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Pyridoxine and Pyridoxal Analogs. V. Syntheses and Infrared Spectra of Schiff Bases[1,2]

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Synthesis and properties are described for crystalline Schiff bases obtained by reactions of five amino acids with the pyridoxal analogs, 3-hydroxypyridine-4-aldehyde and 3-hydroxypyridine-2-aldehyde, and with various methoxypyridinealdehydes, simple pyridinealdehydes and substituted benzaldehydes. Analysis of the infrared spectra indicates that the solid Schiff bases derived from the two isomeric *o*-hydroxypyridinealdehydes and from salicylaldehyde have the tautomeric enamine rather than the conventional imine structures. Evidence is given for intramolecular hydrogen bonding involving the aromatic hydroxyl group, the amino acid carboxylate group and the nitrogen atom of the Schiff base.

Introduction

The material presented in this paper is an outgrowth of the work described earlier[4-7] on the synthesis and characterization of new analogs of pyridoxine and pyridoxal. It was thought that these simpler analogs would permit a more accurate determination of the structure and reactivity of hydroxypyridinealdehydes, and their role in various metal ion-catalyzed reactions. This idea has been borne out in the work completed thus far on spectral assignments and elucidation of solution equilibria of the parent aldehydes. The present paper is concerned with synthesis and infrared spectral studies of Schiff bases derived from the reactions of various amino acids with hydroxypyridinealdehydes, methoxypyridinealdehydes, simple pyridinealdehydes and substituted benzaldehydes.

Only a relatively small number of crystalline Schiff bases of pyridoxal and its analogs are known. Two Schiff bases of simple amino acids and pyridoxal, pyridoxylidene-glutamic acid[8] and pyridoxylidene-DL-alanine,[9] have been prepared as yellow crystalline potassium salts. Also, a number of crystalline Schiff bases derived from pyridoxal and aromatic and aliphatic amines have been reported.[10,11]

Experimental

General Procedure for the Preparation of *o*-Hydroxy Schiff Bases.—A solution of 2 mmoles of 1% standard carbonate-free potassium hydroxide in absolute methanol (or 4 mmoles in the case of glutamic acid) was added under an atmosphere of dry nitrogen to 2 mmoles of the crystalline amino acid (chromatographically pure, Mann Research Laboratories, New York). The amino acid was stirred with gentle warming, if necessary, until it had completely dissolved in the methanol–KOH solution. The solution was then cooled to 0°–10°, and 2 mmoles (0.2462 g.) of the freshly sublimed hydroxypyridinecarboxaldehyde,[5] or 2 mmoles (0.2443 g.) of salicylaldehyde dissolved in 5 ml. of absolute methanol, was added rapidly. Immediately, the color of the solution changed from slightly yellow to deep lemon-yellow, and the *p*H decreased from 10 to about 6. The reaction was allowed to come to completion by stirring for not more than 5 minutes at 0 to −10°. The product was crystallized out either 1, by diffusion of excess absolute ether into the solution under a nitrogen atmosphere, or, 2, by evaporation of the solution in a rotating film evaporator below 0° at less than 1 mm. pressure, followed by addition of ether. The products were recrystallized from methanol and ether. Depending on the aldehyde and amino acid components employed, the color of the solid Schiff bases varied from bright lemon-yellow to deep yellow. The products proved to be analytically pure and satisfactory for spectroscopic measurements. Yields and microanalytical results are compiled in Table I.

General Procedure for the Preparation of *o*-Methoxy and of Unsubstituted Schiff Bases.—Schiff bases not having an *o*-hydroxy group were prepared in the manner described above, except that the maintaining of low temperatures was not required. The Schiff base solution gave crystalline precipitates upon addition of ether only in a few cases. Usually, considerable difficulty was encountered, and freeze drying of the extremely hygroscopic materials obtained proved the best method to obtain crystalline products. All the Schiff bases of the *o*-methoxy and unsubstituted aldehydes, in contrast to those derived from the *o*-hydroxyaldehydes, are characterized by the formation of colorless or only slightly yellow solids. Yields and microanalytical results are given in Table I.

Infrared Spectra.—The spectra were recorded in the region 4000–650 cm.$^{-1}$ with a Perkin–Elmer model 21 double beam spectrometer equipped with sodium chloride optics. The solid Schiff bases were dried at room temperature at 0.1 mm. pressure before mixing with weighed amounts of potassium bromide in an atmosphere of dry nitrogen. Dispersion of the substances in the excess KBr prevented combination with water vapor during transfer to the pellet die. Calibration of the spectrophotometer in the 1700–1200 cm.$^{-1}$ region was performed with water vapor and methane gas, and in the 4000–2000 cm.$^{-1}$ region, with polystyrene and CO_2 gas. The probable error of the infrared data was found to be ±5 cm.$^{-1}$ at 3000 cm.$^{-1}$ and ±1 cm.$^{-1}$ at 1700 cm.$^{-1}$.

