#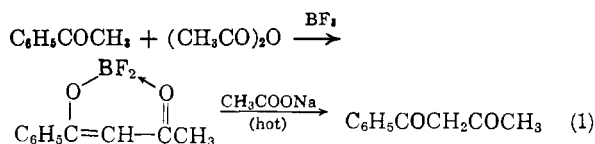 Acetylation of Benzenesulfonylacetone with Acetic Anhydride by Means of Boron Fluoride to Form the Terminal Methyl Derivative[1,2]

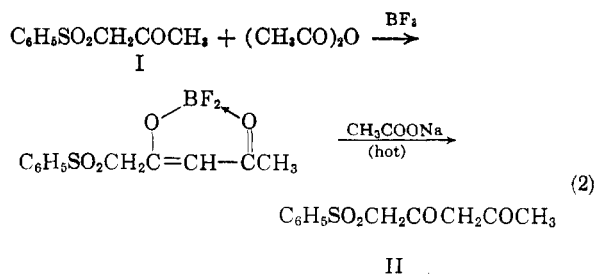DONALD F. TAVARES, WILLIAM IVO O'SULLIVAN,[3] AND CHARLES R. HAUSER

Like a methyl ketone, not a β-diketone, benzenesulfonylacetone (I) underwent acetylation with acetic anhydride in the presence of boron fluoride to afford the terminal methyl derivative in high yield. This product was cyclized with hydrazine to form a pyrazole, coupled with benzenediazonium chloride to give a phenylhydrazone, and independently synthesized from 1-bromoacetylacetone and sodium benzenesulfinate. A reason for the preferential acetylation at the terminal methyl group of I rather than at the methylene group is suggested.

The methyl or methylene group of ketones can generally be acylated with aliphatic anhydrides by means of boron fluoride to form the corresponding β-diketones.[4] The reaction may be illustrated by the acetylation of acetophenone to form benzoylacetone (Equation 1).

$$C_6H_5COCH_3 + (CH_3CO)_2O \xrightarrow{BF_3}$$

$$C_6H_5\overset{\overset{\displaystyle O\diagdown BF_2\diagup O}{|\qquad\quad ||}}{C}=CH-CCH_3 \xrightarrow[\text{(hot)}]{CH_3COONa} C_6H_5COCH_2COCH_3 \quad (1)$$

However, the methyl or methylene group of benzoylacetone fails to undergo acetylation with acetic anhydride under similar conditions. Instead this β-diketone is converted merely to its boron difluoride complex,[5] which is produced also in the acetylation of acetophenone (see Equation 1).

Although benzenesulfonylacetone (I) may be regarded as a sulfur analog of benzoylacetone, this sulfone ketone was found in the present investigation to react with acetic anhydride and boron fluoride like an ordinary ketone to afford the sulfone β-diketone II in yields of 70–85%. Presumably II was produced in the reaction mixture as its boron difluoride complex, from which II was liberated with hot sodium acetate solution (Equation 2).

$$C_6H_5SO_2CH_2COCH_3 + (CH_3CO)_2O \xrightarrow{BF_3}$$
$$\underset{I}{}$$

$$C_6H_5SO_2CH_2\overset{\overset{\displaystyle O\diagdown BF_2\diagup O}{|\qquad\quad ||}}{C}=CH-CCH_3 \xrightarrow[\text{(hot)}]{CH_3COONa}$$

$$(2)$$

$$C_6H_5SO_2CH_2COCH_2COCH_3$$

$$II$$

Actually such an acetylation was anticipated because I was known[6] not to react with ethanolic ferric chloride nor with cupric acetate, which readily convert benzoylacetone to enol-type products. Therefore an enol-type boron difluoride complex was not expected until after acetylation, after which the β-diketone portion of the molecule could be involved (see Equation 2).

The acetylation product was shown to be a β-diketone, not a possible *O*-acetyl derivative, by a positive enol test with ethanolic ferric chloride, by formation of a copper chelate with cupric acetate, and by cyclization with hydrazine to give a pyrazole. Of the two possible β-diketones, II and III, the former structure was found to be the correct one. Therefore the pyrazole may be assigned structure IV.

$$\underset{III}{\overset{\overset{\displaystyle COCH_3}{|}}{C_6H_5SO_2CHCOCH_3}} \qquad \underset{IV}{C_6H_5SO_2CH_2\overset{\overset{\displaystyle N—NH}{||\qquad|}}{\underset{\diagdown CH\diagup}{C\qquad CCH_3}}}$$

That the product was the terminal methyl derivative II, not the methylene derivative III, was supported by its NMR spectrum[7] which showed, besides the phenyl peak, three peaks at 30, 91, and 173 cycles on the high field side of benzene. These signals were assigned to the β-diketone methylene hydrogen, the sulfone ketone methylene hydrogen, and the methyl hydrogen, respectively. The relative areas were approximately 1:2:3. Although there are two β-diketone methylene hydrogens, one of them is evidently largely enolized as should be expected.

