Ring–Chain Tautomerism in *o*-Acylbenzoic Acids. A Comparison of Experimental Methods and a Study of Substituent Effects[1]

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Ten *o*-acylbenzoic acids containing varying substituents in the aromatic ring have been examined from the point of view of their ability to exist as ring and chain tautomers. Experimental methods employed were the Fischer esterification and infrared, ultraviolet, and n.m.r. spectroscopy. The conclusions about a single acid from all four methods are not always consistent. The n.m.r. method, applicable to *o*-acetylbenzoic acids, is highly recommended for expediency and accuracy. Although more data would be required to make a full analysis of substituent effects, it is clear that groups *ortho* to the carboxy or acyl functions can exert more than merely a steric effect. The results lead to generalizations about the difference between the acetyl and benzoyl series and the relative effectiveness of 3 and 6 substituents.

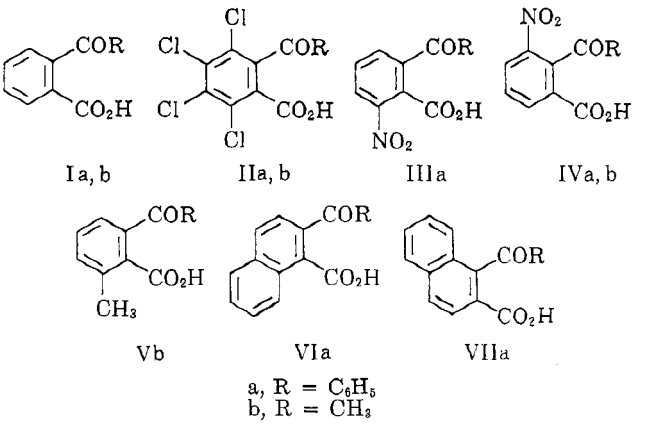
Among the structural types exhibiting ring–chain tautomerism, the β-acyl acids, including *o*-acylbenzoic acids, have been perhaps the most extensively explored from the point of view of numbers of examples and accumulation of direct experimental evidence.[2] In particular, Newman has made a thorough study of ring–chain tautomerism in methyl-substituted *o*-benzoylbenzoic acids with Fischer esterification experiments and by employing infrared and ultraviolet spectroscopy.[3]

From these measurements information on both the kinetic and equilibrium products was obtained. An interpretation of the results was based on possible alternative esterification mechanisms and on a subtle and changing balance between steric[3a] and resonance[3b] effects.

Because the methyl substituent is the only one which has been examined in detail, it is particularly difficult to estimate the relative importance of electronic and steric effects. We therefore undertook the study of a group of *o*-acylbenzoic acids containing widely varying substituents in the "benzoic acid" ring with two goals in mind: (1) to compare results on ring–chain tautomerism obtained by diverse physical and chemical methods; and (2) to determine whether the tendency for formation of ring or chain structure in these acids is predictable on steric and/or electronic grounds.

Synthesis of Acids.—In order to examine a fairly large number of compounds with a variety of substituents at both the 3- and 6-positions, we prepared the *o*-acylbenzoic acids shown in Chart I. They were obtained by one of three methods from the appropriate phthalic anhydride: Friedel–Crafts acylation of benzene or addition of either an organocadmium reagent or a Grignard reagent. Specific mention is warranted for those acids which are new or were synthesized previously by other means. Acids VIa and VIIa were prepared by treatment of 1,2-naphthalic anhydride with phenylcadmium reagent, both being formed in roughly equal amounts. Separation was accomplished by taking advantage of their contrasting solubilities in benzene. The new acid IIb was obtained by similar addition of the methylcadmium reagent to 3,4,5,6-tetrachlorophthalic anhydride. The attack of phenylcadmium reagent on 3-nitrophthalic anhydride led to a mixture of IIIa and IVa, which were separated by selective extraction from chloroform.

CHART I



Assignment of structure Vb (rather than the isomer) to the acid product, from inverse addition of methylmagnesium iodide to 3-methylphthalic anhydride, stems from the expected attack of the Grignard reagent at the unhindered carbonyl, which on electronic grounds should also be more reactive. This is in accord with conclusions by Newman and co-workers[4] on the behavior of aryl Grignard reagents with this same anhydride.

Fischer Esterification.—The esterification experiments were carried out by allowing the acid to react with hydrogen chloride in dry methanol at reflux for an appropriate period of time. The mixture of esters was isolated by conventional means and the composition was determined directly by n.m.r. analysis. This method is based on the recent observations by Lansbury and Bieron that normal and pseudo esters exhibit substantially different chemical shifts.[5] A simple integration of the two peaks attributable to $-OCH_3$ in the normal and pseudo esters gave the relative amounts of each in the mixture. In the case of *o*-acetylbenzoic acids, we could also use the chemical shifts and relative intensities of the $-C-CH_3$ group for analysis and as confirmation of the results based on the $-OCH_3$ group.

Our results on the equilibrium concentrations of normal and pseudo esters in the Fischer esterification of acids I–VII are presented in Table I. A 3-hr. period

(1) This research was supported in part by the Research Corporation and by the Central University Research Fund of the University of New Hampshire.

(2) P. R. Jones, *Chem. Rev.*, **63**, 461 (1963).