Results

Synthesis of Schiff Bases.—In this investigation it was found that the Schiff bases formed by amino acids and the pyridoxal analogs 3-hydroxypyridine-4-aldehyde and 3-hydroxy-pyridine-2-aldehyde were less stable than those formed by aminacids and the corresponding *o*-methoxypyridinealo dehydes,[4,5] pyridine-2- or 4-aldehyde, salicylalde-

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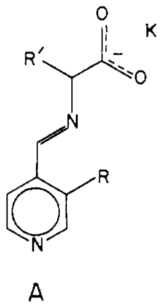
TABLE I

SCHIFF BASES FROM PYRIDINEALDEHYDES AND AMINO ACIDS

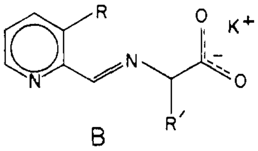
Form	Compound R	Compound R′	No.	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Yield, %
A	H	$CH(CH_3)_2$	I	$C_{11}H_{13}N_2O_2K$	54.07	54.02	5.36	5.72	11.47	11.75	60
A	OCH_3	$CH(CH_3)_2$	II	$C_{12}H_{15}N_2O_3K$	52.53	52.07	5.51	5.76	10.21	10.30	67
A	OH	H	III	$C_8H_7N_2O_3K\cdot H_2O$	40.66	40.68	3.84	4.23	11.86	12.21	57
A	OH	CH_3	IV	$C_9H_9N_2O_3K\cdot H_2O$	43.18	43.45	4.43	4.83	11.19	11.10	70
A	OH	$CH(CH_3)_2$	V	$C_{11}H_{13}N_2O_3K\cdot H_2O$	47.46	47.96	5.43	5.50	10.07	10.09	70
A	OH	$CH_2C_6H_5$	VI	$C_{15}H_{13}N_2O_3K\cdot H_2O$	55.19	55.36	4.63	4.88	8.58	8.55	34
A	OH	$(CH_2)_2CO_2K$	VII	$C_{11}H_{10}N_2O_5K_2\cdot H_2O$	38.13	38.17	3.49	3.47	8.08	8.56	78
B	H	$CH(CH_3)_2$	VIII	$C_{11}H_{13}N_2O_2K$	54.07	53.64	5.36	5.44	11.46	11.52	73
B	OCH_3	$CH(CH_3)_2$	IX	$C_{12}H_{15}N_2O_3K\cdot H_2O$	49.29	48.91	5.86	5.81	9.58	9.26	43
B	OH	H	X	$C_8H_7N_2O_3K\cdot H_2O$	40.66	40.33	3.84	4.11	11.85	12.43	65
B	OH	CH_3	XI	$C_9H_9N_2O_3K\cdot H_2O$	43.18	43.00	4.43	4.48	11.19	11.48	49
B	OH	$CH(CH_3)_2$	XII	$C_{11}H_{13}N_2O_3K$	50.75	50.64	5.03	5.33	10.76	10.73	62
B	OH	$CH_2C_6H_5$	XIII	$C_{15}H_{13}N_2O_3K\cdot H_2O$	55.19	55.13	4.63	4.42	8.58	8.52	72
B	OH	$(CH_2)_2CO_2K$	XIV	$C_{11}H_{10}N_2O_5K_2\cdot H_2O$	38.13	37.75	3.49	3.46	8.09	8.44	93
C	OCH_3	$CH(CH_3)_2$	XV	$C_{13}H_{16}NO_3K$	57.11	56.66	5.90	5.90	5.12	5.18	92
C	OH	$CH(CH_3)_2$	XVI	$C_{12}H_{14}NO_3K\cdot H_2O$	51.96	52.40	5.81	5.68	5.05	5.58	84

hyde or *o*-methoxybenzaldehyde. Formation of the Schiff bases was very rapid, even at temperatures ranging from 0 to −20°, when the pyridoxal analogs were combined with the potassium salts of the amino acids in methanol. The deep yellow, crystalline Schiff bases precipitated directly in all but a few instances upon slow addition (preferably by diffusion) of a non-polar solvent, such as dioxane or ether. The *o*-hydroxypyridinealdimines prepared in this manner are unstable only when in contact with moisture or when exposed to light.

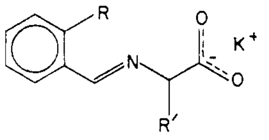
Thus, compounds I–XVI, comprising three series of Schiff bases, described by the general formulas A, B and C, were prepared. The group



A



B



C

R′= H, CH_3, $CH(CH_3)_2$, $CH_2C_6H_5$, CH_2CH_2COOK

R = H, OH, OCH_3

R, in the *o*-position to the aldimine group, was $-H$, $-OCH_3$ or $-OH$ depending on the type of aldehyde used, and the group R′ was $-H$, $-CH_3$, $-CH(CH_3)_2$, $-CH_2C_6H_5$ or $-(CH_2)_2CO_2K$, indicating Schiff bases derived from the amino acids glycine, alanine, valine, phenylalanine or glutamic acid, respectively.