Structure II was further supported by the infrared spectrum of its copper chelate, which showed bands in the regions of 6.10–6.45 and 6.52–6.60 μ as reported for the chelates of β-diketones unsubstituted at the methylene group.[8] Only the

(1) Supported by the U. S. Army Research Office (Durham).

(2) Reported in part at the Cleveland Meeting of the American Chemical Society, April 1960.
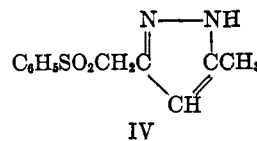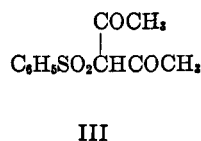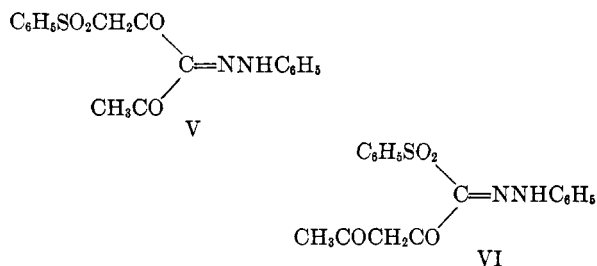
(3) On leave from the University College, Dublin, Ireland.

(4) See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **VIII**, (1954).

(5) R. M. Manyik, Ph.D. thesis, Duke University, p. 13 (1953).

(6) See W. I. O'Sullivan, D. F. Tavares, and C. R. Hauser, *J. Am. Chem. Soc.*, **83**, 3453(1961).

(7) We are indebted to Dr. G. S. Paulett of Rohm and Haas Co., Huntsville, Ala., for this determination and interpretation.

(8) R. P. Dryden and A. Winston, *J. Phys. Chem.*, **62**, 635 (1958).

latter band was found in the spectrum of the chelates of alkyl substituted β-diketones.[8]
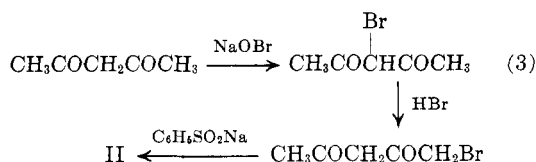
Structure II was established by treatment with benzenediazonium chloride to form a monophenyl-hydrazone, V or VI, since such a structure as III could afford only an azo derivative.[9] Presumably an azo derivative was an intermediate.[9] The product was soluble in dilute sodium hydroxide solution and its ultraviolet spectrum had a strong absorption maximum in the 350–400-mμ region, which is considered characteristic of the phenylhydrazone group.[10]

$$C_6H_5SO_2CH_2CO$$
$$C{=}NNHC_6H_5$$
$$CH_3CO$$
$$V$$

$$C_6H_5SO_2$$
$$C{=}NNHC_6H_5$$
$$CH_3COCH_2CO$$
$$VI$$

These properties of the product were similar to those of phenylhydrazones VII[11] and VIII,[6] which were prepared for the purpose of comparison. The phenylhydrazone from II seemed more likely to be V than VI, since its ultraviolet spectrum was more like that of VII than that of VIII.

$$CH_3CO$$
$$C{=}NNHC_6H_5$$
$$CH_3CO$$
$$VII$$

$$C_6H_5SO_2$$
$$C{=}NNHC_6H_5$$
$$CH_3CO$$
$$VIII$$
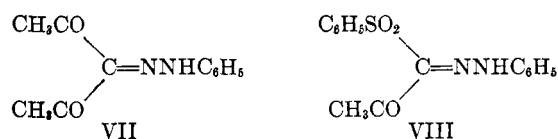
Structure II was confirmed by an independent synthesis involving the isomerization of 3-bromo-acetylacetone to its 1-bromo derivative and condensation of the latter compound with sodium benzenesulfinate (Equation 3).

