THE PREPARATION OF *p*-BROMOPHENACYL ESTERS AND THE CHARACTERIZATION OF *p*-BROMOPHENACYL FORMATE¹

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ABSTRACT

The compound, m.p. 140°C., widely used as a derivative for the identification of formic acid was found to be *p*-bromophenacyl alcohol and not *p*-bromophenacyl formate. *p*-Bromophenacyl alcohol was also the product from an attempt to prepare *p*-bromophenacyl pyruvate. *p*-Bromophenacyl formate, m.p. 92°C., was prepared in 80% yield by refluxing equivalent amounts of the reactants in 66% alcohol for 30 min. This ester is readily hydrolyzed under the conditions used for its preparation and the hydrolysis appears to be catalyzed by salts of carboxylic acids. The melting point of *p*-bromophenacyl alcohol depended on the rate of heating, varying from 137°C. with slow heating to 142°C. with the rapid heating obtained on a melting point bar.

Judefind and Reid (6) first used the reaction between p-bromophenacyl bromide and the sodium salts of carboxylic acids for preparing crystalline derivatives suitable for identification of the acids. This is an excellent method particularly for identifying small amounts of volatile acids since the aqueous solution of the salts can be evaporated and then taken up in dilute alcohol for the reaction. The yields are good and the derivatives show a marked increase in weight over the original acid. A method of obtaining formic acid as a crystal-line compound suitable for its identification and for measurements of carbon-14 activity was needed in this laboratory. The p-bromophenacyl ester was judged to be the most suitable after examining the literature, because of its relatively high melting point and apparent ease of preparation.

Judefind and Reid (6) were unable to obtain a crystalline derivative of formic acid. However, Hurd and Christ (5) had no difficulty in obtaining a crystalline compound, m.p. 140°C., which they reported to be p-bromophenacyl formate. This compound is listed as such in tables of derivatives (10, p. 222) and has been widely used to identify formic acid.

The most frequently described conditions for the preparation of p-bromophenacyl esters prescribe the use of about four equivalent weights of sodium salt for each mole of p-bromophenacyl bromide and a reflux period of one to two hours. When this procedure was used to prepare the formic ester from sodium formate labeled with carbon-14, the compound melting at 140°C. was readily obtained; actually it melted at 142°C. with rapid heating on the Dennis melting point bar (2). However, the substance was *nonradioactive*. Analysis for the elements indicated that the compound was probably pbromophenacyl alcohol. A sample of authentic p-bromophenacyl alcohol was prepared by hydrolysis of p-bromophenacyl acetate using the procedure of Judefind and Reid (6). The authentic alcohol melted at 142°C. and this melting point was unchanged on admixture with the reaction product of p-bromophena-

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cyl bromide and excess sodium formate. The two compounds possessed identical infrared absorption spectra (see Fig. 1).

On attempting to prepare p-bromophenacyl formate using equivalent amounts of reactants, we obtained a new compound, m.p. 92°C. The yield was 86% after a reflux period of 30 min. and 45% after heating for one hour. The substance possessed the elementary composition expected for p-bromophenacyl formate and, when prepared from carbon-14 labeled sodium formate, the product had the intensity of radioactivity expected from the activity of the sodium formate used.

It is thus established that the compound previously reported (6) as *p*-bromophenacyl formate is in fact *p*-bromophenacyl alcohol. *p*-Bromophenacyl



FIG. 1. Infrared absorption spectra.

Curve 1. Authentic p-bromophenacyl alcohol, m.p. 142°C.
Curve 2. Compound, m.p. 142°C., from reaction of p-bromophenacyl bromide with excess sodium formate.
Curve 3. p-Bromophenacyl formate, m.p. 92°C.

curve o. p-bromophenacyr formate, m.p. ob e.

formate melts at 92° C. and is further characterized by its infrared spectrum shown in Fig. 1.

Langenbeck and Baehren (7) have shown that phenacyl esters undergo hydrolysis with exceptional ease. The esters of formic acid and α -ketoacids are well known (10, p. 65) to be highly sensitive to hydrolytic conditions. It therefore would be expected that phenacyl esters for formic acid and α -ketoacids, such as pyruvic acid, would be exceptionally prone to hydrolysis. When *p*-bromophenacyl formate was treated for 80 min. with an equivalent amount of either sodium formate or sodium acetate under the temperature and pH conditions used for the preparation of the ester, the substance was hydrolyzed in high yield (80-90%) to *p*-bromophenacyl alcohol, but it was recovered

unchanged (78% yield) under the same conditions if the carboxylic salts were omitted. Thus, the hydrolysis of the ester appears to be catalyzed by salts of carboxylic acids. On treating p-bromophenacyl acetate with sodium formate in aqueous alcohol, the acetate was recovered unchanged, m.p. 85°C. yield 74%. p-Bromophenacyl pyruvate like the formate is readily hydrolyzed by the conditions used for its preparation. When p-bromophenacyl bromide was treated with four equivalents of sodium pyruvate under the usual conditions for the preparation of p-bromophenacyl esters, p-bromophenacyl alcohol was isolated as a reaction product in 81% yield. The pyruvic ester appears to be formed less quickly and to be more sensitive to hydrolysis than the formic ester since, under the conditions which gave high yields of the formate, only unreacted p-bromophenacyl bromide and p-bromophenacyl alcohol could be readily isolated from the reaction product. It is possible that in the past certain acids such as pyruvic acid may have been mistaken for formic acid because of the characterization of the latter acid using p-bromophenacyl alcohol as a derivative.