Infrared Spectra.—Because of the insolubility of the new Schiff bases in non-polar solvents and because of their reactivity with all polar solvents, the infrared spectra were measured in potassium bromide media. Absorption frequencies and the corresponding band assignments are listed in Table II. The absorption maxima of a few crystalline or liquid pyridine aldehydes which were reported and interpreted earlier[5] are given for comparison.

Spectra of Unsubstituted and *o*-Methoxy Schiff Bases.—If the spectra of the simplest Schiff bases, such as N-(2-pyridylmethylene)-valine (Fig. 1) or N-(3-methoxy-4-pyridylmethylene)-valine (Fig. 2), are compared with those obtained from the parent pyridinealdehydes, characteristic changes in the spectra are observed. The carbonyl stretching frequencies of the aldehydes (1700–1715 cm.$^{-1}$) and their low intensity companions of uncertain origin[5] (C=O, st. II, 1650–1675 cm.$^{-1}$) are replaced by the specific imine absorption band (C=N, st. imine, 1630–1640 cm.$^{-1}$). The first C=C/C=N ring stretching vibration, which normally appears as a moderately strong band near 1580–1610 cm.$^{-1}$ in this type of pyridine compound,[5] is replaced by a very strong and broad band centered about the same location. In several of the Schiff bases this band is resolved into two components, assignable to the first aromatic ring stretching vibration and the asymmetric stretching vibration of the carboxylate group, located near 1596 and 1586 cm.$^{-1}$, respectively. In the majority of the compounds, however, only one band appears in this region. Since it is much stronger and broader than aromatic ring stretching vibrations, it must be regarded as a combination of the ring and carboxylate absorptions. Because of the broadness of this band, the imine absorption near 1635 cm.$^{-1}$ is not always clearly resolved, but appears as a shoulder or a side peak in most of the compounds investigated (see Figs. 1 and 2).

The other skeletal frequencies observed in the aldehydes remain remarkably unaffected by conversion to the imines. Thus it is seen in Figs. 1 and 2 that there is no change in the frequencies of the two bands, located at 1440 and 1470 cm.$^{-1}$ in the unsubstituted compounds, and at 1420 and

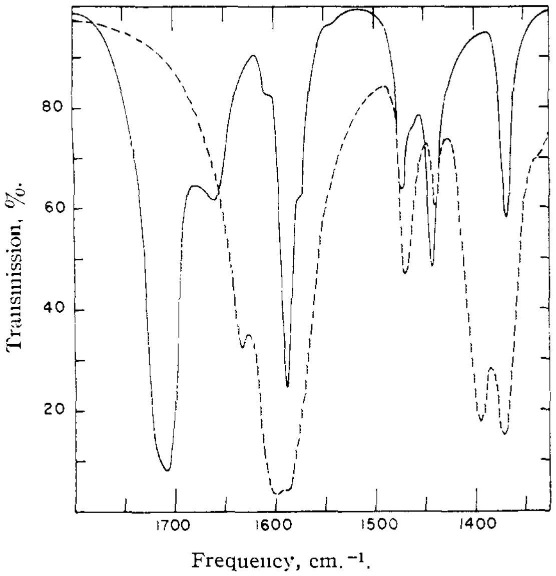


Fig. 1.—Infrared spectra of 2-pyridinecarboxaldehyde (———), liquid, capillary, and of N-(2-pyridylmethylene)-valine (- - - -), KBr disc.

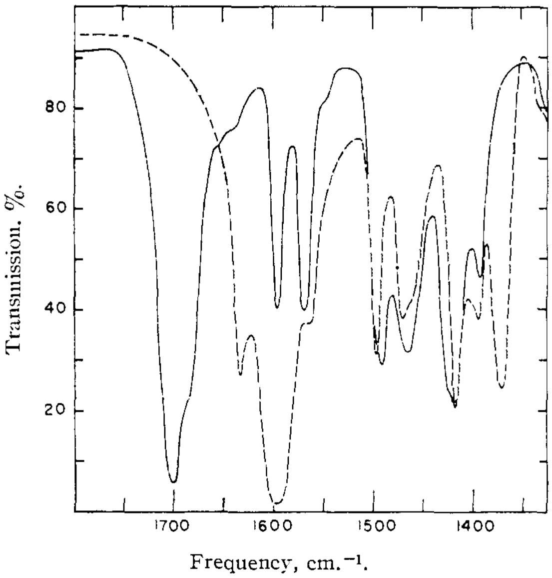


Fig. 2.—Infrared spectra of 3-methoxypyridine-4-carboxaldehyde (———), liquid, cap., and of N-(3-methoxy-4-pyridylmethylene)-valine (- - - -), KBr disc.

