[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AT DUKE UNIVERSITY]

MIXED BENZOINS. I

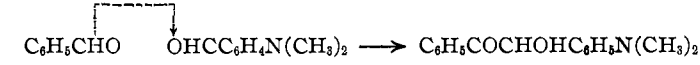
BY JOHANNES S. BUCK AND WALTER S. IDE

RECEIVED JUNE 21, 1929 PUBLISHED JANUARY 8, 1930

By mixed benzoins is understood unsymmetrical benzoins, that is, benzoins formed from two different aldehydes, or, in other words, containing different substituents in the two rings. A considerable amount of theory has been written on simple benzoin formation but there is little of practical value. Staudinger[1] is one of the few authors to speculate on the question of mixed benzoins. To support his views he prepared two mixed benzoins. Fischer[2] also prepared two mixed benzoins but made no speculations. These four compounds, together with one prepared by Ekecrantz and Ahlqvist,[3] represent the total number of mixed benzoins prepared heretofore by the condensation method.

Staudinger regards benzoin formation as due to the migration of a hydrogen atom from one aldehyde group to the carbonyl group of the other aldehyde, and hence he divides aldehydes into two main types—Type A having a reactive carbonyl group and a non-mobile hydrogen atom, and Type B, which has a mobile hydrogen atom but does not possess an active carbonyl group. The criterion for Type A is not stated; presumably it is the ability of the aldehyde to react with the usual aldehyde reagents. Type B is characterized by the rate of auto-oxidation. There are necessarily many intermediate aldehydes possessing both an active carbonyl group and a mobile hydrogen atom (although in varying degrees). Benzaldehyde, which forms a benzoin, belongs to this class.

On Staudinger's views the aldehydes of Type B donate the hydrogen atom and hence the nucleus of this aldehyde appears in the resulting benzoin next to the carbonyl group of the CHOH-CO chain. This may be illustrated by an example.



The method used by Staudinger was to heat two selected aldehydes, one each of Types A and B, in alcoholic potassium cyanide solution. Clearly, since neither aldehyde can form its own simple benzoin, and since only one mixed benzoin can be formed, the method will give excellent yields, provided always that the aldehydes are typical.

The case of the majority of aldehydes, which are not exclusively of either type, presents serious difficulties, since both simple benzoins and two

[1] Staudinger, *Ber.*, **46**, 3535 (1913).

[2] Fischer, *Ann.*, **211**, 214 (1882).

[3] Ekecrantz and Ahlqvist, *Arkiv Kemi, Mineral. Geol.*, **3**, Nr. 13, 26 S (1908–1910).

mixed benzoins may all be formed simultaneously. Their separation would then be a matter of chance depending on their relative solubilities. Fischer's two mixed benzoins were evidently obtained only because of their favorable solubilities.

The authors sought to make the production of mixed benzoins a more general process by considering the reaction from a dynamic point of view. They consider that the speed of formation of the simple benzoin is a rough index either of the mobility of the hydrogen atom or of the reactivity of the carbonyl group (without, at this stage, making any distinction). Aldehydes forming simple benzoins, and therefore possessing to some extent both a reactive carbonyl group and mobile hydrogen atom, are henceforth referred to as Group 1. Aldehydes which form no simple benzoin, and therefore possess only a mobile hydrogen atom or a reactive carbonyl group (but not both), are classed as Group 2. The speed of formation of a simple benzoin may be roughly indicated by primes, thus 1′′′′ signifies that the aldehyde forms a simple benzoin very rapidly. The relation between Staudinger's and the authors' grouping is simply that Group 1 possesses in varying degree the properties of both Types A and B. Group 2 is either of Type A or of Type B.

By adding the aldehydes at different speeds to the reaction mixture and by varying the time of heating, the authors have been able to isolate a number of new mixed benzoins and to improve the yields of some already known. Doubtless a considerable number of others could be prepared by similar methods. The rates of addition and the times of heating have to be determined by trial, since data on the speed of formation of benzoins are practically non-existent.

To illustrate the argument, consider one mole of an aldehyde of Group 2 in boiling alcoholic potassium cyanide solution. No reaction will take place. If now one mole of an aldehyde of Group 1 is run in at such a rate that it does not accumulate in the reaction mixture, it will form little of its own simple benzoin, being at high dilution, but will (on mass action considerations) form large amounts of one mixed benzoin. The formation of one mixed benzoin is also necessitated by the aldehyde of Group 2 possessing only a mobile hydrogen atom or a reactive carbonyl group, but not both.

