after trituration with methanol. Recrystallization from methanol gave golden crystals of **2-methyl-3-carboxy-6,7-dimethoxy-1-tetralone**, m.p. 202–204.5°.

Anal. Calcd. for $C_{14}H_{16}O_5$: C, 63.62; H, 6.10. Found: C, 63.51; H, 6.32.

This compound was soluble in sodium bicarbonate solution, and gave a red precipitate with 2,4-dinitrophenylhydrazine.

Monoethyl Ester of 2-Bromo-4,5-dimethoxybenzylsuccinic Acid. (A) **Stobbe Condensation.**—A reaction of 89 g. (0.537 mole) of veratraldehyde with 110 g. (0.632 mole) of ethyl succinate in the presence of sodium ethoxide prepared from 13 g. (0.565 g. atom) of sodium was carried out as described previously.[1] The crude acid-ester was isolated (126 g.) and was not purified.

(B) **Hydrogenation.**—The acid–ester obtained as described in (A) was hydrogenated in glacial acetic acid in the presence of 10 g. of 5% palladium–charcoal catalyst at 80°, as described previously.[1] Ninety per cent. of the theoretical amount of hydrogen was absorbed during a period of 8 hours. The crude product was isolated by filtration of the catalyst and evaporation of the acetic acid, and weighed 128 g.

(C) **Bromination.**—A solution of the crude acid–ester from (B) (128 g., 0.43 mole) in 600 ml. of dry benzene was treated with 70 g. (0.44 mole) of bromine and 0.5 g. of magnesium. The solution was warmed on the steam-cone for two hours after the initial exothermic reaction subsided. It was cooled, diluted with ethyl acetate, washed with four portions of water, and dried over magnesium sulfate. Evaporation of the solvents and trituration of the dark residue with ether afforded 72 g. (36% from veratraldehyde) of crystalline product, m.p. 95–98°, which was sufficiently pure for further reactions. Recrystallization from ether gave colorless crystals, m.p. 110–112°.

Anal. Calcd. for $C_{15}H_{19}O_6Br$: C, 48.01; H, 5.10. Found: C, 48.19; H. 4.85.

3-Carbethoxy-5-bromo-7,8-dimethoxy-1-tetralone.—A mixture of 72 g. of the bromo-acid-ester from the preceding experiment and 400 g. of polyphosphoric acid was heated on the steam-cone with stirring for a half-hour. The cooled solution was hydrolyzed with ice and water, and the product was extracted with ethyl acetate. The organic solution was washed with dilute sodium hydroxide solution, dilute acetic acid and sodium bicarbonate solution, and was dried over magnesium sulfate. Evaporation of the solvent and distillation *in vacuo* of the dark, residual oil afforded 33.5 g. of bright-yellow oil, b.p. 218–227° (2-3 mm.), which crystallized very slowly, and which darkened gradually upon exposure to air. Recrystallization of the distilled material from the ether gave 26.3 g. (39%) of colorless crystals, m.p. 96.5–98.5°, which *exploded* when an attempt was made to burn a sample for carbon–hydrogen analysis. The infrared spectrum (chloroform) had peaks at 5.78 and 5.92 μ.

The 2,4-dinitrophenylhydrazone was recrystallized from ethyl acetate; orange crystals, m.p. 232–232.5°.

Anal. Calcd. for $C_{21}H_{21}O_8N_4Br$: C, 46.94; H, 3.94. Found: C, 46.41; H, 3.66.

Attempts to alkylate this keto-ester with γ-bromobutyronitrile and ethyl bromoacetate in the presence of sodium amide led to the formation of dark, tarry products and partial recovery of the starting material.

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Acetoacetylation of Aromatic Compounds by Boron Fluoride to Form β-Diketones. Failure with Boron and Aluminum Chlorides[1]

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Meerwein and Vossen[3] observed that the Friedel–Crafts type of acetylation of benzene or toluene with acetic anhydride by boron fluoride produced small amounts of the corresponding acetoacetophenones along with the acetophenones. The β-diketone was obtained in good yield by further treatment of acetophenone with the anhydride and the reagent.

