Registry No.—Ethyl ether, 60-29-7.

Acknowledgment.—We gratefully acknowledge the research support of the National Science Foundation (Grant No. GP-5312) and the Petroleum Research Fund (Grant No. 1382-Al) for their financial contributions to this project. We are also indebted to Messrs. John Christianson, Larry Grina, and Steven Desiack for assistance in various phases of this project and to Mr. William Stiles for the construction of the cooling baths used in these experiments. The assistance of the National Science Foundation (Grant No. GP-3642) in the purchase of the nmr spectrophotometer is greatly appreciated.

Ring-Chain Tautomers of 6-Substituted 2-Acetylbenzoic Acids

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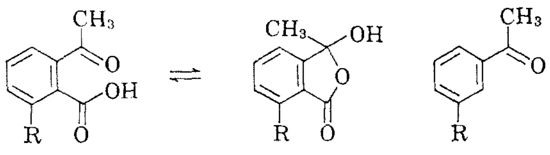
Received April 21, 1967

During an investigation in these laboratories, 2-acetyl-6-nitrobenzoic acid and the corresponding 6-amino and 6-hydroxy analogs were prepared according to published procedures.[1] These substances are of a class which could show ring-chain tautomerism, A ⇌ B. The literature contains conflicting reports on the structure of 2-acetylbenzoic acid when the infrared spectrum was the criterion used. Grove and Willis[2] concluded that 2-acetylbenzoic acid in the solid state exists in the ring form B, whereas Jones and Congdon,[3] in a similar study, favored the chain form A. Wheeler[4] indicated that the ultraviolet spectrum supported the ring structure for the compound in solution. The subject of ring-chain tautomerism has been extensively studied, and was reviewed by Jones.[5] He suggested that nuclear magnetic resonance (nmr), which had not been used up to that time in such studies, should be very effective for ring-chain structural determinations. The advantage of nmr spectroscopy was demonstrated subsequently by Lansburg and Bieron[6] for normal and pseudo-ester tautomers. Similarly, Erley and coworkers[7] later reported that a single methyl peak at high field (δ 1.98 in deuteriochloroform) was evidence for the ring structure for 2-acetylbenzoic acid (Ic). This view was later modified[8] in favor of a ring-chain tautomeric mixture (predominantly ring tautomer) in fast equilibrium, A ⇌ B, rather than the single tautomer B. A similar interpretation could account for the single methyl peak observed at δ 1.83 for 2-acetyl-6-methylbenzoic acid[8] in chloroform, although it is clear that the ring form predominates.



A B II

Ia, R = NH_2
b, R = OH
c, R = H
d, R = NO_2

We have found that the nmr spectrum of Ic in *dimethyl sulfoxide-d_6 solution* showed the presence of *both* forms A and B, with methyl bands located at δ 2.45 and 1.78, respectively. The former band is attributed to the chain form A, since acetophenone showed a methyl singlet at δ 2.58; the latter band is assigned to the ring form (B). Relative intensities of the bands indicated a ratio of 1:2 for A and B, and led to a weighted average chemical shift of δ 2.00. This value is in good agreement with δ 1.98 for the methyl peak observed in $CDCl_3$ solution by Erley and coworkers.[8] Furthermore, we found that the two bands coalesced to a single band at δ 2.02 when a trace of hydrochloric acid was added to promote fast interconversion of tautomers.

The infrared data (potassium bromide disks) for the four acetylbenzoic acids are listed in Table I. Ia showed zwitterion absorption and the spectrum was not obvious support for either tautomer. The strong intensity of a band at 3280 (bonded OH), a shoulder at 1742, and a strong band at 1704 cm^{-1} (chelated lactol carbonyl) indicated predominance of the ring form for Ib. A maximum at 1727 cm^{-1} indicated a ring tautomer for Ic, but the broadness (half-band width 90 cm^{-1}) indicated the presence of some chain form. The spectrum of Id showed bands at 1720 and 1695 cm^{-1} assigned to carboxylic acid and ketone groups.

The ultraviolet data (see Table I) indicated that Ia, Ib, and Ic[5] were predominantly in the ring form (entries 1, 2, and 3 resembled entries 9, 10, and 11, respectively, rather than entries 5, 6, and 7, respectively), and that Id was predominantly in the chain form (entry 4 resembled entry 8 rather than entry 12).

The nmr data for four 2-acetylbenzoic acids and the four corresponding acetophenones are summarized in Table I, and the following conclusions were made. (1) 2-Acetyl-6-nitrobenzoic acid (Id) exists predominantly as the chain structure A. (2) 2-Acetyl-6-hydroxybenzoic acid (Ib) and 2-acetyl-6-aminobenzoic acid (Ia) exist predominantly as the ring structure B. (3) 2-Acetylbenzoic acid (Ic) exists as a *mixture* of ring-chain tautomers A and B in a ratio of 2:1 (*vide supra*). The methyl group of the acetophenones and the chain tautomers (A) falls in the range of δ 2.53 ± 0.15 ppm, whereas that of the ring tautomers (B) falls in a different range, δ 1.73 ± 0.05 ppm. Also, the chemical shift of the methyl group of acetophenones was dependent upon the conjugative effect of the substituent *meta* to the ketonic substituent (with respect to δ values: $NO_2 > H > OH > NH_2$). The preference of 2-acetylbenzoic acids toward ring formation apparently follows the reverse trend: $NH_2 \cong OH > H > NO_2$.