1490 cm.$^{-1}$ in the *o*-methoxy compounds, which are assigned to the second and third components of the C=C/C=N ring stretching vibrations. Similarly, the band associated with the symmetric deformation of the CH_3 group in the methoxy-aldehyde[5] (Fig. 2), located at 1463 cm.$^{-1}$, is found as a doublet at 1466 cm.$^{-1}$ in the valine Schiff base. Splitting in this case may be attributed to the difference in the CH_3 groups bound to oxygen and those bound to carbon. Finally, the absorption observed below 1400 cm.$^{-1}$ in the aldehydes, which has been attributed to a C–C st. vibration in conjugated aldehydes,[5] also appears at the same location in the Schiff bases.

In the 1350–1500 cm.$^{-1}$ region, therefore, only one new band, located between 1365 and 1400 cm.$^{-1}$, appears in these Schiff bases. This absorption is attributed to the symmetric stretching vibration of the carboxylate group (COO^-, st. symm.). The appearance of both the asymmetric and the symmetric carboxylate ion group frequencies shows that, in the Schiff bases prepared, the carboxylic acid is the most acidic group.

Spectra of *o*-Hydroxy Schiff Bases.—In contrast to the compounds described above, the spectra of the Schiff bases derived from hydroxyaldehydes are quite different from those obtained from the parent aldehydes, as is indicated (Fig. 3). In these Schiff bases, the chelated carbonyl stretching vibration of the aldehyde (1677–1688 cm.$^{-1}$) is replaced by two new bands at 1613 and 1642 cm.$^{-1}$ assigned to the imine C=N absorption frequency and a band resulting from the superposition of the —COO^- st., asymm., and the C=C/C=N ring st. bands. Also, a new absorption band, assigned to the symmetric COO^- vibration, appears at 1402 cm.$^{-1}$, whereas the ring stretching vibrations at 1352, 1426 and 1472 cm.$^{-1}$ remain close to their original positions in the aldehyde. When this procedure is followed through, it is noted (Table II) that in all of the Schiff bases derived from *o*-hydroxyaldehydes the new strong band near 1510 cm.$^{-1}$ remains unassigned. This band is absent in the spectra of all the simpler Schiff bases lacking the *o*-hydroxy group, whereas in the hydroxyaldehyde Schiff bases it is characterized by remarkably constant frequency, varying only between 1500 and 1518 cm.$^{-1}$ in the eleven Schiff bases investigated. The intensity of the imine absorption in the hydroxyaldehyde Schiff base (Fig. 3, for example) is much higher than usually found in imines, and is also much higher than in the imines prepared from methoxy- or unsubstituted aldehydes in this research (Figs. 1 and 2, for example).

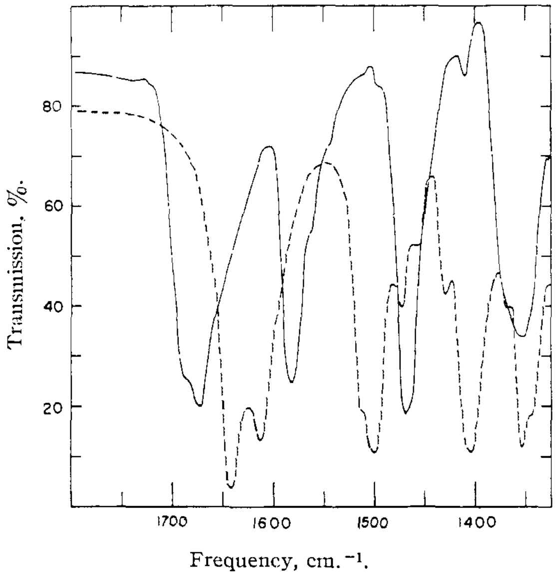


Fig. 3.—Infrared spectra of 3-hydroxypyridine-2-carboxaldehyde (———), KBr disc, and of N-(3-hydroxy-2-pyridylmethylene)-alanine (- - - -), KBr disc.

TABLE II

INFRARED SPECTRA OF SCHIFF BASES[a] IN THE 2000–1400 CM.$^{-1}$ REGION[b]

