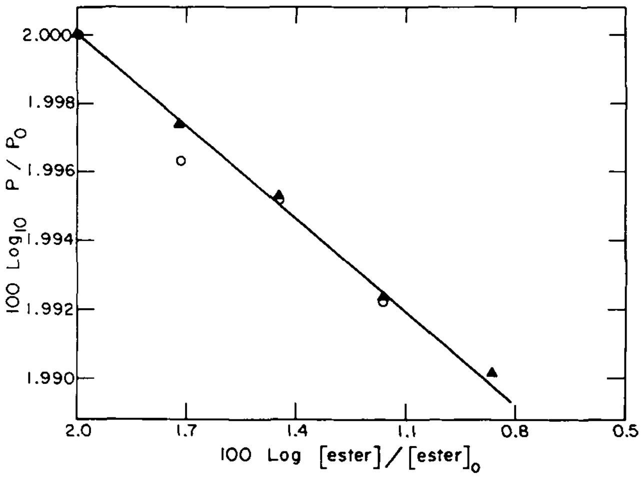
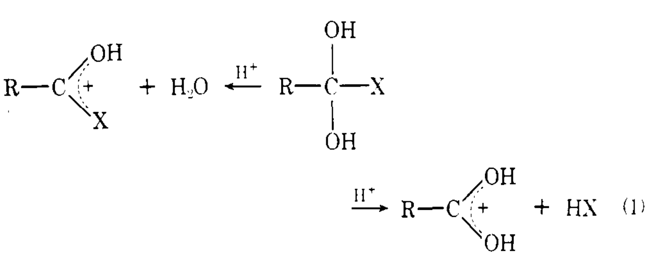


Figure 1. Concurrent hydrolysis and exchange of phenyl acetate; P, P_0 = % ^{18}O (excess) at times t and 0, (○,▲) = duplicate experiments.

intermediate is probably acid catalyzed with expulsion of a neutral leaving group and formation of a resonance stabilized cation, eq 1 (where the proton transfer may occur simultaneously with leaving group departure or in a prior equilibrium).



$$R{-}\overset{+}{C}(OH)X + H_2O \overset{H^+}{\longleftarrow} R{-}C(OH)_2{-}X \overset{H^+}{\longrightarrow} R{-}\overset{+}{C}(OH)_2 + HX \qquad (1)$$

Three factors are then important in determining k_H/k_E: (1) the intrinsic leaving group abilities of HX vs. H_2O, (2) the basicities of X vs. OH, and (3) the relative stabilities of the cationic products (i.e., the driving force for expulsion[11]). For phenyl acetate 1 and 3 favor the forward process (expulsion of PhOH) while 2 favors the reverse (expulsion of H_2O), the observed k_H/k_E ratio then suggesting that the former are more important.

This is the opposite situation to that found in considering amide hydrolysis and exchange, where again hydrolysis dominates (e.g., for benzamide, k_H/k_E = 320[12]). Here, however, one must argue that factor 2, the much greater basicity of nitrogen, is the more important, since 1 and 3 must favor expulsion of OH over NH_2.

Acknowledgments. The author gratefully acknowledges the financial support of the National Research Council of Canada.

Registry No.—*o*-Phenyl-*N*-methylacetimidate, 22084-79-3; acetonitrile, 75-05-8; phenyl acetate, 122-79-2; phenol, 108-95-2.

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Carbon-13 Nuclear Magnetic Resonance Spectra of Kojic Acid and Other 4-Pyrone Derivatives

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4-Pyrone derivatives are common flavoring agents and food preservatives which have been investigated with regard to bactericidal activity.[1] Considerable uncertainty remains as to the degree of aromaticity of kojic acid and of its parent structure, 4-pyrone, despite the application of a large number of chemical and spectroscopic criteria.[2,3] Thus, 4-pyrones are reported to give substitution products upon bromination.[4] The lack of reactivity of 4-pyrones in Diels–Alder reactions is remarkable.[5] The dipole moment of 4-pyrone (ca. 4 D) is substantially larger than that calculated for a non-resonance-stabilized molecule (ca. 2 D).[3,6,7]

The ^1H NMR spectra have been interpreted in terms of ring current effects, which were considered to reflect a high degree of aromaticity.[6] Abraham has questioned deductions regarding the degree of aromaticity based on ring current effects,[8] and these observations remain controversial. The vicinal ^1H coupling constant between H-2 and H-3 (5.9 or 6.2 Hz)[3,9] is similar both to aromatic compounds and to 2-cyclohexenone.