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TABLE I

PHYSICAL DATA OF 2-ACETYLBENZOIC ACID AND RELATED COMPOUNDS

Entry	Compound	Nmr data, δ^{CH_3}		Ultraviolet spectral data		Infrared data, cm^{-1}
		Ring	Chain	$\lambda_{max}^{2\text{-propanol}}$	$\epsilon \times 10^{-3}$	
	2-Acetylbenzoic acids					
1	Ia (R = NH_2)	1.68		218, 250, 335,	20.00, 7.70, 4.50,	3348, 3356, 1724, 1706, 1623
2	Ib (R = OH)	1.77		223, 302	6.15, 4.12	3280, 2700, 2500, 1742 (sh), 1704
3	Ic (R = H)	1.78	2.45	228, 272, 280	9.00, 0.98, 0.97	3257, 1727
4	Id (R = NO_2)		2.38	217	15.00	3300–3100, 2700–2500, 1720, 1695
				$\mu_{max}^{ethanol}$	$\epsilon \times 10^{-3}$	
	Acetophenones					
5	IIa (R = NH_2)		2.48	231,[a] 225 (infl), 368,	22.90, 10.00, 1.90	
6	IIb (R = OH)		2.53	218,[a] 252.5	25.12, 10.00	
7	IIc (R = H)		2.58	224,[a] 278	12.60, 1.00	
8	IId (R = NO_2)		2.68	226,[a]	22.40	
9	Methyl *o*-aminobenzoate[a]			247, 337	5.01, 5.01,	
10	Methyl *o*-hydroxybenzoate[a]			238, 306	9.33, 4.37	
	3-Ethyl-7-hydroxyphthalide[a]			234, 300	7.00, 4.60	
11	Methyl benzoate[a]			228, 273, 280	12.00, 0.87, 0.73	
	Phthalide[b]			227, 273, 280	9.90, 1.72, 1.66	
12	Ethyl *o*-nitrobenzoate			255 (infl), 325 (infl)	4.47, 0.52	

[a] "Organic Electronic Spectral Data," Vol. I–IV, Interscience Publishers, Inc., New York, N. Y. 1946–1966, various editors. [b] W. A. Schroeder, P. E. Wilcox, K. N. Trueblood, and A. O. Dekker, *Anal. Chem.*, **23**, 1740 (1951).

Summary.—Based upon nmr spectra of 6-substituted 2-acetylbenzoic acids in dimethyl sulfoxide-d_6 solutions, the presence of ring and chain tautomers could be deduced from the position of the methyl bands. A high-field signal indicated the presence of the ring form, while a low-field signal indicated the presence of the chain form.

Experimental Section

2-Acetylbenzoic acid was obtained from Aldrich Chemical Co., Inc., Milwaukee, Wis. 53210. The 6-nitro, 6-amino, and 6-hydroxy derivatives were prepared according to published procedures. Infrared spectra of samples in potassium bromide disks were determined on a Beckman IR-5 instrument. Ultraviolet spectra were measured on a Cary spectrophotometer (Model 14M). Nuclear magnetic resonance spectra (10–15% w/w dimethyl sulfoxide-d_6 solutions with tetramethylsilane as internal reference) were obtained on a Varian A-60 spectrometer. Melting points were checked on a Uni-melt Thomas–Hoover capillary melting point apparatus for comparison with literature values.[1]

Registry No.—Ia-B, 13619-67-5; Ib-B, 13619-68-6; Ic-A, 577-56-0; Ic-B, 1828-76-8; Id-A, 13619-70-0; IIa, 99-03-6; IIb, 121-71-1; IIc, 98-86-2; IId, 121-89-1; ethyl *o*-nitrobenzoate, 610-34-4.

Acknowledgment.—We wish to thank Mr. John A. Romano for assistance in the preparation of the compounds.

Absence of Rearrangement in the *p*-Nitrophenethyl Group

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p-Nitrophenethyltrimethylammonium iodide labeled with tritium was prepared[1] by Scheme I. Since one or more of these reactions could proceed by way of a nonclassical carbonium ion with possible rearrangement, it was necessary to establish the amount of rearrangement which occurred during the synthesis.

SCHEME I

$$\text{phenylacetic acid} \xrightarrow{\text{LiAlH}_4} \text{phenethyl alcohol} \xrightarrow[\text{and hydrolysis}]{\text{fuming HNO}_3\text{ on ester}}$$

$$p\text{-nitrophenethyl alcohol} \xrightarrow[\text{HBr}]{48\%}$$

$$p\text{-nitrophenethyl bromide} \xrightarrow[\text{N(CH}_3)_3]{\text{KI,}}$$

$$p\text{-nitrophenethyltrimethylammonium iodide}$$

Lee and Spinks[2] found that rearrangement occurred to the following extents when 2-phenylethanol-1-^{14}C was treated with thionyl chloride alone (49.4%), with thionyl chloride in pyridine (0.0%), with 48% hydrobromic acid (6.2%), with 55% hydriodic acid (2.7%), and with phosphorus and iodine (6.4%). Roberts and Regan[3] treated a number of 2-(*p*-substituted phenyl)-ethylamines with nitrous acid in water and in acetic acid and found that the most rearrangement (45%) occurred in acetic acid with 2-(*p*-methoxyphenyl)-ethylamine and that the least rearrangement (about 5%) occurred with 2-(*p*-nitrophenyl)ethylamine in water or acetic acid. The reaction of 2-phenylethylamine with nitrous acid in acetic acid, which has been reinvestigated with the aid of gas chromatography,[4] gives both 1-phenylethyl acetate (I) and 2-phenylethyl acetate (II). When 2-phenylethylamine-1-^{14}C is used, I shows 0.23% migration of carbon-14 and II shows 27% migration.

In this investigation, 2-(*p*-nitrophenyl)ethyl-1-^{14}C-trimethylammonium iodide was prepared by the same scheme shown earlier, each compound was oxidized with alkaline permanganate to benzoic acid or *p*-nitrobenzoic acid, and these acids were assayed for radioactivity. The results, given in Table I, indicate that

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