(3) (a) M. S. Newman and C. W. Muth, *J. Am. Chem. Soc.*, **73**, 4627 (1951); (b) M. S. Newman and C. Courduvelis, *J. Org. Chem.*, **30**, 1795 (1965).

(4) M. S. Newman and C. D. McCleary, *J. Am. Chem. Soc.*, **63**, 1542 (1941); M. S. Newman and C. W. Muth, *ibid.*, **72**, 5191 (1950).

(5) P. T. Lansbury and J. F. Bieron, *J. Org. Chem.*, **28**, 3564 (1963).

TABLE I

FISCHER ESTERIFICATION OF ACIDS I–VII

Acid	Time, hr.	Ester, %	Type of ester, % Normal	Pseudo
Ia	3	59	100, 98[a]	0
IIa	0.25	53[b]	76	24
	3	87[b]	83	17
IIIa	3	91	100	0
IVa	3	60[b]	100	0
Va	...	...	63[a]	
VIa	3	83	0	100
VIIa	3	100	42	58
Ib	0.25	82	40	60
	3	66	25	75
IIb	0.25	73	0	100
	3	53	0	100
IVb	3	73	87	13
Vb	3	79	0	100

[a] Reference 3b. [b] Acid recovered.

has previously been assumed to be sufficient to attain equilibrium.[3,6] We checked the variation in composition with time for three of the acids, Ib, IIa, and IIb. That 3 hr. was ample time to attain equilibrium is shown by the observation that the pseudo methyl ester of IIb, the exclusive product after 3 hr., was itself unchanged after being treated an additional 3 hr. under the same conditions. Furthermore, the pseudo ester was the sole product from the acid after only 15 min. at reflux. In this case at least equilibrium is attained very rapidly indeed. Both Ib and IIa gave mixtures after 15 min. which were not greatly different in composition from the equilibrium values, and the predominant isomer remained the same (pseudo ester in the case of Ib, normal ester in the case of IIa). This is in sharp contrast to the recent results of Newman and Courduvelis,[3b,6] who observed the predominance of kinetic product after 15 min. at 55.5° with 3,6-dimethylbenzoic acid. One explanation for the difference is our more vigorous conditions, possibly being sufficient to establish equilibrium in a much shorter period. It may also be a reflection of the greater reactivity of acetylbenzoic acids compared to benzoylbenzoic acids. That the yields of ester from both Ib and IIb were higher after the shorter reaction period suggests a secondary reaction (very likely condensation) in the acetyl series.

Certain conclusions about the effect of substituents on the equilibrium composition of esters are forthcoming from the results. (1) When there is any difference in effect between a 3 and 6 substituent, it is such that the 6 substituent exerts a stabilization of the pseudo ester. The 3 substituent has little or no effect. This generalization is warranted by Newman's observation on the 3- and 6-methylbenzoylbenzoic acids[3b] and also fits the comparative equilibrium positions for VIa *vs.* VIIa; Ia *vs.* IIa; and Ib *vs.* IIb in the present work. (2) The effect of a substituent is not solely steric in nature. If that were the case, one would expect the pseudo ester of IIIa to be more stable than the pseudo ester of Va, whereas the reverse is actually observed. (3) A pseudo ester in the *o*-acetyl series is energetically favorable by comparison to the pseudo ester with similar substituents in the *o*-benzoyl series (Compare Ia and Ib, IIa and IIb, IVa and IVb, and Va and Vb). This is readily explained for the unsubstituted acids Ia and Ib, since the loss of resonance stabilization from the normal ester of Ia would be unfavorable to formation of the cyclic tautomer. A similar argument would hold for the pair Va and Vb but not for the pair IVa and IVb, where resonance stabilization even in the chain tautomer is small because of the steric effect. It may be that a 3 substituent destabilizes the cyclic ester for steric and/or electronic reasons, but that this effect is more significant in the benzoyl series. This distinction between the two series may be important in closely related problems, such as the kinetics of esterification and saponification of *o*-acylbenzoic acids.[7]

Infrared Spectra.—Ideally the ring and chain structures of these anhydrous *o*-acylbenzoic acids should exhibit characteristically different spectra.[2] One assumes that only the ring structure shows typical –OH absorption (3300–3600 cm.$^{-1}$) while the carbonyl bands for the ring ("lactol") and chain ("keto acid") compounds would differ in position and number. Because of the lack of "pure" tautomers, a quantitative analysis is not possible. The infrared spectra of all acids were measured as mulls (Nujol and halocarbon, 4000–650 cm.$^{-1}$) because of their extremely low solubility in chloroform. Thus, results are qualitative, and one can hope to determine only whether both isomers are present in the solid state to any appreciable extent. (The limit of sensitivity of the spectrophotometer is probably 5%.) The infrared measurements are shown in Table II. All spectra except that of VIIa give evidence of only one tautomer.

TABLE II

INFRARED SPECTRA OF ACIDS[a]

Acid	ν, cm.$^{-1}$ OH region	Carbonyl region	Predominant (or exclusive) isomer
Ia	3000	1695, 1665	Chain
IIa	3280	1740	Ring
IIIa	2800	1715, 1675	Chain
IVa	2900	1710, 1690	Chain
VIa	3300	1723	Ring
VIIa	3300	1725, 1675	...
Ib	3260	1725	Ring
IIb	3180	1755	Ring
IVb	2950	1710, 1690	Chain
Vb	3350	1750	Ring

[a] Determined as Nujol mulls, except for Ia which was determined in chloroform, and Vb which was determined as liquid film.