The most damaging evidence against aromaticity is the very low magnetic susceptibility, which is regarded by Beak et al. as indicative of essentially no aromatic character.[10]

To the best of our knowledge, no ^{13}C NMR studies of kojic acid or pyrone derivatives have appeared,[11] although Goldstein and co-workers were able to obtain some significant data from the study of ^{13}C satellites in ^1H spectra.[9] The ^{13}C chemical shifts determined in this study are recorded in Table I, and the various ^{13}C–H coupling constants are listed in Table II. In general, the ^{13}C data, like the observations mentioned above, are similar to α,β-unsaturated ketones in some respects and to aromatic heterocycles in other respects. In toto, we feel that these data and the data cited above support the postulate that a degree of aromaticity is present in the 4-pyrone system.

Scheme I illustrates the chemical shifts of kojic acid in relation to various model compounds. In the nonaromatic

Scheme I

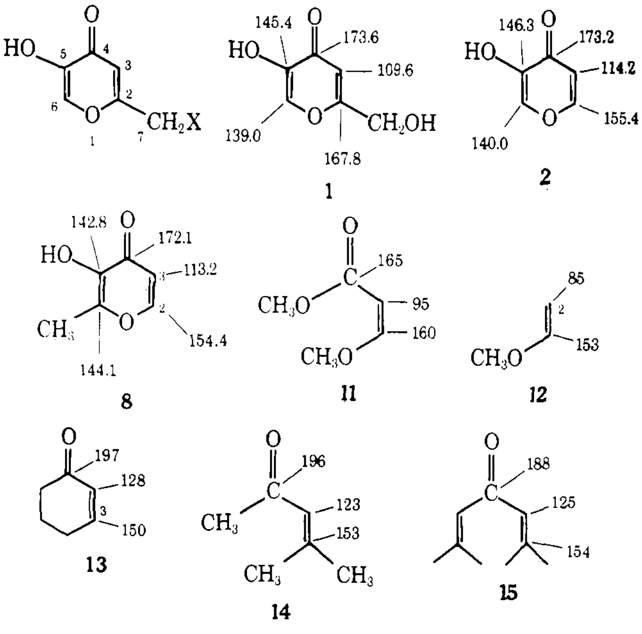
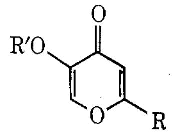


Table I. ^{13}C Chemical Shifts (ppm)[f] and Difference in Chemical Shift vs. a Standard Compound 2 ($\Delta\delta$)[g]



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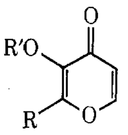

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Registry No.	Compound	R	R′	C-2	C-3	C-4	C-5	C-6[i]	R
501-30-4	**1**	CH_2OH	H	167.8 (12.2)	109.6 (−4.5)	173.5 (0.5)	145.4 (−1.0)	139.0 (−1)	59.3
496-63-9	**2**	H	H	155.4	114.2	172.9	146.4	139.9	
7559-81-1	**3**	CH_2Cl	H	161.5 (6.1)	113.0 (−1.2)	173.4 (0.5)	145.8 (−0.6)	139.8 (0)	41.2
6269-25-6	**4**[h]	CH_2OH	CH_3[a]	167.7 (12.2)	110.5 (−3.6)	172.5 (−0.4)	147.7 (1.3)	138.2	59.1
40838-34-4	**5**[h]	CH_2Cl	CH_3[a]	161.4 (6.0)	113.8 (−0.4)		147.8 (1.4)	139.3 (1)	41.0
26209-93-8	**6**	CH_2OAc[b,d]	Ac[d]	162.7 (7.3)	114.4 (0.1)	171.3 (−1.7)	140.2 (−6.2)	149.0 (9)	60.8
		CH_2OAc[c]	Ac	162.1	114.9	171.9	140.9	147.6	60.8
		CH_2OAc[e]	Ac[e]	164.5	114.1	174.6	140.2	149.9	60.2
499-78-5	**7**	COOH	H	152.6 (−2.8)	115.6 (1.4)	173.3 (0.5)	147.3 (1.0)	140.4 (0)	160.5
118-71-8	**8**	CH_3	H	154.3 (−1.1)	113.2 (−1.1)	172.1 (−0.8)	142.6 (−3.8)	148.9 (9)	13.8
1968-51-0	**9**	CH_2OH	H	154.9 (−0.4)	113.3 (−0.8)	173.1 (0)	142.4 (−4.0)	150.1 (10)	54.9