$$CH_3COCH_2COCH_3 \xrightarrow{NaOBr} CH_3CO\overset{Br}{\overset{|}{C}}HCOCH_3 \quad (3)$$
$$\downarrow HBr$$
$$II \xleftarrow{C_6H_5SO_2Na} CH_3COCH_2COCH_2Br$$

Although neither the 3-bromo- nor the 1-bromo-acetylacetone was isolated, the former compound was indicated to be present by a positive test for active halogen, and its essentially complete conversion to the 1-bromo derivative was supported by a negative test for active halogen. Recently[6] crude 1-bromobenzoylacetone was prepared similarly and condensed with sodium benzenesulfinate.
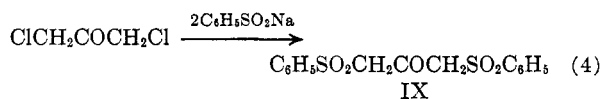
Incidentally the independent synthesis of II (Equation 3) was accompanied by the formation of

some of compound IX, the structure of which was established by comparison with an authentic sample prepared by the method of Otto and Tröger[12] (Equation 4).

$$ClCH_2COCH_2Cl \xrightarrow{2C_6H_5SO_2Na} $$
$$C_6H_5SO_2CH_2COCH_2SO_2C_6H_5 \quad (4)$$
$$IX$$

A blank experiment with 3-bromoacetylacetone and sodium benzenesulfinate failed to yield any of the product obtained from the boron fluoride-catalyzed acetylation of I. Apparently some condensation occurred to form III, an acetyl group of which was cleaved to give I (10%). Also some oxidation-reduction took place to produce sodium benzenesulfonate and presumably acetylacetone. Although this β-diketone was not isolated, benzoylacetone has recently[6] been obtained in the analogous reaction of 3-bromobenzylacetone with sodium benzenesulfinate, the other products being sodium benzenesulfonate and benzenesulfonylacetophenone.

DISCUSSION

The boron fluoride-catalyzed acetylation represented by Equation 2 is of interest not only because the sulfone ketone I reacts like a ketone rather than a β-diketone, but also because the reaction involves the methyl group instead of the methylene group. Corresponding acetylations of methyl ethyl ketone and phenylacetone occur preferentially at the methylene group[4] apparently because of favorable hyperconjugative effects on this group. Acetylation at the terminal methyl group of I presumably involves the intermediate formation of enol type complex Ib, which condenses with the carbonium ion from the anhydride.[4] Intermediate Ib might have arisen either from ionization of a methyl hydrogen as indicated in coordination complex Ia or from ionization of a methylene hydrogen followed by equilibration of the resulting enol complex Ic. Because of attraction of the partial positive charge on the sulfur atom[13] for the bonding pair of electrons of the methylene hydrogen, preferential ionization of a methyl hydrogen might be favored. However, even if both Ib and Ic are present in equilibrium, preferential acetylation of Ib should be favored for steric reasons.

$$C_6H_5\overset{O}{\underset{O}{\overset{\uparrow}{\underset{||}{S}}}}{-}\overset{H}{\underset{|}{C}}H{-}\overset{O\to BF_3}{\underset{H}{\overset{||}{C}}}CH_2 \qquad C_6H_5SO_2CH_2\overset{O-\bar{B}F_3H^+}{\overset{|}{C}}{=}CH_2$$
$$Ia \qquad\qquad\qquad\qquad Ib$$

$$C_6H_5SO_2CH{=}\overset{O-\bar{B}F_3H^+}{\overset{|}{C}}CH_3$$
$$Ic$$

(9) See S. M. Parmerter, *Org. Reactions*, **X**, 1 (1959).

(10) R. H. Wiley and C. H. Jarboe, Jr., *J. Am. Chem. Soc.*, **77**, 403 (1955); F. Ramirez and A. F. Kirby, *J. Am. Chem. Soc.*, **75**, 6026 (1953); **76**, 1037 (1954).

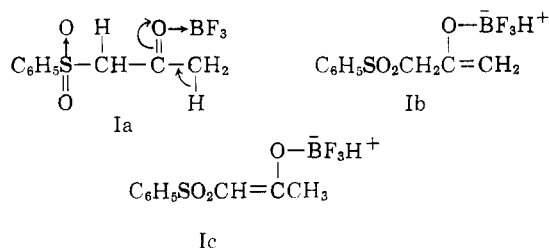(11) C. Bülow and F. Schlotterbeck, *Ber.*, **35**, 2187 (1902).