Drake and Bronitsky (3) found that p-phenylphenacyl esters are suitable derivatives for acids such as formic acid. However, they used conditions similar to those which we have found suitable for the preparation of p-bromophenacyl formate and it seems probable that their superior results are due more to the procedure used rather than the reagent. In general it is to be recommended for the preparations of p-substituted phenacyl esters that equivalent amounts of reactants be used and that the reaction time be kept to a minimum.

It is of interest to note that the procedure recently introduced by Erickson *et al.* (4) for the preparation of *p*-bromophenacyl esters by reaction of *p*-bromo-*a*-diazoacetophenone with the acid in dioxane apparently gives crude *p*-bromophenacyl alcohol when formic acid is used.

EXPERIMENTAL

Chemicals

Radioactive sodium formate was prepared by hydrogenation of sodium bicarbonate using palladium black as the catalyst (11). p-Bromophenacyl bromide was made following the directions of Langley (8) and recrystallized to a constant melting point of 109°C. p-Bromophenacyl acetate was prepared in the usual way (6).

Methods

Melting points were determined using the Dennis melting point apparatus (2) as manufactured by the Parr Instrument Co. This apparatus was calibrated against several pure compounds with known melting points each time it was used. The results are corrected melting points accurate to about 0.5°C.

The activity of barium carbonate and p-bromophenacyl formate labeled with carbon-14 was determined using a windowless counter operating with helium-isobutane in the Geiger region. Appropriate resolving-time corrections were made and all results referred to a cellulose acetate standard, of the same area, which was made from carbon-14 labeled cellulose. The samples were mounted by filtration on disks of Whatman No. 3 paper using a special funnel which ensured uniform distribution and constant surface area (9). Successive mounts made from the same material did not usually differ by more than 2-4% (9). Activity determinations were made using "infinitely thick" samples.

p-Bromophenacyl Formate

Ten milliliters of molar sodium formate was made acid to phenol red by dropwise addition of 0.10 N hydrochloric acid. Ethanol (20 ml.) and pbromophenacyl bromide (2.8 gm.) were added and the mixture refluxed gently for 30 min. It was then evaporated to about 15 ml. on a steam bath and cooled in refrigerator. The crystals were filtered off, washed with a little aqueous ethanol (20%), then with water, and dried at room temperature. The yield was 2.1 gm. (86%) of colorless leaflets melting at 91.5°C. Recrystallization from ethanol-petroleum raised the melting point to 92°C. A similar experiment using a reflux time of one hour gave a yield of 1.1 gm. (45%).

Calculated for C₉H₇O₃Br: C = 44.47%H = 2.90% Br = 32.87%C = 44.34% H = 3.01% Br = 33.65%Found:

p-Bromophenacyl Formate from C¹⁴ Labeled Sodium Formate

A molar sodium formate solution was prepared from formate labeled with carbon-14. One aliquot (0.5 ml.) was oxidized to carbon dioxide by refluxing with mercuric oxide (3 gm.), water (25 ml.), and syrupy phosphoric acid (5 ml.). The carbon dioxide was trapped in N sodium hydroxide, precipitated as barium carbonate (1), and its activity measured. Another aliquot (3 ml.) was converted to the p-bromophenacyl ester using the same proportions as above. The activity of the ester was measured after recrystallizing to constant melting point and activity. A portion of this pure ester was then converted to barium carbonate using the Van Slyke combustion fluid (12) and its activity again measured. The activities found were as follows (counts per minute at infinite thickness):

BaCO ₃ from oxidation of sodium formate	11,840
<i>p</i> -Bromophenacyl formate	9560

p-Bromophenacyl formate

BaCO₃ from oxidation of p-bromophenacyl formate 1345

These values are in excellent agreement with those expected for a compound with the formula C₉H₇O₃Br containing one carbon derived from the formate. Thus the equivalent weight with respect to formate carbon is $197 \times 11,840/9560$ = 243, which coincides with the theoretical value. The activity of the barium carbonate obtained on oxidation of this ester should be 11,840/9 = 1315. The value found above agrees within the experimental error (2-4%) for mounting active barium carbonate samples (9).

Preparations of p-Bromophenacyl Alcohol

Ten milliliters of 5N sodium formate was made acid to phenol red by dropwise addition of 0.01 N hydrochloric acid. Ethanol (20 ml.) and p-bromophenacyl bromide (2.8 gm.) were added and the mixture refluxed gently for one hour. After concentrating to half volume and cooling in refrigerator 1.5 gm. (70%) of crystals melting at 140°C. was obtained. Recrystallization from alcohol and toluene-petrol ether gave 1.1 gm. of needles melting at 142°C.