Ultraviolet Spectra.—By a comparison of position maxima and intensities in the ultraviolet region we have drawn conclusions as to the predominant or exclusive isomer present in dilute ethanol solution (methanol in one case). The results are tabulated in Table III. In the case of VIIa, where we were able to purify both isomeric esters as model compounds, we can calculate the relative amounts of each tautomeric acid by a simple ratio of intensities of the bands at 291 and 312 mμ. The value comes out to be 83% ring tautomer. A similar estimate was not possible with Ia, according to Newman and Muth,[3a] because the spectra of both ester samples show significant ab-

(6) M. S. Newman and C. Courduvelis, *J. Am. Chem. Soc.*, **86**, 1893 (1964).

(7) (a) M. S. Newman and S. Hishida, *ibid.*, **84**, 3582 (1962). (b) M. L. Bender and M. S. Silver, *ibid.*, **84**, 4589 (1962).

TABLE III

ULTRAVIOLET SPECTRA OF ACIDS AND ESTERS[a,b]

	Acid		Esters				
			Normal		Pseudo		
No.	λ_{max}, mμ	log ε	λ_{max}, mμ	log ε	λ_{max}, mμ	log ε	Predominant (or exclusive) tautomer
Ia	244	3.69	244	4.15	280	3.18	
					244	4.15	Chain
IIa	244	4.01	247	3.19[c]	...	...	Chain(?)
IIIa	248	4.28	247	4.03	...	...	Chain
IVa	246	3.96	246	4.07	...	...	Chain
VIa	292	3.78	...	...	306	3.80	
	234	4.51			241	4.50	Ring
VIIa	291	3.72	240	4.50	312	3.80	
	228	4.56[d]	227	4.41	225	4.59	Ring
Ib	279	3.00	...	...	278	2.95[e]	
	272	3.00			272	2.88	
	229	3.98			230	4.18	Ring
IIb	305	2.95	...	...	305	3.16	
	295	2.92			295	3.06	
	222	4.44			224	4.59	Ring
IVb	247	3.72	247	3.72[f]	...	...	
	216	4.28	217	3.84			Chain
Vb	284	2.68	...	...	284	3.06	
	235	3.71			234	3.57	Ring

[a] Spectra were determined in 95% ethanol except acid Ib (methanol). [b] Concentrations were 5×10^{-5} *M* except IVa (10^{-4}) and Vb (6×10^{-5}). [c] Found to be 83% normal by n.m.r. analysis. [d] Midpoint of a broad maximum. [e] Found to be 75% pseudo by n.m.r. analysis. [f] Found to be 87% normal by n.m.r. analysis.

sorption at 244 mμ.[8] Here as with some other acids we used the absence of a typical maximum (in this case at 280 mμ) as evidence against the presence of that corresponding tautomer in the free acid. Where we used as models a mixture of esters of known composition (with acids IIa, Ib, and IVb), this was taken into account in the semiquantitative estimate.

N.m.r. Spectra.—N.m.r. spectroscopy was a reialble and extremely simple method of determining the composition of products from the Fischer esterifications. As first observed by Lansbury and Bieron,[5] the chemical shifts measured in carbon tetrachloride owing to $-OCH_3$ are at substantially lower field when they are part of a chain structure (normal ester) than when they make up a ring (pseudo) ester. In Table IV the chemical shifts for normal and pseudo esters from acids I–VII as measured in chloroform have been assembled. The structures of the tautomeric esters are substantiated by their infrared spectra in every case. Values for the esters of *o*-benzoylbenzoic acid (Ia) are comparable to those published.[5] The Δ values ($\delta_{MeO(pseudo)} - \delta_{MeO(normal)}$) range from 0.28 p.p.m. for the esters from IIa to 0.84 p.p.m. for those from Ib. There is a similar distinction in chemical shift of the C–CH_3 protons in the esters from *o*-acetylbenzoic acids. Here the Δ values ($\delta_{Me(pseudo)} - \delta_{Me(normal)}$) are 0.70 and 0.65 for esters of Ib and IVb, respectively. The corresponding Δ value for the methyl esters of 8-acetyl-1-naphthoic acid is 0.75.[5]

TABLE IV

CHEMICAL SHIFTS (τ) FOR NORMAL AND PSEUDO METHYL ESTERS[a]

	Normal ester		Pseudo ester	
Parent Acid	$-OCH_3$	$-CH_3$	$-OCH_3$	$-CH_3$
Ia	6.53	...	6.74	...
IIa	6.36	...	6.64	...
IIIa	6.27	...	...	...
IVa	6.32	...	...	...
VIa	...	...	6.67	...
VIIa	6.27	...	6.67	...
Ib	6.10	7.47	6.94	8.17
IIb	...	...	6.82	8.05
IVb	6.05	7.30	6.77	7.95
Vb	...	...	6.95	8.21

[a] All spectra were determined in chloroform except the first (carbon tetrachloride) and second (deuteriochloroform) entries, with tetramethylsilane as internal standard.