(12) R. Otto and J. Tröger, *Ber.*, **25**, 3422 (1892).

(13) See Guiseppe Cilento, *Chem. Revs.*, **60**, 147 (1960).

It should be mentioned that, whereas the sulfone ketone I and benzoylacetone react differently towards boron fluoride, they react similarly towards bases. Thus, like the β-diketone, I has recently[6] been converted by a molecular equivalent of an appropriate base to the methylene carbanion, and by two molecular equivalents of potassium amide in liquid ammonia to the dipotassio salt X which reacted as if it were the methyl carbanion. For example, X was benzoylated with methyl benzoate to give XI, which is an analog of II.

$$\overset{\text{K}}{\underset{\text{X}}{C_6H_5SO_2CHCOCH_2K}}$$ $$\underset{\text{XI}}{C_6H_5SO_2CH_2COCH_2COC_6H_5}$$
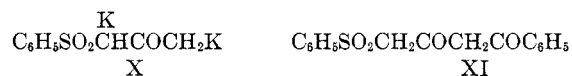
Although the analogous acetylation of dipotassio salt X with ethyl acetate to form II probably could not be effected satisfactorily because of potassium-hydrogen exchange,[14] II might be obtained by acetylation of the corresponding dilithio salt of I. Such an acetylation of dilithiobenzoylacetone has been observed.[15] However, the present boron fluoride method appears superior.

EXPERIMENTAL[16]

Benzenesulfonylacetone (I). This compound (m.p. 57°) was prepared from chloroacetone and sodium benzenesulfinate in ethanol.[17]

Its NMR spectrum in chloroform showed a phenyl peak at 49 cycles on the low field side of benzene and a CH_2 peak at 93 cycle and a CH_3 peak at 173 cycles on the high field side of benzene.

Acetylation of I by boron fluoride to form II. The method employed was adapted from that described for acylations of ketones by the inverse addition procedure.[18] Acetic acid (12 g., 0.2 mole) was saturated with boron fluoride at 0–5° until the contents of the flask became a powdery solid.[18] A solution of 3.3 g. (0.017 mole) of benzenesulfonylacetone (I) in 5.2 g. (0.05 mole) of acetic anhydride was added with ice bath cooling and vigorous stirring during 2–3 min. After 30 min., the ice bath was removed and stirring was continued for 4 hr. The reaction mixture was poured onto a solution of 0.1 mole of sodium acetate in 100 ml. of water and refluxed for 30 min. After cooling, the reaction mixture was extracted with ether. The ether extract was stirred with an excess of a saturated sodium bicarbonate solution in a large beaker to neutralize the acid. The ether layer was separated, washed

with water, and dried over anhydrous magnesium sulfate. Removal of the ether yielded 3.47 g. (85%) of 1-benzene-sulfonylpentane-2,4-dione (II), m.p. 96–98° and at 98–99° after recrystallization from ethanol. It gave a cherry red color with ethanolic ferric chloride. Its infrared spectrum showed peaks at 3.25, 3.37, 3.45, 6.25–6.4 (broad), 6.95, 7.15, 7.73 (broad), and 8.7 μ. Its NMR spectrum in chloroform had, in addition to the phenyl peak, three peaks at 30, 91, and 173 cycles on the high field side of benzene.

Anal. Calcd. for $C_{11}H_{12}O_4S$: C, 54.98; H, 5.04; S, 13.34. Found: C, 55.08; H, 5.09; S, 13.36.

The experiment was repeated with 0.05 mole of I, 0.15 mole of acetic anhydride, and 0.6 mole of acetic acid saturated with boron fluoride.[18] After decomposing the reaction mixture with hot sodium acetate solution and extracting with ether, the ether extract was washed with saturated sodium bicarbonate solution until the acid was neutralized, then with water. The ether solution was shaken with excess saturated cupric acetate solution to precipitate 9.8 g. (73%) of the blue-grey copper chelate of II, m.p. 229–233° and at 243–245° after recrystallization from ethanol. Its infrared spectrum showed peaks at 6.32, 6.6,6.9, 7.58, and 8.7 μ.

Anal. Calcd. for $C_{22}H_{22}O_8S_2Cu$: C, 48.74; H, 4.09; S, 11.82. Found: C, 48.55; H, 4.22; S, 11.78.