We have obtained satisfactory yields of the corresponding β-diketones from toluene, anisole and mesitylene by employing a larger excess (four moles) of the anhydride (Table I). Some of the intermediate ketone was also usually isolated. The acetoacetylation is illustrated below with toluene. The procedure employed was unsatisfactory with benzene and acetic anhydride and with toluene and propionic anhydride even though the intermediate ketones were formed in fair yields (23–30%).

$$p\text{-}CH_3C_6H_5 \xrightarrow[BF_3]{(CH_3CO)_2O} p\text{-}CH_3C_6H_4COCH_3 \xrightarrow[BF_3]{(CH_3CO)_2O} p\text{-}CH_3C_6H_4COCH_2COCH_3$$

TABLE I

ACETOACETYLATION OF AROMATIC COMPOUNDS WITH ACETIC ANHYDRIDE BY BORON FLUORIDE

Aromatic cpd.	β-Diketone	B.p. or m.p.,[a] °C.	Yield, %
Benzene	Benzoylacetone	....	2[b]
Toluene	*p*-Methylbenzoylacetone	149–151 (13.5 mm.)[c]	43
Anisole	*p*-Methoxybenzoylacetone	M.p. 53–54.5[d,e]	51
Mesitylene	Mesitoylacetone	139–141 (8.5 mm.) M.p. 44.5–45.5[f,g]	57

[a] Melting points and boiling points are uncorrected. [b] Isolated as copper salt, m.p. 195–196° (W. Wislicenus and W. Stoeber, *Ber.*, **35**, 545 (1902)). [c] *Anal.* Calcd. for $C_{11}H_{12}O_2$: C, 74.96; H, 6.87. Found: C, 74.85; H, 7.12. The copper salt (light greenish blue) melted at 213–215°. Meerwein and Vossen (ref. 3) reported 155–156° (13 mm.) as the b.p. of the β-diketone and 129–130° as the m.p. of the copper salt. [d] E. Besthorn and G. Jaegle, *Ber.*, **27**, 910 (1894). [e] The copper salt (blue-green) melted at 210–211.5°. [f] R. C. Fuson and C. F. Woodward (THIS JOURNAL, **55**, 3474 (1933)) reported 45–46°. [g] The copper salt (dark grayish blue) melted at 193–194°.

That the products were β-diketones and not diketones having both of the acetyl groups attached to the aromatic rings was established by their characteristic enol test with ferric chloride, their complete solubility in alkali, and their conversion in high yield to copper salts with copper acetate. In these cases, exclusive acetylation at the α-hydrogen of the intermediate ketone evidently occurred even with acetomesitylene. However, in another connection, we have observed acetylation at the aromatic ring as well as at the α-hydrogen on treating mesitylacetone and acetic anhydride with boron fluoride, although no pure product was isolated.

In contrast to boron fluoride, boron chloride and aluminum chloride failed to effect the acetoacetylation of toluene in the presence of excess acetic anhydride, only the usual Friedel–Crafts acetylation to form the ketone being observed. Not even a trace of β-diketone could be detected by means of the sensitive ferric chloride enol test. Aluminum chloride has been observed to effect the diacetylation of mesitylene with excess acetyl chloride, but the second acetyl group as well as the first entered the aromatic ring.[4]

We further found that boron chloride fails to ef-

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(1) Paper L on Condensations.

(2) Carbide and Carbon Chemicals Company Fellow, 1946–1947.

(3) H. Meerwein and D. Vossen, *J. prakt. Chem.*, **141**, 149 (1934).

(4) C. A. Thomas, "Anhydrous Aluminum Chloride in Organic Chemistry," Reinhold Publ. Corp., New York, N. Y., 1941, pp. 220, 222.

fect the acetylation of the α-hydrogen of cyclohexanone or acetophenone with acetic anhydride to form the β-diketone; instead some of the ketone underwent self-condensation. Moreover, neither boron chloride nor aluminium chloride brought about acetylation of the α-hydrogen of even *p*-nitrophenylacetone, which is relatively reactive.

Similar observations were reported recently by Perfetti and Levine[5] who showed that neither aluminum chloride nor stannic chloride can effect the acetylation of acetophenone to form benzoylacetone. However, these workers did realize this acetylation with zinc chloride and ferric chloride, although the temperature employed (110°) is much higher than that (0°) known to effect the reaction with boron fluoride.

Experimental

Acetoacetylations by Boron Fluoride.—A mixture of the aromatic compound (0.20 mole) and acetic anhydride (0.80 mole) was saturated with boron trifluoride at 0–10° in two to three hours and then stirred for an additional period to make a total reaction time of four hours. A solution of 100 g. of sodium acetate in 500 ml. of water was added and the reaction mixture refluxed 15–30 minutes. The mixture was cooled and extracted two or three times with 30–60° ligroin. The combined ligroin solution was washed three times with small portions of water and once with saturated sodium bicarbonate solution. The ligroin solution was then extracted several times with cold 2% sodium hydroxide solution until the ligroin phase no longer gave a positive enol test. The combined alkaline solution was acidified at 0° and the β-diketone taken up in ether, from which it was recovered by fractionation of the dried solution (Table I). The ligroin phase was dried and fractionated, yielding the monoketone and some high-boiling residue.