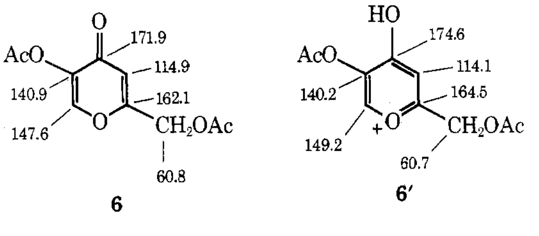
[a] OCH_3 56.1 ppm. [b] Me_2SO-d_6 solution. [c] $CDCl_3$ solution. [d] CH_3CO at 19.9 and 20.3 (CH_3) and 167.3 and 169.4 (CO). [e] $CDCl_3$ plus 1 equiv of TFA. [f] Vs. Me_2SO-d_6 taken as 39.4 ppm from Me_4Si. [g] Data taken from spectra run on a mixture of the compound in question vs. **2**. Minor differences may exist with difference in indicated chemical shift vs. that of **2** given in table. [h] $\Delta\delta$ taken from individual spectra, not competitive runs. [i] $\Delta\delta$ values inaccurate owing to broadness of the peak.

model, **13,** C-3 is deshielded because of the resonance effect of carbonyl, which induces a high positive charge density on this carbon.[12] In **12,** the opposite effect is seen for C-2, owing to resonance with the ether oxygen.[13] In **12,** C-1 is strongly deshielded by oxygen. Compound **11,** which contains both carbonyl and ether groups, shows a composite of the effects exhibited by **12** and **13.** The pyrone derivatives **2** and **8** are similar to **11,** but the difference in chemical shift between C-2 and C-3 ($\Delta\delta_{2,3}$ 41 ppm) is much less extreme. The model compounds **14** and **15** show that the effect of one vs. two double bonds conjugated with carbonyl is rather small,[14] and a similar effect is expected in **2** or **8** vs. **11.**[15] The relatively small $\Delta\delta_{2,3}$ for **2** may reflect an evening of charge distribution due to a degree of aromaticity (compare $\Delta\delta_{2,3}$ for furan, 40 ppm, compared to that calculated for methyl propenyl ether, >50 ppm).[16]

The carbonyl resonance is highly shielded in **1** and **2,** and not at all similar to other ketones (e.g., **13–15**).[17] The carbonyl chemical shift is more like that of an ester than a ketone. The shielded nature of the carbonyl is the result of rather low positive charge density on C-4 due to extensive delocalization.[12]

In acid solution, the protonated pyrone system is considered to have a greater degree of aromaticity.[3] However, in Me_2SO-d_6 solutions, not much change in chemical shift of the various carbons was noted upon addition of trifluoroacetic acid (TFA).[13,18] The solvent itself is fairly basic,[19] and the possibility exists that the solvent and substrate were in competition for acid. Most substrates were insoluble in $CDCl_3$, and investigations in this solvent were limited to **6** which was adequately soluble in $CDCl_3$ in both the protonated and unprotonated forms. The chemical shifts of **6** were found to be rather similar in $CDCl_3$ and Me_2SO-d_6. Addition of slightly over 1 equiv of TFA produced a moderate change in the chemical shift of C-2, C-4, and C-6.[17,18] These are precisely the carbons which possess a positive charge in certain resonance forms of the ion **6′**. On the other hand, C-3 and C-5 are slightly shielded.[20] However, the changes in the chemical shifts or coupling constants (Table II) were hardly striking.[17] Although 4-pyrones are reported to be comparatively strong bases,[6] the question remains whether the substrate was fully protonated (as opposed to a hydrogen bond between acid and carbonyl). The instability of the substrate precluded use of a stronger acid.[21]

Scheme II



6 **6′**

Substituent Effects. The shielding effects of CH_2X and of OR are similar to either alkene or benzene systems (e.g., for CH_3, the α effect is ~9 ppm, and the β effect is −3 ppm; for OH the α effect is ~30 ppm, and the β effect is ~−15 ppm).[22]

With regard to long-range shieldings, comparison of **1** with **2** shows that the CH_2OH group at C-2 shields C-5 by ~1 ppm. In **3,** the CH_2Cl group has a smaller effect. In **8,** the C-6 CH_3 shields C-3 by ~1 ppm (using **2** as a model). On the other hand, a −R substituent, COOH (as in **7**), at C-2 deshields C-5 by 2 ppm. The direction of chemical shift change is similar to aromatic heterocycles, e.g., furan.