A point of great interest concerns the effect of substitution on the position of δ. It can be seen from Table IV that both δ_{MeO} and δ_{Me} for normal or pseudo esters in both the benzoyl and acetyl series shift in accord with the inductive effects of the ring substituents. Thus, the methyl-substituted esters exhibit values at higher field than those of the parent esters, while values for the chloro and nitro esters are lower. This suggests a correlation of δ with σ_I as has been observed with *m*-fluorobenzene derivatives.[9] Although the relationship between σ_I and δ_{MeO} or δ_{Me} pseudo esters of Ib, IIb, IVb, and Vb is close to linearity, considerably more data must be accumulated before a conclusion is warranted.

Two approaches to estimating the position of ring–chain equilibrium in the free acids by n.m.r. spectroscopy come to mind. One is analysis of the –OH peak owing to presence of the ring tautomer. We were unable to detect a peak assignable to –OH even in those acids which appear to be largely cyclic, presumably because of the low concentration of sample in chloroform. The other approach, applicable only to the *o*-acetylbenzoic acids, is a comparison of δ_{Me} for the acids and their esters. Table V is a compilation of the available δ_{Me} values. If the peaks from the acids are due to a single isomer (that is, if equilibration between tautomers is slow relative to the chemical shift), the

(8) Newman and Courduvelis[3b] have very recently revised the ultraviolet analysis of the *o*-benzoylbenzoic acids based on absorption in the 325–340-mμ region.

(9) R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Andersen, and G. T. Davis, *J. Am. Chem. Soc.*, **85**, 709 (1963).

TABLE V
N.M.R. ANALYSIS OF RING–CHAIN TAUTOMERISM

Acid	δ_{Me}	$\delta_{Me(normal\ ester)}$	$\delta_{Me(pseudo\ ester)}$	% ring tautomer
Ib	8.02	7.47	8.17	79
IIb	7.97	...	8.05	Predominant
IVb	7.67	7.30	7.95	57
Vb	8.17	...	8.21	Predominant

slight downfield shift for IIb and Vb in going from the pseudo ester to the ring tautomeric acid is reasonable on the basis of a greater deshielding effect from –OH than from $-OCH_3$. On the other hand, if the equilibration is fast relative to the chemical shift, the δ_{Me} values in the acids are time averages from the two isomers. This seems most likely the case for IVb, where the shift is relatively large. We can then estimate the equilibrium composition[10] from a ratio of shifts in δ_{Me}, provided δ_{Me} values are available for both tautomeric esters, as is the case for Ib and IVb. The method is based on the assumption that the pure acid tautomers would exhibit δ_{Me} values identical with those in the model esters. If there is a small shift in δ_{Me} from pseudo ester to ring tautomeric acid, the equilibrium mixture would be even richer in cyclic isomer than calculated; thus our values for ring tautomer represent minima. Although the normal esters of IIb and Vb were not available as models, the close similarity in δ_{Me} for acids and pseudo esters indicates a marked predominance of the ring tautomers. To settle the question of the rate of equilibration of acid tautomers requires low-temperature apparatus, which was not available to us at the time of this work.

Conclusions.—Table VI contains a summary of results from Fischer esterification, infrared[11], ultraviolet,[12] and n.m.r. spectroscopy. The predominant isomer (acid or ester) is noted, provided a substantial preference for one isomer was indicated from the results. It is surprising that the conclusions for the various acids are usually in agreement, even though methods entail widely varying experimental conditions. It would not have been unexpected, for example, that the predominant isomer in the solid state would be different from the favored one in dilute methanol solution. Because the results from the Fischer esterification and the spectral methods are most often consistent, it is indicated that the acid and ester are both energetically favored in the same tautomeric form, a generalization which could not have been predicted. In cases where the results are not consistent, we would strongly favor those from physical measurements as evidence for the stabler tautomeric structure of the free acid.

TABLE VI

	Predominant isomer			
Acid	Fischer esterification	Infrared	Ultraviolet	N.m.r.
Ia	Chain[a]	Chain	Chain[a]	...
IIa	Chain	Ring	Chain(?)	...
IIIa	Chain	Chain	Chain	...
IVa	Chain	Chain	Chain	...
VIa	Ring	Ring	Ring	...
VIIa			Ring	...
Ib	Ring	Ring[b]	Ring[c]	Ring[b]
IIb	Ring	Ring	Ring	Ring
IVb	Chain	Chain	Chain	
Vb	Ring	Ring	Ring	Ring

[a] Reference 3. [b] Reference 11. [c] Reference 12.

(10) E. L. Eliel, *Chem. Ind.* (London), 568 (1959).
(11) W. J. Potts, D. S. Erley, P. R. Jones, and P. J. Desio, *ibid.*, 1915 (1964).
(12) O. H. Wheeler, *Can. J. Chem.*, **39**, 2603 (1961).

The work reported here illustrates the complexity of measuring and explaining ring–chain tautomeric equilibria. The experimental methods based on physical measurements appear more promising; particularly the n.m.r. approach is direct and dependable. Interpretation of structural effects has led to some preliminary generalizations, which, hopefully, can be expanded or modified with the accumulation of more data.

Experimental Section[13]

***o*-Benzoylbenzoic Acid.**—Pure, anhydrous *o*-benzoylbenzoic acid was prepared by recrystallizing student preparation grade acid[14] from benzene. The acid was made anhydrous[14] and had a melting point of 127° (lit.[14] m.p. 126–127°).