The copper chelate was decomposed by treatment with 10% sulfuric acid solution, and the free sulfone β-diketone was extracted with ether. The ether solution was washed with water and dried over anhydrous magnesium sulfate. Removal of most of the ether precipitated II as white needles, m.p. 98–99°. This melting point was not depressed on admixture with a sample of II obtained as described above.

3-Benzenesulfonylmethyl-5-methylpyrazole (IV). A mixture of 6 g. (0.025 mole) of 1-benzenesulfonylpentane-2,4-dione (II) and 6 g. of hydrazine hydrate in 50 ml. of ethanol was heated on a steam bath for 1 hr. Most of the ethanol was evaporated at reduced presure, and water was added to the residue. The resulting precipitate was collected on a funnel, washed with water, and recrystallized from very dilute aqueous ethanol to yield 3.3 g. (52%) of white needles of 3-benzenesulfonylmethyl-5-methylpyrazole (IV), m.p. 143–146°. Further recrystallizations from 95% ethanol raised the melting point to 146–147.5°.

Anal. Calcd. for $C_{11}H_{12}O_2N_2S.H_2O$: C, 55.42; H, 5.92; N, 11.75; S, 13.45. Found: C, 55.20; H, 5.65; N, 11.94; S, 13.76.

Coupling of II with benzenediazonium chloride. To a stirred slurry of 2.4 g. (0.01 mole) of 1-benzenesulfonyl-pentane-2,4-dione (II), 1.2 g. (0.015 mole) of sodium acetate, 2 ml. of water, and 20 ml. of 95% ethanol at 5–10° was added slowly a cold (0–5°) solution of benzenediazonium chloride prepared from 0.93 g. (0.01 mole) of aniline, 0.73 g. (0.01 mole) of sodium nitrite, 2 ml. of water, and 5 ml. of 5 N hydrochloric acid. After stirring for 30 min. at 5–10° and 90 min. at room temperature, 30 ml. of water was added. The resulting precipitate was collected on a funnel, washed several times with water, and recrystallized from absolute ethanol to give 2.08 g. (61%) of phenylhydrazone V or VI, m.p. 164–165.5°. This product was soluble in 5% sodium hydroxide solution. Its infrared spectrum showed peaks at 3.27, 3.38, 3.43, 5.93, 6.08, 6.25, 6.7, 7.65, 8.6, and 8.85 μ. Its ultraviolet spectrum had λ_{max} 223 (broad), 274, 367 mμ; log ε 4.61, 3.97, 4.28.

Anal. Calcd. for $C_{17}H_{16}O_4N_2S$: C, 59.28; H, 4.68; N, 8.13; S, 9.31. Found: C, 59.12; H, 4.52; N, 7.98; S, 9.20.

Independent synthesis of II. To a stirred, cooled solution of 20 g. (0.20 mole) of freshly distilled acetylacetone in 1000 ml. of 0.25 N sodium hydroxide was added slowly a cold mixture of 29.6 g. (0.18 mole) of bromine and 80 g. (0.78 mole) of sodium bromide in 300 ml. of water, followed by 70 ml. of 1 N hydrobromic acid. The resulting oil was taken up in ether. The ether solution was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to leave 19.8 g. (55%) of

(14) Such an exchange has been observed between dipotassiobenzoylacetone and ethyl propionate; R. J. Light and C. R. Hauser, *J. Org. Chem.*, **25**, 541 (1960).

(15) S. D. Work and C. R. Hauser, unpublished result.

(16) Melting points were taken on a Fisher-Johns melting point apparatus. Infrared spectra were produced with Perkin-Elmer, Models 21 and 137 infrared spectrophotometers by the potassium bromide method. Ultraviolet spectra were determined with a Warren Spectracord spectrophotometer using 2×10^{-5} M solution in methanol with a 1-cm. sample cell. Elemental analyses were by Galbraith Microchemical Laboratories, Knoxville, Tenn.

(17) R. Otto and W. Otto, *J. prakt. Chem.*, [2], **36**, 403 (1887).

(18) See R. M. Manyik, F. C. Frostick, Jr., J. J. Sanderson, and C. R. Hauser, *J. Am. Chem. Soc.*, **75**, 5030 (1953).

crude 3-bromoacetylacetone as a dark yellow oil.[19] This crude material was stored in a refrigerator under nitrogen. Addition of a drop of this product to a solution of potassium iodide in 2 ml. of water and 5 ml. of acetic acid under nitrogen produced immediately the dark brown color of iodine.