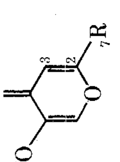
Coupling Constants. Perhaps the most interesting data occur for the coupling constants recorded in Table II. In many cases, it was possible to achieve a complete inventory of coupling constants. The spectra were not simulated, as all coupled protons were separated by large amounts compared to the coupling constants.[23] Signs of coupling constants were not determined, and are not implied in Table II. Structures **2′, 4′,** and **8′** illustrate typical data.

As in furan,[24] the one-bond coupling constant of the carbon nearest oxygen is near 200 Hz, whereas ^1J for C-3 is much smaller, ca. 167 Hz. In **2,** $^2J_{C3\text{-}H2}$ is 8.7 Hz, and $^2J_{C2\text{-}H3}$ is 6.5 Hz, similar to pyrone itself.[9] Substitution at C-2 appears to reduce the two-bond coupling constant; in **2, 8,** and **9** the value is ca. 6.5 Hz, but in **1, 4,** and **6,** it is ca. 4.7 Hz.

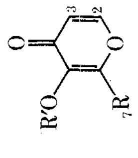
The coupling through O-1 ($^3J_{C2\text{-}H6} \sim 8$ Hz) is comparatively large, similar to findings in pyridine systems.[25,26] The coupling through carbonyl is also quite large ($^3J_{C5\text{-}H3} \sim 6$ Hz). It is noteworthy that sizable ^1H coupling constants were also found by Goldstein et al. in pyrone itself ($^4J_{H2\text{-}H6} = 1.1$ and $^4J_{H3\text{-}H5} = 2.8$ Hz).[9]

The coupling constants involving carbonyl are $^2J_{C4\text{-}H3} \sim$

Table II. ${}^{13}C-{}^{1}H$ Coupling Constants



1-7



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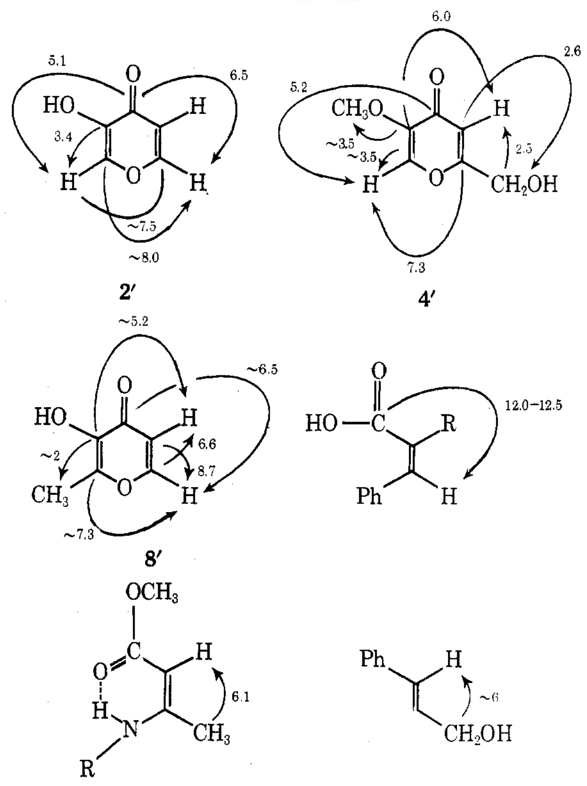
Compd	R	R′	${}^3J_{C2-H6}$	${}^2J_{C2-H7}$	${}^2J_{C2-H3}$	${}^1J_{C3-H3}$	${}^3J_{C3-H7}$[f]	${}^2J_{C4-H3}$	${}^3J_{C4-H6}$	${}^3J_{C5-H3}$	${}^2J_{C5-H6}$	${}^1J_{C6-H6}$	${}^3J_{C7-H3}$
1	CH_2OH	H	7.3	~4.7	~4.7	166.5	2.6	1.5	5.1	5.4	3.5	197.5	
2[c]	H	H	7.5		6.5	167		~1.5	5.1	5.5	3.4	198	
4[a]	CH_2OH	CH_3	~7.5	~4.5	~4.5	167.2	2.6	1.4	5.2	6.0	~3.5	198	2.5
6[b]	CH_2OAc	Ac	8.0	~4.9	~4.9	169	2.8	1.5	5.0	6.0	~2.0	201.7	
7	COOH	H	7.9		3.8			1.6	5.0	5.1	3.6	200	3.0
8[d]	CH_3	H			6.6	167.6				5.2			
9[e,g]	CH_2OH	H			6.4	168.0		1.5		5.5			