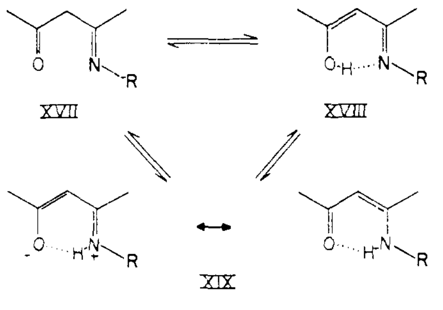
Compound	No.	Assignment[c]												
		C=O, st. aldehyde	C=O, st. II	C=N, st. imine	C=O, st. amide I	COO^- st.[d] asymm.	C=C C=N ring st.	C=C/ C=N ring st.	C=C, conj. amide, st.	C=C/ C=N ring st.	CH_2 + CH_3 symm. def.	C=C/ C=N ring st.	COO^-, st. symm.	CH_3, def. symm., or C–C st. conj.
4-Pyridinecarboxaldehyde	—	1712s	1671m	—	—	—	1595w	1563s	—	1491w	—	1414m	—	1390m
N-(4-Pyridylmethylene)-valine	I	—	—	1640s	—	1588vs	......	1564ssh	—	1469msh	1461m	1409ssh	1370s	1395s
3-Methoxy-4-pyridinecarboxaldehyde	—	1703s	—	—	—	—	1595m	1564m	—	1489m	1463m	1418s	—	1391w
N-(3-Methoxy-4-pyridylmethylene)-valine	II	—	—	1632s	—	1596vs	......	1563msh	—	1493s	1466m	1413s	1368m	1391m
3-Hydroxy-4-pyridinecarboxaldehyde	—	1687ssh	1674s	—	—	—	1602m	1583m	—	1498w	—	1413s	—	1357m
N-(3-Hydroxy-4-pyridylmethylene)-														
glycine	III	—	—	—	1640ssh	1612vs	......	......	1518m	1474w	1447m	1399msh	1377m	......
alanine	IV	—	—	—	1632ssh	1605s	......	......	1516m	1469wsh	1450m	1404m	1384m	1357m
valine	V	—	—	—	1632ssh	1600vs	......	1567msh	1512m	1463msh	1442m	......	1367s	1340msh
phenylalanine	VI	—	—	—	1632ssh	1603vs	......	1562msh	1512m	1493msh	1439m	......	1367s	1339msh
glutamic acid	VII	—	—	—	1624s	1581vs	......	......	1516m	1471m	1441m	......	1390s	1340m
2-Pyridinecarboxaldehyde	—	1713s	1665w	—	—	—	1588s	1573w	—	1472m	—	1439m	—	1367m
N-(2-Pyridylmethylene)-valine	VIII	—	—	1632s	—	1596vs	1588vs	......	—	1466m	1435w	......	1391s	1367s
3-Methoxy-2-pyridinecarboxaldehyde	—	1708s	1640vw	—	—	—	1576s	1562msh	—	1469s	1460ssh	1430s	—	1395m
N-(3-Methoxy-2-pyridylmethylene)-valine	IX	—	—	1639ssh	—	1588vs	......	1562msh	—	1464m	1451m	1431m	1364s	1390m
3-Hydroxy-2-pyridinecarboxaldehyde	—	1688ssh	1677s	—	—	—	1580s	1564msh	—	1468s	—	1408w	—	1352m
N-(3-Hydroxy-2-pyridylmethylene)-														
glycine	X	—	—	—	1649s	1613s	......	......	1509m	1441m	......	......	1390s	1359m
alanine	XI	—	—	—	1642s	1613s	......	......	1500s	1472m	1457wsh	1426m	1402s	1352s
valine	XII	—	—	—	1643ssh	1631vs	......	......	1509s	1463m	1433m	......	1395m	1360s
phenylalanine	XIII	—	—	—	1642ssh	1628vs	......	......	1511msh	1493s	1454m	1427m	1395m	1359m
glutamic acid	XIV	—	—	—	1627vs	1577vs	......	......	1509msh	1499m	1446m	......	1397s	1360m
2-Methoxybenzaldehyde	—	1688s	1666msh	—	—	—	1602s	1585wsh	—	1485s	1468m	1439m	—	1395m
N-(2-Methoxy-benzylidene)-valine	XV	—	—	1632m	—	1591vs	......	1559msh	—	1484m	1463m	1434m	1366m	1391m
Salicylaldehyde	—	1665s	1646m	—	—	—	1621m	1580s	—	1486m	—	1459m	—	1385m
N-Salicylidenevaline	XVI	—	—	—	1634s	1604s	......	......	1513m	1489m	1564m	1407m	1374m	......

[a] Potassium salts as listed in Table I. [b] All substances (except liquids) were measured as crystalline solids employing KBr pellet technique. [c] Because of the relative broadness of most of the stronger bands, ν_{max} values are to be considered within an accuracy of ±2 cm.$^{-1}$ only. — = band is absent from spectrum; ......, = band is invisible, due to overlap with strong neighboring bands. [d] Overlapping the N–H, bend. (Amide II) absorptions in the hydroxy-Schiff bases.

Discussion

Enamine Structure of Schiff Bases.—The anomalous absorptions near 1510 cm.$^{-1}$, the unusual intensity of the "imine" frequency absorptions (1625–1650 cm.$^{-1}$), as well as other observations discussed below, led to a reinterpretation of the spectra and of the structures of these compounds. It is concluded that the most probable origin of the absorption band found in the region of the imine stretching frequencies in the hydroxyaldehyde Schiff bases is the carbonyl stretching vibration of an amide (amide I band), whereas the new band in the 1510 cm.$^{-1}$ region is assigned to the C=C stretching vibration observed in amide vinylogs. The structure of these compounds, accordingly, is reinterpreted as that of the tautomeric amide form XXIV, of the Schiff base, possibly in equilibrium with smaller fractions of the tautomeric hydroxyaldimine form XXIII. The possibility for the formation of such tautomeric forms was indicated by Metzler.[12] However, no attempts were made by prior investigators to distinguish between the electronic absorption spectra of the two tautomeric species and, consequently, the structure of these Schiff bases with respect to the position of the proton had not been previously elucidated.