To a cold solution of 5.55 g. of crude 3-bromoacetylacetone in 20 ml. of glacial acetic acid was added 25 ml. of 30–32% acetic acid–hydrogen bromide solution (Eastman Kodak Co.). After stirring at room temperature for 5 hr., the reaction mixture was poured into water, and the resulting mixture was extracted with ether. The ether extract was washed with water and dried over anhydrous magnesium sulfate. Most of the solvent was removed under reduced pressure at room temperature to leave 2.69 g. (49%) of crude 1-bromoacetylacetone as a dark yellow oil (probably containing some acetic acid). A negative test[20] for active halogen was obtained with a few drops of this product (see above).

A solution of 2.69 g. (0.015 mole) of the crude 1-bromoacetylacetone and 3.2 g. (0.0155 mole) of sodium benzene-sulfinate dihydrate in 150 ml. of 95% ethanol was refluxed for 24 hr. Most of the alcohol was removed under reduced pressure and cold water was added to the residue. The pale yellow aqueous–ethanol layer was decanted from a dark oil which had separated and was cooled in a refrigerator for several hours. The resulting precipitate (84.4 mg.), which was identified as compound IX (see below), was removed by filtration. The filtrate was concentrated and cooled to afford 140.2 mg. (3.9% based on crude 1-bromoacetylacetone)

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(19) 3-Bromoacetylacetone has been reported to distill at 96° at 13 mm. accompanied by the evolution of hydrogen bromide and production of much residue; K. von Auwers and E. Auffenberg, *Ber.*, **50**, 951 (1917). It has been reported to melt at 23–24° but the method of isolation was not clear; L. Birchenbach, K. Kellerman, and W. Stein, *Ber.*, **65B**, 1074 (1932).

On attempted distillation of it at 34° and 0.2 mm., we obtained a low yield of a pale yellow oil, which darkened rapidly in air. On cooling, it deposited white crystalline material which decomposed readily.

(20) In this test only a yellow color was produced like that observed with chloroacetone under similar conditions.

of sulfone β-diketone II, m.p. 94–97° and at 98–99° after recrystallization from ethanol. This melting point was not depressed on admixture with a sample of II obtained from the boron fluoride acetylation of I. The infrared spectra of the two samples were identical.

More (94 mg.) of dibenzenesulfonylacetone (IX) was isolated from the dark oil mentioned above by dissolving it in hexane-ethyl acetate and allowing the solution to stand. The total yield of this product, m.p. 148–150°, was 3.5% based on crude 1-bromoacetylacetone. It was identified by the mixed melting point method and by comparison of infrared spectra employing an authentic sample of IX (m.p. 148–149°) prepared from sodium benzenesulfinate and 1,3-dichloro-acetone.[12]

In another experiment, 10.5 g. of crude 3-bromoacetylace-tone was isomerized to give 12.7 g. of crude 1-bromoacetyl-acetone (containing acetic acid), which was distilled *in vacuo* to afford 1.14 g. of a middle fraction, b.p. 57° at 0.9 mm. A solution of this product and 1.3 g. of sodium benzenesulfinate dihydrate in 60 ml. of 95% ethanol was refluxed for 24 hr. and the reaction mixture worked up essentially as described above to give 205.8 mg. of II and 233.2 mg. of IX. These yields correspond to 1.21 and 0.97%, respectively (based on crude 1-bromoacetylacetone). The relative yield of II to IX in this experiment is not significantly different from that (3.9 to 3.5%) obtained from the crude, undistilled 1-bromo-acetylacetone (see above).

Blank experiment with 3-bromoacetylacetone. A solution of 2.69 g. (0.015 mole) of crude 3-bromoacetylacetone and 3.2 g. (0.0155 mole) of sodium benzenesulfinate dihydrate in 150 ml. of 95% ethanol was refluxed for 24 hr. After evaporating the ethanol, the residue was triturated with dry ether, and the resulting mixture was filtered. Evaporation of the ether filtrate left a dark residue which was taken up in hexane–ethyl acetate; cooling the solution precipitated 283.7 mg. (9.5%) of I (identified by the mixed melting point method). The ether insoluble solid material on the funnel (see above) consisted partly of sodium benzenesulfonate (identified by infrared spectrum) and partly of sodium bromide since treatment of it with aqueous silver nitrate gave a precipitate, part of which was insoluble in concd. nitric acid. Silver benzenesulfonate (or benzenesulfinate) is soluble in this acid.

DURHAM, N. C.