3,4,5,6-Tetrachloro-2-benzoylbenzoic Acid.—This acid was prepared by following the procedure for that of β-benzoylpropionic acid[16] as a model, from 97.2 g. (0.34 mole) of tetrachlorophthalic anhydride, 175.0 g. (2.25 moles) of dry benzene, and 100.0 g. (0.75 mole) of powdered anhydrous aluminum chloride. By recrystallization from ethanol–water 82.0 g. (66.3%) of a white, powdery acid was obtained, m.p. 191–192° (lit.[16] m.p. 200°).

Anal. Calcd. for $C_{14}H_6Cl_4O_3$: C, 46.19; H, 1.66; Cl, 38.95. Found: C, 46.08; H, 1.71; Cl, 39.03.

3-Nitro-2-benzoylbenzoic and 6-Nitro-2-benzoylbenzoic Acids.—The cadmium reagent was prepared as previously described[17] from 6.3 g. (0.26 g.-atom) of magnesium, 40.8 g. (0.26 mole) of bromobenzene, 47.7 g. (0.26 mole) of cadmium chloride, and 350 ml. of ether. To this mixture was added 50.0 g. (0.26 mole) of 3-nitrophthalic anhydride,[18] with stirring, in 15 min. Stirring and heating under reflux were maintained for 6.5 hr., then the flask was surrounded by an ice bath, and the mixture was decomposed with dilute sulfuric acid. The solution was filtered and 23.6 g. of a mixture of 3-nitrophthalic acid and 3-nitrophthalic anhydride was obtained. The ether layer was separated from the water layer and combined with ether washings of the water layer. The combined ether layer was washed with 0.2 mole of potassium carbonate, and the alkaline solution was acidified with 10% hydrochloric acid. A brown solid (20.5 g.) consisting of a mixture of two keto acids separated and was removed by filtration. Separation was accomplished by crystallization from chloroform in which 3-nitro-2-benzoylbenzoic acid was the less soluble. The chloroform-soluble 6-nitro-2-benzoylbenzoic acid (11.3 g., 16.0%) was dissolved in 10% potassium carbonate, and the alkaline solution was slowly acidified with 10% hydrochloric acid over a period of 2 days: m.p. 156–160° (lit.[19] m.p. 159–160°). The chloroform-insoluble 3-nitro-2-benzoylbenzoic acid (9.1 g., 12.9%) was similarly purified: m.p. 231–235° (lit.[19] m.p. 237°).

1-Benzoyl-2-naphthoic and 2-Benzoyl-1-naphthoic Acids.—The preparation from 1,2-naphthalic anhydride[20] and phenylcadmium reagent was carried out as above. The crude solid (6.6 g.) consisted of a mixture of the two keto acids. Separation

(13) Microanalyses were determined by Galbraith Laboratories, Knoxville, Tenn. The boiling points and melting points are uncorrected. The melting points were taken in a Hershberg melting point apparatus. The infrared absorption spectra were determined with a Perkin-Elmer Model 21 infrared spectrophotometer with sodium chloride optics or a Perkin-Elmer Model 337 grating infrared spectrophotometer. The n.m.r. spectra were determined with a Varian Model A-60 n.m.r. spectrometer. The ultraviolet absorption spectra were determined with a Perkin-Elmer Model 4000 recording spectrophotometer and a Beckman Model 2400 DU spectrophotometer.
(14) L. Fieser, "Experiments in Organic Chemistry," 3rd Ed., D. C. Heath and Co., Boston, Mass., 1957, p. 160.
(15) L. F. Somerville and C. F. H. Allen, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1959, p. 81.
(16) G. Kircher, *Ann.*, **238**, 338 (1887).
(17) P. R. Jones and S. L. Congdon, *J. Am. Chem. Soc.*, **81**, 4291 (1959).
(18) B. H. Nicolet and J. A. Bender, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1961, p. 410.
(19) J. Tirouflet, *Bull. Soc. Sci. Bretagne*, **Spec. No. 26**, 7 (1951).
(20) E. B. Hershberg and L. F. Fieser, ref. 15, p. 423.

was accomplished by crystallization from benzene in which 1-benzoyl-2-naphthoic acid was the less soluble. The benzene-soluble 2-benzoyl-1-naphthoic acid (1.4 g., 12.8%) was dissolved in 10% potassium carbonate and the alkaline solution was acidified with 10% hydrochloric acid: m.p. 139–141° (lit.[21] m.p. 141.8–142.8°). The benzene-insoluble 1-benzoyl-2-naphthoic acid (1.5 g., 13.6%) was similarly purified: m.p. 223–225° (lit.[21] m.p. 223.5–224.5°).

o-Acetylbenzoic Acid.—The procedure was one previously described[17]: m.p. 114–117° (lit.[17] m.p. 114–115°).

3,4,5,6-Tetrachloro-2-acetylbenzoic Acid.—The cadmium reagent was prepared from 3.4 g. (0.14 g.-atom) of magnesium, 19.8 g. (0.14 mole) of methyl iodide, 25.6 g. (0.14 mole) of cadmium chloride, and 250 ml. of ether. Solid tetrachlorophthalic anhydride (40.0 g., 0.14 mole) was added over a period of 25 min. This mixture was heated under reflux for 5.5 hr., with stirring. The mixture was decomposed and worked up in the same way as in the previous cases. A white solid was obtained from the acidification of the alkaline solution. Upon recrystallization from dioxane–water 19.1 g. (49.9%) of 3,4,5,6-tetrachloro-2-acetylbenzoic acid was obtained, m.p. 184–186°.