Related Aliphatic Compounds.—The hydroxyaldehyde Schiff bases under investigation are structurally related to the imines of the 1,3-dicarbonyl compounds in the manner indicated schematically by omitting the dashed lines in formulas XX, XXI and XXII. The simple 1,3-ketimines, such as acetylacetoneimine XVII, may enolize to the enolimine XVIII and keto-enamine forms XIX. Spectral studies of the structures of these compounds seem to favor the enamine structure. Thus, a number of ultraviolet spectroscopic investigations[13,14,15,16] of acetylacetoneimines and bisacetylacetoneëthylenediimines as well as a recent study of the n.m.r. spectra of the latter[17] showed the absence of the non-enolized ketimine form XVII and existence of these compounds to a large extent in the enamine tautomeric form XIX.



Cromwell, *et al.*,[18] and Weinstein and Wymann[19] found that the spectra of the acetylacetoneimines could be interpreted completely only on the assumption that they exist primarily in the form of the tautomeric amide structure XIX. Just as in the case of the simple unconjugated amides,[20] two bands were found in the solid imines derived from primary amines and acetylacetone: amide I, located at 1610 ± 10 cm.$^{-1}$, and amide II, located at 1590 ± 5 cm.$^{-1}$. Assignment of the former to the C=O stretching, and the latter to the N—H bending mode of vibration was based on a comparison with the spectra of the N-dialkyl derivatives which lacked the second band, and by the behavior of the two bands in going from solution to solid state. In addition, a further band, characteristic of all acetylacetone-imines, was found between 1520 and 1540 cm.$^{-1}$ and was assigned to a C=C stretching vibration[18,19] or to a C=N stretching vibration.[21]

Comparison of these observations with the results obtained in this investigation indicates a close analogy. Thus, the new band observed in the hydroxyaldehyde Schiff bases, between 1500 and 1518 cm.$^{-1}$, may be attributed to a C=C or C=N stretching vibration of the conjugated amide. The bands between 1625 and 1650 cm.$^{-1}$ may be assigned to the amide I absorption, and the broad band between 1580 and 1630 cm.$^{-1}$ to a superposition of the amide II and the symmetrical carboxylate stretching vibration.

Although the authors were unsuccessful in the preparation of the N-alkyl Schiff bases, the O-alkyl Schiff bases (*e.g.*, compounds II, IX and XV) as well as the Schiff bases derived from unsubstituted pyridinealdehydes (I, VIII), which are analogous to one of the possible tautomeric structures, do not have an absorption band near 1510 cm.$^{-1}$. For this reason, the assignment of this band to the C=C stretching vibration in conjugated amides appears justified.

The Imine Stretching Absorptions.—Further evidence for the structure of the *o*-hydroxyaldehyde Schiff bases under investigation is obtained from study of the C=N stretching frequencies. In previous investigations[5,22] it was shown that in the parent *o*-hydroxyaldehydes the frequency of the carbonyl stretching vibration is progressively lowered from its position in the analogous *o*-methoxyaldehydes as the strength of intramolecular hydrogen bonding is increased. Similar correlations would be expected for a comparison of the imine stretching vibrations in the unchelated *o*-methoxy Schiff bases with the hydrogen bonded *o*-hydroxy Schiff bases, if the latter exist in the hydroxy-imine form XX. In Table III are listed the imine stretching frequencies of three *o*-methoxy Schiff bases (compounds II, IX and XV), and the average value for the highest absorption band of the corresponding *o*-hydroxy Schiff bases in the 1500 to 2000 cm.$^{-1}$ region. If the hydroxy Schiff

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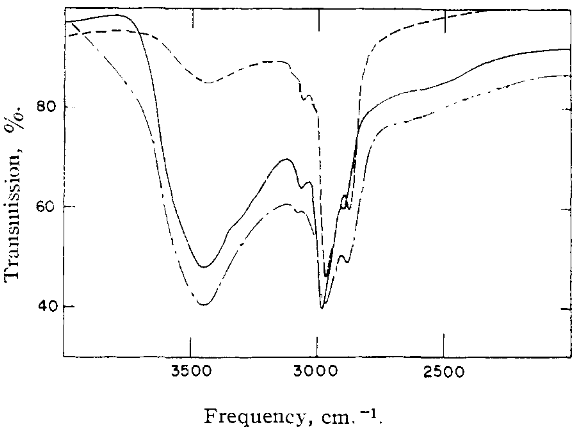
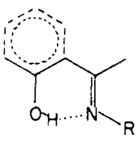
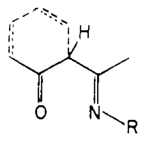


Fig. 4.—Infrared spectra of N-(2-pyridylmethylene)-valine (– – – –), N-(3-methoxy-2-pyridylmethylene)-valine (– · – · –) and N-(3-hydroxy-2-pyridylmethylene)-valine (———), all as KBr disc.