17

Calculated for C ₈ H ₇ O ₂ Br:	C = 44.67%	H = 3.28%	Br = 37.16%
Found:	C = 44.76%	H = 3.31%	Br = 36.35%
When prepared as above	using carbon-14	labeled sodiu	m formate this com-
pound was obtained free of	radioactivity, in	dicating abser	nce of formate carbon

in the molecule.

Determination of the molecular weight by the Rast method (using camphor) gave successive readings, on heating and cooling the same sample, corresponding to molecular weights of 412, 320, 283, 243, 224, and 220. The calculated value ($C_8H_7O_2Br$) is 214.9. Another experiment gave an initial weight of 545 decreasing gradually to 189 over a period of two and one-half hours' heating.

A sample of *p*-bromophenacyl alcohol was prepared by the method of Judefind and Reid (6). After recrystallizing from water and then from toluene it was obtained with the same melting point (142°C.) as the product of the reaction between *p*-bromophenacyl bromide and excess sodium formate. A mixture of the two melted at 142°C. The melting point seems to depend on the rate of heating. A sample heated slowly (15 min. for the last 10°) in a capillary tube melted at 137-136.5°C., in close agreement with the value of 136.6°C. reported by Judefind and Reid (6). However, the determination of the melting point with a heating time of about one second using the Dennis melting point apparatus (2) gave the above indicated melting point of 142°C. Comparison of the infrared spectra shown in Fig. 1 also shows these two samples of *p*-bromophenacyl alcohol to be identical.

The molecular weight determinations recorded above show a gradual decrease from an initial high value close to that expected for a monomer. This suggests that *p*-bromophenacyl alcohol, like acetoin, is associated in the crystalline state by a linkage which slowly dissociates on heating. The dependence of the melting point on the rate of heating also supports this view. *Relative Stability of the Formyl and Acetyl Esters of p-Bromophenacyl Alcohol*

Two millimoles of p-bromophenacyl formate and p-bromophenacyl acetate in 4 ml. of ethanol were treated separately with 2 ml. of a molar solution of sodium formate made acid to phenol red. After refluxing for 80 min., the resulting acidic solution was concentrated to half volume and cooled. The p-bromophenacyl acetate was recovered unchanged, m.p. 85°C., yield 74%. The p-bromophenacyl formate was converted to p-bromophenacyl alcohol, m.p. 142°C. in 86% yield. When the sodium formate solution was replaced by water p-bromophenacyl formate was recovered in 78% yield from the resulting acidic reaction mixture. One millimole of sodium acetate, 82 mgm., was dissolved in 1 ml. of water and the solution was made acid to phenol red by dropwise addition of 0.01 N hydrochloric acid. To the resulting solution 243 mgm. of p-bromophenacyl formate, 1 mM., and 2 ml. of ethanol were added and the mixture was refluxed for 80 min. The reaction mixture was diluted with 1 ml. of water and cooled. The crystalline product, 192 mgm., washed with water and air dried, melted at 138.5-140.5°C. and this melting point was not depressed by admixture of p-bromophenacyl alcohol.

47

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458

NEISH AND LEMIEUX: PREPARATION OF ESTERS

Attempted Preparations of p-Bromophenacyl Pyruvate

A molar solution of sodium pyruvate was made acid to phenol red by the dropwise addition of 0.1 N hydrochloric acid. Ten milliliters of the solution was added to 2.8 gm., 10 mM., of p-bromophenacyl bromide in 20 ml. of ethanol and the mixture was refluxed for a half hour. On cooling at about 4°C. for two hours, the solution deposited crystals which after recrystallization from ethanol melted at 108-109°C. and this melting point was not depressed by admixture of p-bromophenacyl bromide. The yield was 0.50 gm. The combined filtrates were evaporated in vacuo to about 15 ml. The air-dried precipitate which formed weighed 1.98 gm. This material was dissolved in 6 ml. of boiling ethanol and, on cooling to room temperature, 0.27 gm. of a crystalline material, m.p. 125-136°C.; was deposited. Recrystallization of this substance from toluene and then from ethanol gave a product, m.p. 140-141.5°C. The melting point was not depressed by mixing with *p*-bromophenacyl alcohol. Ten milliliters of the acidic sodium pyruvate solution was added to 0.70 gm., 2.5 mM., of p-bromophenacyl bromide in 20 ml. of ethanol and the solution was refluxed for two hours. The resulting solution was evaporated in vacuo to about 15 ml. and cooled. The crystals which formed were washed with 20%ethanol and air dried. Recrystallization from 4 ml. of ethanol gave 0.39 gm., 72% yield, of material, m.p. 140.5-141.5°C. The melting point was not depressed by admixture of p-bromophenacyl alcohol.

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