Three other cases remain to be considered. If both aldehydes are of Group 2, but one of Type A and the other of Type B, a single mixed benzoin will be formed under any conditions. This is Staudinger's case. If both aldehydes are of Group 2 and both of Type A or both of Type B, then no mixed, or simple, benzoin will be formed. Lastly, as is usually the case, if both aldehydes are of Group 1, then necessarily four products will be formed, two simple and two mixed benzoins. However, by adding both aldehydes, say 1′ and 1′′′ at such rates that aldehyde 1′ is always present in relatively great excess to 1′′′ (but usually at small concentration) and

adjusting the rate of addition so that neither aldehyde accumulates, the formation of the simple benzoin from 1''' is largely suppressed, while the simple benzoin from 1' (slow aldehyde) has not had time to form to any extent. The conditions then favor the formation of the mixed benzoins, but the fact that aldehyde 1' must nearly approach either Type A or B will cause one mixed benzoin to preponderate. The present paper largely deals with reactions of this type. In the limiting case, where both aldehydes are of Group 1 and have about the same speeds of formation of simple benzoins, both simple and mixed benzoins are necessarily formed, whatever conditions are used. In one case of this type the authors have succeeded in isolating both of the mixed benzoins.

The position of the CHOH group in the mixed benzoin could only be definitely settled by synthesizing the compound in some other way which would leave no doubt as to its position. However, as previously explained, when one aldehyde belongs to Type A or to Type B, the position of the CHOH group can be assigned with fair certainty, for it will be next to the nucleus of the Type A aldehyde or furthest from the nucleus of the Type B aldehyde. The possibility of assigning a correct structure when both aldehydes belong to Group 1 depends upon which type (A or B) the aldehydes are most nearly related to.

It has been shown by Lachman[4] that in the ordinary benzoin reaction a number of side-products are formed. The amount, however, is not serious if the heating be not too prolonged. In the present work the side-products were avoided as much as possible, but they undoubtedly render the separation of mixed benzoin more difficult.

Nomenclature.—In the literature mixed benzoins are named from the two aldehydes, with the termination -oin. The authors suggest placing this termination after the aldehyde with the reactive carbonyl group, or, which is the same thing, after the aldehyde whose CHO becomes CHOH. Thus, $CH_2O_2C_6H_3COCHOHC_6H_5$ is piperbenzoin and $CH_2O_2C_6H_3CHOH\text{-}COC_6H_5$ is benzpiperoin. If the structure is doubtful a query mark is placed after the name.

Experimental

The experimental procedure, in general, is very simple. A three-necked flask contains the alcoholic potassium cyanide solution, which is kept boiling briskly on a steam-bath. Two burets and a reflux condenser are fitted to the three necks. The time of addition and the amount of one aldehyde first added have been determined by trial from a number of experiments. In general both aldehydes were added at the same rate after the preparation was begun. The amounts of water, alcohol and potassium cyanide were also varied—the optimum values are given.

[4] Lachman, THIS JOURNAL, **46**, 709 (1924).

Furo-*p*-dimethylaminobenzoin.—To a boiling solution of 7.5 g. of *p*-dimethylaminobenzaldehyde and 3.0 g. of potassium cyanide in 55 cc. of 65% alcohol was added 5.0 g. of furfural over a period of forty-five minutes. On standing overnight a crystalline product separated. After recrystallization from alcohol the compound forms buff plates melting at 168° and is very soluble in chloroform, moderately soluble in benzene and alcohol and slightly soluble in ether and ligroin; yield, 30%.

Anal. Calcd. for $C_{14}H_{15}O_3N$: N, 5.71. Found: N, 5.99.

***o*-Chloro-*p*-dimethylaminobenzoin.**—A solution of 7.5 g. of *p*-dimethylaminobenzaldehyde, 7.5 g. of *o*-chlorobenzaldehyde and 2.0 g. of potassium cyanide in 45 cc. of 65% alcohol was refluxed for one hour. On addition of ice water, a solid separated and was recrystallized from alcohol; yield, 36%.

It forms white needles melting at 166° and is very soluble in chloroform, moderately soluble in benzene and alcohol, slightly soluble in ligroin and ether.

Anal. Calcd. for $C_{16}H_{16}O_2ClN$: N, 4.83. Found (Kjeldahl): N, 4.77, 4.69.

***m*-Bromo-*p*-dimethylaminobenzoin.**—This compound was prepared by heating a solution of 7.5 g. of *p*-dimethylaminobenzaldehyde, 9.0 g. of *m*-bromobenzaldehyde and 3.0 g. of potassium cyanide in 45 cc. of 65% alcohol for an hour. On adding ice water a solid product separated and was recrystallized from alcohol; yield, 50%. It forms buff prisms melting at 145° and is very soluble in chloroform, moderately soluble in alcohol and benzene and slightly soluble in ether and ligroin. Analyses were made by the Kjeldahl method.

Anal. Calcd. for $C_{16}H_{16}O_2NBr$: N, 4.19. Found: N, 4.01, 4.13.

Benzpiperoin.—Fifteen grams of piperonal in saturated alcoholic solution are added during one and three-fourths hours to a boiling solution of 10.6 g. of benzaldehyde in 120 cc. of 50% alcohol containing 5.0 g. of potassium cyanide. The oil which separated on cooling was removed and dissolved in alcohol. The product crystallized in a few hours and was recrystallized from alcohol; yield, 28%. It forms white needles, m. p. 120°, very soluble in chloroform, moderately soluble in alcohol, ether, ligroin and benzene.