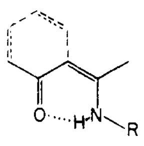
bases exist in the form XX, this absorption band, found near 1630–1640 cm.$^{-1}$, would have to be assigned to the C=N stretching vibration. It is noted that, in contrast to the large negative shifts of the carbonyl frequencies, the C=N frequencies in the hydroxy-imines appear to shift to higher values, so that Δν(C=N) is positive. In a recent analysis of the infrared data of a wide variety of aromatic *o*-hydroxy Schiff bases, Freedman[23] also observed unexpectedly small or positive Δν(C=N) values, although the spectra in the O—H stretching region would indicate that hydrogen bonding in the imines is stronger than in the analogous oxygen compounds. A reasonable explanation for these seemingly unexpected C=N frequency shifts upon chelation is possible if the higher frequency absorptions are considered to be due to an entirely different type of group than C=N, namely the amide vinylogs XIX and XXII. These absorptions are therefore assigned to amide I bands of these compounds, lowered from the usual amide I frequency by intramolecular hydrogen bonding. Thus it seems that the observed "positive Δν(C=N) shift," rather than the expected negative shift, provides additional evidence for the existence of these Schiff bases in the tautomeric amide structures.



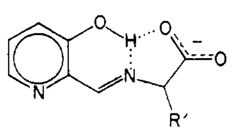
XX



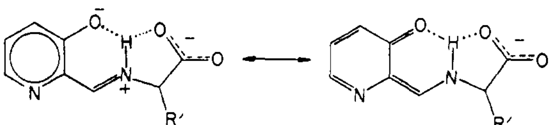
XXI



XXII



XXIII



XXIV a XXIV b

TABLE III

INFLUENCE OF HYDROGEN BONDING ON "IMINE" STRETCHING FREQUENCIES

Type of compound	ν(C=N), cm.$^{-1}$ of O-methyl cpds.	1630–1640 cm.$^{-1}$, hydroxy cpds.[a]	Δν(C=N), cm.$^{-1}$	Δν(C=O),[b] cm.$^{-1}$
3-Substd. 4-pyridine-aldimines	1632	1634	+2	−22
o-Substd. benzaldimines	1632	1634	+2	−28
3-Substd. 2-pyridine-aldimines	1639	1644	+5	−41

[a] Average for monocarboxylic amino acid Schiff bases. [b] Shift between ν(C=O) of *o*-methoxy and *o*-hydroxyaldehydes; *cf.* ref. 5.

Influence of Aromatic Ring.—The Schiff bases prepared in this investigation differ from the simple acetylacetoneimines as indicated in XX–XXII in that one of the carbon–carbon bonds of the hydrogen-bonded chelate ring is also part of an aromatic nucleus. The resonance in the aromatic ring would reduce somewhat the stabilizing resonance interactions between the nitrogen and oxygen atoms in XX and XXII, while rendering structure XXI virtually impossible. The equilibrium between XX and XXII is probably not greatly influenced by the aromatic group, although it may be shifted more toward the enol-imine form XX than is the case for the aliphatic compounds, as the result of greater stabilization of enols by aromatic rings. Thus, while the present analysis of infrared spectra indicates that the Schiff bases derived from amino acids and *o*-hydroxy aromatic aldehydes exist predominantly in the keto-enamine form, these theoretical considerations lead to the conclusion that smaller amounts of the other tautomeric form may also be present.

Spectra of *o*-Hydroxy Schiff Bases in the 4000–2000 Cm.$^{-1}$ Region.—A previous study of the characteristic differences in the infrared spectra of the parent 3-hydroxypyridine-2- and 4-aldehydes in crystalline form and in dilute solutions[5] showed the presence of strong intermolecular hydrogen bonding in the solid state. These results would lead one to expect similar spectral changes for the Schiff bases of these compounds, characterized by the replacement of the medium sharp *intra*molecular chelate O—H. . .O band near 3200 cm.$^{-1}$ by a very broad *inter*molecular O—H. . .N band about 2500 cm.$^{-1}$. However, the infrared absorption curves for the solid Schiff bases of all three types, including those of the *o*-hydroxy forms, showed only one band near 3400 cm.$^{-1}$ of medium width (Fig. 4), instead of the expected broad and intense absorption bands near 2500 cm.$^{-1}$. This result is interpreted as evidence that only very weak intermolecular hydrogen bonding takes place in the solid hydroxyaldehyde Schiff bases. The strong absorption band found near 3400 cm.$^{-1}$ in most of

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[23] H. H. Freedman, *J. Am. Chem. Soc.*, **83**, 2900 (1961).

these compounds is due to one mole of crystal water, retained in most of the samples (*cf.* Table I). The absorption frequency attributable to *intra*molecular hydrogen bonding in the hydroxyaldehyde Schiff bases should appear near 3200–3300 cm.$^{-1}$, and would thus overlap the intense water O–H stretching absorption. The infrared evidence for the lack of strong intermolecular hydrogen bonding is in agreement with other physical properties of these substances (*e.g.*, some of the Schiff bases are soluble in dioxane and even chloroform). In view of the experimental evidence given above, the structures of the hydroxyaldehyde Schiff bases must be those indicated by formulas XXIII and XXIV. According to this interpretation, the neighboring carboxylate groups participate in binding the proton in a bifurcated hydrogen bond. Thus, the proton would be completely surrounded by electron donor sites, and the approach of a second molecule of the Schiff base to form an intermolecular hydrogen bond would be prevented. The structures thus indicated for the two principal tautomeric forms of a representative Schiff base contain the hydrogen atom bound in a manner very similar to what would be expected for the metal chelates formed by these Schiff bases.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, URBANA, ILL.]