[a] ${}^3J_{C5-CH_3O} = \sim 3.5$; ${}^1J_{CH_3O-CH_3O} = 144.5$. [b] ${}^4J_{COCH_3-H6} = 0.8$; ${}^2J_{COCH_3-COCH_3} = 7.1$. [c] ${}^1J_{C2-H2} = 199.5$; ${}^2J_{C3-H2} = 8.7$; ${}^3J_{C4-H2} = 5.1$ or 6.5; ${}^3J_{C6-H2} \sim 8$. [d] ${}^2J_{C3-H2} = 8.7$; ${}^1J_{C2-H2} = 199.3$; ${}^2J_{C6-H7} \sim 7.3$; ${}^3J_{C6-H2} \sim 7.3$; ${}^3J_{C5-H7} \sim 2.2$. [e] ${}^1J_{C2-H2} = 197.5$; ${}^2J_{C3-H2} = 8.5$; ${}^3J_{C5-H7} = 2.0$. [f] H-7 is one of the protons of the protons of the R group. [g] Tentative assignment for ${}^3J_{C6-H2} \sim 5.6$.

Scheme III



1.5 and ${}^3J_{C4-H6} \sim 5$ Hz. The three-bond coupling constants are the source of a major difference between α,β-unsaturated carbonyl compounds and the pyrone derivatives of this study. In a study of over 20 α,β-unsaturated carbonyl compounds, ${}^3J_{CH}$ for trans nuclei has fallen in the range of 9–16 Hz,[27,28] which is substantially larger than the 5–6-Hz values observed in the pyrones. Representative compounds are shown in Scheme III. In alkenes, couplings between sp^3-hybridized groups (e.g., methyl) and a cis hydrogen are commonly ~6 Hz, whereas in the pyrones the value is ~3 Hz, similar to toluene. In comenic acid (**7**) the coupling constant between COOH and the cis hydrogen is ~3 Hz, substantially less than the 6–7-Hz values found in crotonic acid or cinnamic acid. In pyrones, the electronegative oxygen (O-1) should reduce ${}^3J_{CH}$, but hardly to the extent observed.

Experimental Section

Several possible solvents were tried, but only Me_2SO-d_6 was useful for all compounds. The concentrations used follow: **1**, 0.1 g/ml; **2**, 0.2 g/ml; **3**, 0.1 g/ml; **4**, 0.1 g/ml; **5**, 0.02 g/ml; **6**, 0.2 g/ml (Me_2SO-d_6 or $CDCl_3$, the latter also plus 0.2 and 0.35 ml TFA); **7**, 0.1 g/ml; **8**, 0.2 g/ml; and **9**, 0.1 g/ml. At the request of the referee, mixtures of **2** and each of the other compounds were run where material was available; the concentrations used in these cases was 0.017 g/ml of each component. The latter runs were the source of the $\Delta\delta$ values quoted in Table I. The data were taken on a Varian XL-100 instrument. For the normal runs, as in Table I, a 5K spectral width was used with a 0.4-s acquisition time, a 0.2-s pulse delay, and a 40-μs pulse width (tip angle ~60°). The error in the data acquisition calculated by the computer was 0.09 ppm. Usually 5K of transients were collected. For the data in Table II, a 1 or 2K spectral width was used with 1K filtering. A 4- or 2-s acquisition time was used along with a 1.5-s pulse delay, and a 30–40-μs pulse width. The error in data acquisition calculated by the computer in these cases was 0.5–0.25 Hz depending on spectral width. About 5–10K of transients were collected.

Kojic acid was obtained from Aldrich Chemical Co. For some experiments, an older commercial product was used that had been recrystallized a number of times. Both showed no apparent impurities. Maltol (**8**) was obtained from Fritzsche Bros. This material appeared pure by ${}^{13}C$ NMR and further purification was not attempted.

The following compounds were prepared by literature methods.

Pyromeconic acid (3-hydroxy-4-pyrone) (2), mp 116–117 °C (lit.[29] mp 117 °C).

2-Chloromethyl-5-hydroxy-4-pyrone (3), mp 165–166 °C (lit.[30] mp 166–167 °C).

2-Hydroxymethyl-5-methoxy-4-pyrone (5), mp 119–120 °C (lit.[31] mp 119–121 °C).