Anal. Calcd. for $C_9H_4Cl_4O_3$: C, 35.80; H, 1.34; Cl, 46.95. Found: C, 36.01; H, 1.43; Cl, 46.92.

The original ether solution, dried over anhydrous calcium chloride overnight, was evaporated under reduced pressure to yield a white solid. After recrystallization from isopropyl alcohol, 0.6 g. (1.4%) of 4,5,6,7-tetrachloro-3,3-dimethylphthalide was obtained, m.p. 163–165°.

Anal. Calcd. for $C_{10}H_6Cl_4O_2$: C, 40.03; H, 1.51; Cl, 47.29. Found: C, 40.15; H, 1.87; Cl, 47.33.

3-Nitro-2-acetylbenzoic Acid.—The acid was prepared as previously described[22]: m.p. 159–161° (lit.[22] m.p. 159–160°).

6-Methyl-2-acetylbenzoic Acid.—The Grignard reagent was prepared from 3.6 g. (0.15 g.-atom) of magnesium, 21.3 g. (0.15 mole) of methyl iodide, and 150 ml. of ether. It was then added to a solution of 3-methylphthalic anhydride[4] (25.0 g., 0.15 mole) in 150 ml. of ether over a period of 3 hr. The reaction mixture was heated for 8 hr. under reflux, with stirring, was cooled by means of an ice bath, and was decomposed with dilute sulfuric acid. The solution was filtered and the ether layer was separated and combined with ether washings of the water layer. The combined ether solution was washed with 10% potassium carbonate and the alkaline solution was acidified with 10% hydrochloric acid. An orange oil separated which failed to crystallize. The combined oil and aqueous mixture was extracted with ether. The ether was evaporated with the recovery of the orange oil. The oil was dissolved in benzene–pentane and the resulting solution was refrigerated with the separation of a white solid. Upon recrystallization from benzene–pentane, 5.2 g. (19.4%) of 6-methyl-2-acetylbenzoic acid was obtained, m.p. 122–124°.

Anal. Calcd. for $C_{10}H_{10}O_3$: C, 67.39; H, 5.66. Found: C, 67.47; H, 5.62.

Fischer Esterification Experiments.—The procedure was that previously described,[23] in which the acid was esterified in methanolic hydrogen chloride at reflux for 3 hr. Any variations in conditions are noted below. Ester was isolated by decomposition of the cooled reaction mixture in water, extraction with ether, and washing of the organic layer with saturated sodium bicarbonate. After the remaining ethereal solution had been dried and concentrated, the residual ester was analyzed directly by n.m.r. (see below). Then the ester or mixture of esters was isolated and purified as indicated for each of the following specific cases.

o-Benzoylbenzoic Acid.—The crystalline residue was washed with ice-cold methanol, dried, and recrystallized from petroleum ether (b.p. 60–80°); only the normal methyl ester (12.5 g., 59%) was obtained, m.p. 54–56° (lit.[23] m.p. 51.0–51.8°).

3,4,5,6-Tetrachloro-2-benzoylbenzoic Acid.—A mixture of the normal and pseudo methyl esters (13.2 g., 87.4%) was obtained from 15.0 g. (0.04 mole) of 3,4,5,6-tetrachloro-2-benzoylbenzoic acid, m.p. 81–147° (lit.[16,24] m.p. 92° for the normal ester and 154° for the pseudo ester). Recovered acid (1.0 g., 6.7%) was also obtained, m.p. 188–191°. The above esterification was repeated, but this time the methanol was previously saturated with hydrogen chloride and to this solution was added 2.0 g. (0.005 mole) of the acid. The reaction mixture was allowed to reflux for 15 min. From the ether layer was obtained 1.0 g. (52.6%) of a mixture of normal and pseudo methyl esters, m.p. 82–148°. A white solid was obtained from acidification of the sodium bicarbonate solution with 10% hydrochloric acid. Upon recrystallization from ethanol–water, 0.9 g. (45%) of recovered acid was obtained, m.p. 191–193°.

6-Nitro-2-benzoylbenzoic Acid.—Upon recrystallization from methanol, 2.1 g. (91.3%) of the normal methyl ester of 6-nitro-2-benzoylbenzoic acid was obtained from the esterification of 2.3 g. (0.008 mole) of the acid, m.p. 92–94°.

Anal. Calcd. for $C_{15}H_{11}NO_5$: C, 63.16; H, 3.88; N, 4.91. Found: C, 63.86; H, 4.01; N, 4.94.

3-Nitro-2-benzoylbenzoic Acid.—From 5.0 g. (0.02 mole) of 3-nitro-2-benzoylbenzoic acid there was obtained upon recrystallization from methanol 3.4 g. (59.6%) of the normal methyl ester, m.p. 122–124° (lit.[19] m.p. 122°).

Anal. Calcd. for $C_{15}H_{11}NO_5$: C, 63.16; H, 3.88; N, 4.91. Found: C, 63.09; H, 3.88; N, 4.97.

There was also obtained from acidification of the sodium bicarbonate solution with 10% hydrochloric acid 1.0 g. (20%) of recovered acid, m.p. 219–223° (lit.[19] m.p. 225–226°).