Organic Chemistry of Ferrocene. V.[1a] Cyclization of ω-Ferrocenylaliphatic Acids

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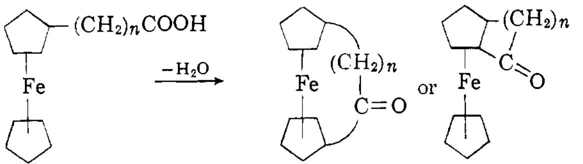
KENNETH G. HARRISON,[1c] RICHARD E. BOZAK AND DONALD E. BUBLITZ

RECEIVED MARCH 22, 1962

The effect of aliphatic chain length on cyclization has been studied in the series β-ferrocenylpropionic acid (Ib), γ-ferrocenylbutryic acid (Ic), δ-ferrocenylvaleric acid (Id) and ε-ferrocenylcaproic acid (Ie). The first member gives the heteroannularly bridged 1,1′-(α-ketotrimethylene)-ferrocene (IIb) while the second and third members give the homoannularly cyclized products IIIc and IIId and ε-ferrocenylcaproic acid gives only a polymer (XVII) of low molecular weight. Synthetic methods employed and some of the reactions of the mono-bridged compound are discussed, as are a pair of geometrical isomers (XIVa and XIVb) obtained from ferrocene-1,1′-dibutyric acid (XIII).

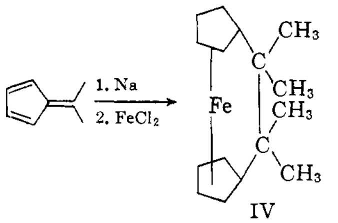
Homoannular and heteroannular cyclizations of ω-ferrocenylaliphatic acids (I) were reported previously in a short note,[2] while the synthesis of those acids was the subject of an earlier paper in this series.[3] The present paper describes details of these cyclizations and presents improved methods of synthesis of certain of the acids. The work described was undertaken to establish what the steric requirements are for cyclization of ω-ferrocenylaliphatic acids (I) to heteroannular or homoannular products (II or III, respectively).



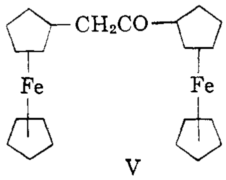
I^{a-e} II^{a-e} III^{a-e}

Ia, IIa, IIIa: $n = 1$
Ib, IIb, IIIb: $n = 2$
Ic, IIc, IIIc: $n = 3$
Id, IId, IIId: $n = 4$
Ie, IIe, IIIe: $n = 5$

Ferrocenylacetic Acid.—Although it would have been quite surprising had ferrocenylacetic acid[3,4] (Ia) undergone either homoannular or heteroannular cyclization, this possibility was tested by treating ferrocenylacetic acid with polyphosphoric acid for 19 hours at 40°; only starting material was recovered. Heteroannular cyclization would have required linking the two rings by a 2-carbon bridge. Although a 2-carbon bridge is possible, as shown by the isolation of 1,1′-tetramethylethyleneferrocene (IV),[5a] the latter compound was prepared by cyclization around the central iron atom by a pre-formed bridge. It is doubtful that a 2-carbon bridge (IIa) can be formed by electrophilic substitution on an intact ferrocene molecule, reaction with 1,2-dichloroethane or oxalyl chloride in the presence of aluminum chloride giving 1,1-diferrocenylethane[5b] and diferrocenyl ketone,[5c] respectively. It is even less likely that the fused 5-4 ring system (IIIa) can be formed by the present methods. Indeed, intermolecular reaction has been observed to predominate in the reaction of ferrocenylacetyl chloride with excess ferrocene



IV



V

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[1] (a) Paper IV, L. Westman and K. L. Rinehart, Jr., *Acta Chem. Scand.*, in press. (b) Alfred P. Sloan Foundation Fellow. (c) Undergraduate Research Participant supported by a grant (NSFG-8521) from the National Science Foundation.

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[4] Although the ferrocenylacetic acid employed in this study was prepared by the Willgerodt reaction (in 25% yield from acetylferrocene),[3] the method of choice is undoubtedly the reaction of N,N-dimethylaminomethylferrocene methiodide with potassium cyanide, followed by nitrile hydrolysis (90% yield from methiodide) [D. Lednicer, J. K. Lindsay and C. R. Hauser, *J. Org. Chem.*, **23**, 653 (1958)], and this method has been used in later work from this Laboratory.[6]

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