With one exception all the Reissert compounds gave benzaldehyde on acid-catalyzed hydrolysis.

Reissert compounds[4] (I and II) result from the addition of an acyl and a cyano group to quinolines and isoquinolines. Initial interest in Reissert compounds arose from the fact that their acid-catalyzed hydrolysis yielded aldehydes, thus providing



I



II

a general method for the preparation of aldehydes from acid chlorides.[4] More recent interest, however, has been in the use of Reissert compounds in the synthesis of various heterocyclic compounds.[4,5]

If Reissert compounds are to be useful reagents for further synthesis, the effect of substituents on the quinoline base must be understood. A survey of the literature has revealed that more than half of the quinolines subjected to this reaction have failed to yield Reissert compounds. In addition to quinoline[6] itself, 6-methoxy-,[7] 7-methoxy-,[8] 6-chloro-,[9] 6-methyl-,[9] and 5,6-benzoquinoline[10] have been shown to yield Reissert compounds. On the other hand when the substituent is the 5-nitro,[7] 5-amino,[7] 5-acetamido,[7] 6-dimethylamino,[7] 6-nitro,[9] 7-nitro,[7] 8-hydroxy,[7] 8-methoxy,[7] 8-nitro,[9] 8-benzoyloxy,[7] 8-acetoxy,[7] or 2-methyl[7] group, the reaction fails. These results seem to point out an obvious steric effect resulting from a substituent in the 2- or 8- position of the quinoline ring, but

(1) Part I, F. D. Popp and W. Blount, *Chem. & Ind.* (*London*), 550 (1961).

(2) Presented in part at the 140th National Meeting of the American Chemical Society, Chicago, Ill., September 1961. A preliminary report was also presented at the Meeting-in-Miniature of the Florida Section of the ACS, Hollywood Beach, Fla., May 1961. This work was supported in part by a grant from the Research Corp.

(3) The major portion of this work has been abstracted from the M.S. thesis of W. B.

(4) W. E. McEwen and R. L. Cobb, *Chem. Revs.*, **55**, 511 (1955).

(5) See L. R. Walters, E. G. Podrebarac, and W. E. McEwen, *J. Org. Chem.*, **26**, 1161 (1961) and references cited therein to earlier work of McEwen and co-workers.

(6) A. Reissert, *Ber.*, **38**, 1603 (1905).

(7) A. Gassman and H. Rupe, *Helv. Chim. Acta*, **22**, 1241 (1939).

(8) E. Spath and O. Brunner, *Ber.*, **57**, 1234 (1924).

(9) I. W. Elliott, Jr., *J. Am. Chem. Soc.*, **77**, 4409 (1955).

(10) Footnote in M. Colonna and S. Fatutta, *Gazz. chim. ital.*, **83**, 622 (1953).