2-Benzoyl-1-naphthoic Acid.—From 0.7 g. (0.002 mole) of 2-benzoyl-1-naphthoic acid 0.5 g. (83.3%) of the pseudo methyl ester was obtained after recrystallization from methanol, m.p. 154–156° (lit.[21] m.p. 153–154°).

1-Benzoyl-2-naphthoic Acid.—An oil consisting of a mixture of normal and pseudo methyl esters (1.4 g.) was obtained from the esterification of 1.5 g. (0.005 mole) of the acid. Crystallization of the oil from methanol yielded a white solid and separation of the esters was accomplished by recrystallization from methanol. The insoluble ester was obtained in a yield of 0.5 g. (35.7%), m.p. 155–157°.

Anal. Calcd. for $C_{19}H_{14}O_3$: C, 78.61; H, 4.86. Found: C, 78.38; H, 4.82.

Upon several recrystallizations from methanol 0.3 g. (21.4%) of the soluble normal ester was obtained; this ester had m.p. 114–116°.

Anal. Calcd. for $C_{19}H_{14}O_3$: C, 78.61; H, 4.86. Found: C, 78.42; H, 4.83.

o-Acetylbenzoic Acid.—From 3.6 g. (0.02 mole) of o-acetylbenzoic acid there was obtained a yellow liquid. Distillation[25] under reduced pressure yielded a colorless liquid (2.3 g., 65.7%) consisting of a mixture of normal[26] and pseudo methyl esters. (*Anal.* Calcd. for $C_{10}H_{10}O_3$: C, 67.39; H, 5.66. Found: C, 67.18; H, 5.61; C, 67.16; H, 5.60.) The above esterification of 1.0 g. (0.006 mole) of the acid was repeated with the shorter reflux period previously used for 3,4,5,6-tetrachloro-2-benzoylbenzoic acid. From the ether layer a yellow liquid was obtained, and distillation[25] under reduced pressure yielded 0.9 g. (81.8%) of a mixture of normal and pseudo methyl esters.

3,4,5,6-Tetrachloro-2-acetylbenzoic Acid.—Upon recrystallization from methanol, 3.2 g. (53.3%) of the pseudo methyl ester of 3,4,5,6-tetrachloro-2-acetylbenzoic acid was obtained from 6.0 g. (0.02 mole) of the acid: m.p. 191–192°.

Anal. Calcd. for $C_{10}H_6Cl_4O_3$: C, 38.02; H, 1.92; Cl, 44.88. Found: C, 38.07; H, 1.97; Cl, 44.69.

Further treatment of the pseudo ester under Fischer esterification conditions for an additional 3 hr. yielded, exclusively, the pseudo methyl ester, m.p. 190–191°. This was confirmed by a mixture melting point determination with the pseudo ester obtained from the 3-hr. reflux period, m.p. 190–191°. The Fischer esterification was again repeated, this time by the procedure with the shorter reflux period. From 2.0 g. (0.007 mole) of the acid there was obtained upon recrystallization from methanol 1.6 g. (72.7%) of the pseudo methyl ester, m.p. 190–191°. That this ester was identical with that obtained after the 3-hr. reflux period was confirmed by a mixture melting point, m.p. 190–191°.

3-Nitro-2-acetylbenzoic Acid.—After recrystallization from methanol a mixture of normal[19] and pseudo methyl esters (3.0 g., 73.2%) was obtained from 4.0 g. (0.02 mole) of 3-nitro-2-acetylbenzoic acid: m.p. 81–134°.

Anal. Calcd. for $C_{10}H_9NO_5$: C, 53.80; H, 4.06; N, 6.28. Found: C, 53.91; H, 4.20; N, 6.08.

6-Methyl-2-acetylbenzoic Acid.—From 0.7 g. (0.004 mole) of 6-methyl-2-acetylbenzoic acid there was obtained upon recrystallization from methanol 0.6 g. (78.9%) of the pseudo methyl ester, m.p. 170–180°.

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Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.54; H, 6.09.

Normal Methyl Ester of *o*-Benzoylbenzoic Acid.[27,28]—Anhydrous *o*-benzoylbenzoic acid was dissolved in a solution of 9.3 g. (0.088 mole) of anhydrous sodium carbonate in 250 ml. of hot water. To this solution was added a hot aqueous solution of silver nitrate (14.9 g., 0.088 mole, in 100 ml. of water). The precipitated silver salt was removed by filtration and the salt was washed first with distilled water and then with ethanol, and finally dried in an oven at 70° for several hours. A slurry of the silver salt in benzene was placed in a round-bottomed flask fitted with a reflux condenser and a calcium chloride tube. Methyl iodide (12.5 g., 0.088 mole) was added, and the contents of the flask were heated for 3 hr. under reflux. The flask was cooled in an ice bath and the benzene solution was filtered. The benzene solution was concentrated, and to the remainder was added a small amount of petroleum ether. This solution was cooled in an ice bath, resulting in the separation of a white solid, which was removed by filtration. Upon recrystallization from petroleum ether (b.p. 60–80°), 6.9 g. (32.6%) of the normal methyl ester was obtained, m.p. 54–55° (lit.[28] m.p. 51.0–51.8°).