2-Acetoxymethyl-5-acetoxy-4-pyrone (6). This material was prepared by acetylation of kojic acid, mp 100–102 °C (lit.[32] mp 102 °C).

Comenic Acid (7). This compound was prepared by catalytic oxidation of kojic acid, mp 220 °C dec (lit.[33] mp not specified).

Hydroxymaltol (2-hydroxymethyl-3-hydroxy-4-pyrone) (9), mp 149–151 °C (lit.[34] mp 152–153 °C).

Acknowledgment. Partial funds for the purchase of the Varian XL-100 NMR instrument were provided by NSF Grant GP-10293, which is gratefully acknowledged.

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(17) Reference 12, p 114.

(18) Reference 12, p 115, shows that TFA causes much greater effect on the CO resonance of acetone (concentration of TFA not specified). See also G. E. Maciel and G. Natterstad, *J. Chem. Phys.,* **69,** 1030 (1965). In ^{1}H spectra, deshieldings of ca. 0.8 ppm for H-3 and ca. 0.5 ppm for H-2 of 4-pyrone have been reported (ref 3), on treatment with TFA.

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Reactions of Nitrogen Compounds with Ruthenium Tetroxide. 2. Oxidation of Tertiary Amines as a Convenient Alternative to von Braun Degradation[1]

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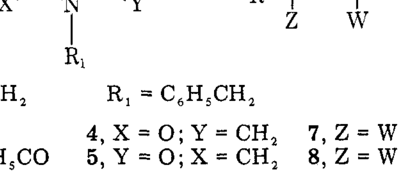
In the course of our previous work on the determination of the absolute configuration of cyclic amines, we correlated (*R*)-(−)-3-methylpiperidine (**1b**, n = 2) with (*R*)-(−)-2-methylglutaric acid (**8b**, n = 2) via (*R*)-(+)-1,5-dibromo-2-methylpentane (**7b**, n = 2), obtained from the benzoyl derivative (**2b**, n = 2) by the von Braun reaction.[2] This scheme could not be used with (*S*)-(+)-3-phenylpiperidine (**1d**, n = 2) and (*S*)-(+)-3-phenylpyrrolidine (**1d**, n = 1), the establishment of whose absolute configuration required much more laborious methods.[3,4]

von Braun's degradation fails with 3-arylamines (**1d**) because of drastic reaction conditions, low yields, and high boiling point of dibromo compound (**7d**). A possible alternative way to the von Braun reaction could be the direct oxidation of cyclic amines with ruthenium tetroxide. Among nitrogen compounds, it has been recently shown that amides[5,6] are oxidized by this reagent, but the few data reported in the literature indicate that only mixtures of intractable products are obtained when amines, without any acyl protection, are reacted with ruthenium tetroxide.[5,7]

In previous work in this field, we observed that ruthenium tetroxide has a low reactivity with the benzyl carbon attached to the nitrogen both in benzyllactams[8] and in *N*-acylamides having a phenyl group on the tertiary carbon adjacent to the nitrogen.[6] On the basis of this, we used ruthenium tetroxide to oxidize the *N*-benzyl derivatives of piperidines (**3a–d**, n = 2) and of pyrrolidines (**3a,d**, n = 1). This gave the corresponding imides (**6**), which were identified by their analytical and spectral characteristics, hydrolysis to the dicarboxylic acids (**8**), and by comparison with reference compounds prepared from the monoamides (**9**).

A very high optical yield was obtained in the oxidation of optically active amines. Hydrolysis of the imide *R*-(+)-**6b** (n = 2), obtained from *R*-(−)-**3b**, gave optically pure (*R*)-(−)-2-methylglutaric acid.[2] Analogously, the amines *S*-(−)-**3d** (n = 1, 2) gave the corresponding imides, which showed an optical rotation with the same sign as, but of a higher absolute



X = Y = H$_2$ R$_1$ = C$_6$H$_5$CH$_2$

1, R$_1$ = H
2, R$_1$ = C$_6$H$_5$CO
3, R$_1$ = C$_6$H$_5$CH$_2$
4, X = O; Y = CH$_2$
5, Y = O; X = CH$_2$
6, X = Y = O
7, Z = W = CH$_2$Br
8, Z = W = COOH
9, Z = COOH; W = CONHCH$_2$C$_6$H$_5$

a, R = H; **b**, R = CH$_3$; **c**, R = C$_2$H$_5$; **d**, R = C$_6$H$_5$ (n = 1, 2)