Anal. Calcd. for $C_{15}H_{12}O_4$: C, 70.30; H, 4.70. Found: C, 69.93; H, 4.97.

Piperbenzoin.—The mother liquors from the preparation of benzpiperoin sometimes deposit, on standing for several days, an isomer, melting at 112°, in a yield of about 16%. It forms white needles, rather more soluble than benzpiperoin, especially in ether.

Anal. Calcd. for $C_{15}H_{12}O_4$: C, 70.30; H, 4.70. Found: C, 70.06; H, 4.87.

Benz-*m*-bromobenzoin (?).—This compound is best prepared by dissolving 18.5 g. of *m*-bromobenzaldehyde in 140 cc. of 50% alcohol containing 5.0 g. of potassium cyanide and boiling for two hours while 15.0 g. of benzaldehyde is run in. An oil separated on cooling and was sludged with benzene. The crystals which formed were recrystallized from alcohol; yield, 32%.

Benz-*m*-bromobenzoin forms white prisms, m. p. 129–130°, very soluble in chloroform and moderately soluble in benzene, alcohol, ether and ligroin.

Anal. Calcd. for $C_{14}H_{11}O_2Br$: C, 57.73; H, 3.77. Found: C, 58.00; H, 4.08.

Piper-*m*-bromobenzoin (?).—Eighteen and one-half grams of *m*-bromobenzaldehyde dissolved in 160 cc. of 50% alcohol containing 5.0 g. of potassium cyanide was treated over one and a half hours with 15.0 g. of piperonal in saturated alcohol solution. The mixture was kept boiling and the piperonal was added at a steady rate. On cooling, the oil which separated was removed and kept in a refrigerator, where it gradually crystallized. The product was recrystallized from ether and then alcohol; yield, 33%.

Piper-*m*-bromobenzoin forms white needles, m. p. 106°, very soluble in benzene and chloroform, moderately soluble in ether, ligroin and alcohol.

Anal. Calcd. for $C_{15}H_{11}O_4Br$: C, 53.73; H, 3.28. Found: C, 53.68; H, 3.38.

Piper-*o*-chlorobenzoin (?).—Three and sixty-five one-hundredths grams of *o*-chlorobenzaldehyde was dissolved in 50 cc. of 50% alcohol containing 3.0 g. of potassium cyanide and the whole was boiled briskly; 3.75 g. of piperonal in saturated alcoholic solution was added at a steady rate over one and three-fourths hours. On cooling, an oil separated which was removed and sludged with ligroin. After twenty-four hours the crystalline product was filtered off and recrystallized from alcohol; yield, 50%.

Piper-*o*-chlorobenzoin forms white needles, m. p. 115°, very soluble in benzene and chloroform, moderately soluble in alcohol, ether and ligroin.

Anal. Calcd. for $C_{15}H_{11}O_4Cl$: C, 61.94; H, 3.78. Found: C, 61.84; H, 4.14.

Summary

By considering the reactivity of aldehydes in the simple benzoin reaction, a method has been worked out whereby mixed benzoins may be obtained from the large majority of aromatic aldehydes. Eight new mixed benzoins have been prepared by the method.

DURHAM, NORTH CAROLINA

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

SUBSTITUTED PHENYLETHYLBARBITURIC ACIDS[1]

BY E. W. BOUSQUET AND ROGER ADAMS

RECEIVED JUNE 27, 1929 PUBLISHED JANUARY 8, 1930

Of the numerous 5,5-disubstituted barbituric acids that have been prepared and offered to the physician as hypnotics, the one which is of peculiar interest is the phenylethyl derivative.[2] This substance is generally accepted by the clinician as having, in addition to the usual soporific value, a specific sedative action toward epileptics, much more marked than appears in the various dialkylbarbituric acids. Phenylethylbarbituric acid (phenobarbital) is more toxic than most of the important dialkyl derivatives, though the ratio of effective dosage and toxicity is not so very different from that of barbital[3] itself. The phenylmethyl[4] and the phenylallyl[5] barbituric acids have also been prepared, but appear to be of less interest than the better-known phenylethyl derivative.

In spite of the importance of phenobarbital, derivatives containing substituents in the benzene ring, with the exception of the *p*-methoxyphenylethylbarbituric acid,[2] which was mentioned in the original patent, have never been prepared. Numerous investigators have obtained barbituric acid derivatives isomeric with phenylalkyl- or phenylallylbarbituric

[1] This communication is an abstract of a portion of a thesis submitted by E. W. Bousquet in partial fulfilment of the requirements for the Degree of Doctor of Philosophy in Chemistry at the University of Illinois.

[2] German Patent 249,722, *Friedländer*, XI, 928 (1912).

[3] Nielsen, Higgins and Spruth, *J. Pharmacol.*, **26**, 271 (1925).

[4] U. S. Patent 1,025,526 (1912).

[5] U. S. Patent 1,056,793 (1912).