Normal Methyl Ester of 3,4,5,6-Tetrachloro-2-benzoylbenzoic Acid.—The silver salt was prepared as described above, from 20.0 g. (0.055 mole) of the acid, 2.9 g. (0.028 mole) of anhydrous sodium carbonate, and 9.3 g. (0.055 mole) of silver nitrate, and decomposed with 7.8 g. (0.055 mole) of methyl iodide. Upon recrystallization from methanol, 8.3 g. (39.9%) of the normal methyl ester was obtained, m.p. 90–92° (lit.[16] m.p. 92°).

Normal Methyl Ester of 1-Benzoyl-2-naphthoic Acid.—The silver salt was prepared from 1.0 g. (0.004 mole) of 1-benzoyl-2-naphthoic acid, 0.2 g. (0.002 mole) of anhydrous sodium carbonate, and 0.7 g. (0.004 mole) of silver nitrate. The ester was prepared from 0.6 g. (0.004 mole) of methyl iodide and the silver salt. The oil remaining after concentration of the benzene solution was diluted with pentane, and a white solid separated and was removed by filtration. Upon several recrystallizations from methanol, 0.6 g. (54.5%) of the normal methyl ester was obtained, m.p. 111–114°. That this ester was identical with that obtained in the Fischer esterification of 1-benzoyl-2-naphthoic acid was confirmed by a mixture melting point determination, m.p. 111–115°.

Pseudo Methyl Ester of *o*-Benzoylbenzoic Acid.—The pseudo ester, prepared as previously described,[28] was obtained in crystalline form (13%) only after the oil had been allowed to stand at room temperature for 4 months: m.p. 80–82° (lit.[28] m.p. 81.4–82.4°).

N.m.r. Analysis of Ester Mixtures.—In every case the ether extract from esterification, washed with base and dried, was freed of solvent by means of a rotary evaporator. A sample of the residue was dissolved in spectral grade chloroform and analyzed directly by n.m.r. spectroscopy.

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The Synthesis of (Hydroxylamino)alkyl Mercaptans

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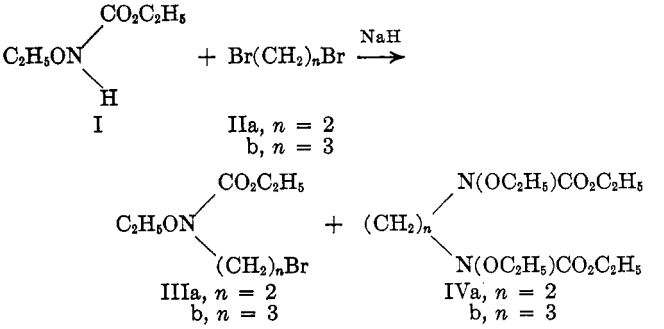
The synthesis of β-(N-ethoxyamino)ethyl and γ-(N-ethoxyamino)propyl mercaptans is reported. This was achieved by converting ethoxyamine first to its urethan which was alkylated by 1,2-dibromoethane and 1,3-dibromopropane to furnish the requisite ω-(N-ethoxy-N-carbethoxyamino)alkyl bromides. The latter were treated with thiourea to yield the corresponding isothiuronium salts, which were hydrolyzed to the mercaptans stated above. A novel migration of a carbethoxy group *from* nitrogen *to* sulfur was observed when β-(N-ethoxy-N-carbethoxyamino)ethyl mercaptan was transformed by hot dilute hydrochloric acid to ethyl S-[β-(N-ethoxyamino)ethyl] thiolcarbonate. In another series of reactions, N-methylhydroxylamine was converted to its urethan, then alkylated by 1,2-dibromoethane and 1,3-dibromopropane to the requisite ω-(N-methyl-N-carbethoxyaminooxy)alkyl bromide. These bromides reacted with sodium thiolacetate to produce the thiolacetate, one of which, *viz.*, S-[β-(N-methyl-N-carbethoxyaminooxy)ethyl] thiolacetate, was hydrolyzed successfully to β-(N-methylaminooxy)ethyl mercaptan. All the products described herein were characterized by their n.m.r. spectra.

In our investigation on the synthesis of hydroxylamine analogs of β-aminoethyl mercaptan as potential antiradiation drugs,[1] we set out to prepare hydroxylamino mercaptans, types $RONH(CH_2)_nSH$ and $R'NHO(CH_2)_nSH$. The synthesis of ω-(alkoxyamino)alkyl mercaptans is presented first and will be illustrated for β-(N-ethoxyamino)ethyl and γ-(N-ethoxyaminopropyl) mercaptans (R = C_2H_5, n = 2 and 3), followed then by that of β-(N-methylaminooxy)ethyl mercaptan (R′ = CH_3, n = 2).

Ethoxyamine, $C_2H_5ONH_2$, was converted first to the urethan I, which was alkylated with 1,2- and 1,3-dibromoalkanes II to give a readily separable mixture of the ω-bromoalkylurethans III, and the bisurethans IV. To substitute a thiol for the bromo group in III, the best results were realized in this series when III



was converted first to the isothiuronium salts V, which were then hydrolyzed. Initially, it was hoped to effect simultaneous hydrolysis of the urethan and isothiuronium groups of V, but it was found experimentally to greater advantage to carry out these hydrolyses to the hydroxylamino thiols stepwise. Relatively short

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