Experiments with Boron Chloride and Aluminum Chloride.—A mixture of toluene (0.20 mole) and acetic anhydride (0.8 mole) was saturated with boron chloride at 10° and the reaction mixture worked up as described above for boron fluoride. There was obtained a 27% yield of *p*-methylacetophenone, b.p. 101–102° at 13 mm.

A mixture of cyclohexanone (0.15 mole) and acetic anhydride (0.30 mole) was saturated with boron chloride in 40 minutes at 10°. After stirring 30 minutes longer, the reaction mixture was decomposed with excess sodium acetate in ice-water. The mixture was extracted with ligroin and, after drying, the ligroin solution was fractionated to give 2-cyclohexylidenecyclohexanone[6] (59%), b.p. 142–143° at 17 mm.[6]; semicarbazone, m.p. 178–179°.[6]

Mixtures of acetophenone and acetic anhydride and of *p*-nitrophenylacetone and this anhydride were treated similarly with boron chloride. There were obtained some dypnone and tarry material, respectively.

A mixture of *p*-nitrophenylacetone (0.02 mole), acetic anhydride (0.06 mole), aluminum chloride (0.14 mole) and 40 ml. of carbon disulfide was stirred 12 hours at room temperature. After distilling most of the solvent, the mixture was poured onto ice and hydrochloric acid to give the original ketone (colored).

In all of these experiments, the products gave negative enol tests with ferric chloride showing the absence of β-diketones.

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[5] B. M. Perfetti and R. Levine, THIS JOURNAL, **75**, 626 (1953).

[6] A. D. Petrov, *Bull. soc. chim.*, [IV] **43**, 1272 (1928).

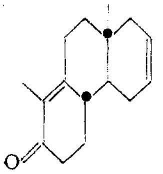
COMMUNICATIONS TO THE EDITOR

A SYNTHESIS OF *dl*-CORTISONE ACETATE

Sir:

We wish to report a direct synthesis of *dl*-cortisone acetate from the Woodward tricyclic ketone,[1] *dl*-1,14-dimethyl-2-keto-$\Delta^{1(11),6,9}$-octahydrophenanthrene. A distinguishing feature of this synthesis is that the cortical side chain and the eleven oxygen function are introduced without protecting the α,β-unsaturated ketone in ring A.

Selective hydrogenation of the Woodward tricyclic ketone with palladium on strontium carbonate gave the oily dihydrotricyclic ketone I ($\lambda^{\text{alc.}}_{\text{max.}}$ 250 mμ, ε15,300. Found: C, 83.5; H, 9.5). I was blocked in the 3 position by the methylanilinomethylene group[1] (m.p. 124–125°. Found: C, 82.8; H, 8.3.). The protected ketone was condensed with β-propiolactone[2] in the presence of potassium amide in ether. Removal of the blocking group yielded *dl*-1-(β-carboxyethyl)-1,14-dimethyl-2-keto-$\Delta^{6,10}$-decahydrophenanthrene as a crystalline isomer[3] (m.p. 171–173°. Found: C, 75.2; H, 8.7). This keto-acid was converted to the enol lactone (m.p. 100–102°) and thence by treatment with methylmagnesium bromide followed by cyclization[1] to the tetracyclic ketone II (m.p. 147–148°. Found: C, 84.9; H, 9.2). II was oxidized with iodine and silver acetate in wet acetic acid[4] to give a β-*cis*-glycol. Reaction with acetone gave *dl*-3-keto-16β,17β-dihydroxy-$\Delta^{4,9(11)}$-D-homoandrostadiene acetonide[5] (m.p. 174–175°). The structure of the acetonide was proved by conver-



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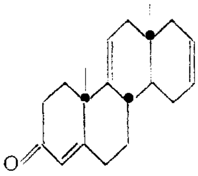
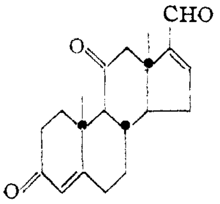


II



III

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[1] *Cf.* R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, THIS JOURNAL, **74**, 4223 (1952).

[2] *Cf.* T. L. Gresham, J. S. Jansen, F. W. Shaver, M. R. Frederick and W. L. Beears, *ibid.*, **73**, 2345 (1951), and earlier papers.

[3] The mother liquor from the isolation of this material undoubtedly contained the epimeric compound.

[4] A reagent described in a private communication from R. B. Woodward; *cf.* S. Winstein and R. E. Buckles, THIS JOURNAL, **64**, 2787 (1942).

[5] It is to be noted that our acetonide differs from Woodward's[1] in that it was derived from a β-*cis*-glycol whereas his was from an α-*cis*-glycol, where α and β designate configuration corresponding to standard steroid convention.