Communications TO THE EDITOR

Cuprous Chloride Catalyzed 2,4-Dichlorophenylation of Benzene in Aqueous Acetone. The Mechanism of the Meerwein Reaction

Sir:

Up to this time the Meerwein reaction[1] has been limited to aliphatic unsaturated compounds. We wish to report the 2,4-dichlorophenylation of benzene under Meerwein reaction conditions and the results of a Sandmeyer reaction in aqueous acetone with 2,4-dichlorobenzenediazonium chloride.

2,4-Dichlorobenzenediazonium chloride (6.00 g.) in a homogeneous mixture of 420 ml. of acetone, 180 ml. of water, 45 ml. of benzene, and 4.32 g. of cupric chloride gave 1.85 g. (29%) of 2,4-dichlorobiphenyl, 0.74 g. (18%) of 1,3-dichlorobenzene, and 0.26 g. (5%) of 1,2,4-trichlorobenzene. Identification of 2,4-dichlorobiphenyl was accomplished by comparison with an authentic sample synthesized by a Gomberg reaction.

Anal. Calc'd for $C_{12}H_8Cl_2$: C, 64.60; H, 3.61; Cl, 31.79. Found: C, 64.80; H, 3.64; Cl, 31.62.

2,4-Dichlorobenzenediazonium chloride (24.50 g.) in a homogeneous mixture of 1724 ml. of acetone, 745 ml. of water, and 17.88 g. of cupric chloride yielded 8.10 g. (48%) of 1,3-dichlorobenzene, 5.50 g. (26%) of 1,2,4-trichlorobenzene, and 5.25 g. (49%) of chloroacetone.

The cuprous chloride in these experiments was generated in the reaction mixture from cupric chloride and acetone, equation (1). This reaction, which was observed independently by us, has been reported recently by Kochi.[2] Since chloroacetone is also formed, equation (1), the yield of chloroacetone reported above represents only the amount produced by the decomposition of the diazonium salt.

Copper salt catalysis is evident from the observation that a solution of 2,4-dichlorobenzenediazonium chloride in 70% aqueous acetone evolves less than 10% of the theoretical volume of nitrogen. 1,5-Di-(2,4-dichlorophenyl)-3-acetylformazan has been isolated from this reaction. Cuprous chloride catalysis is indicated by a correlation of the rate of evolution of nitrogen with the rate of formation of cuprous chloride, equation (1).

Our results, arylation and hydrogen abstraction from acetone, are typical reactions of aryl radicals. Koelsch and Boekelheide,[3] for other reasons, have suggested a radical mechanism for the Meerwein reaction but this mechanism requires the presence of acetate ion. We propose equations (1) through (8) for the usual Meerwein reaction and equations (7′) and (8′) for the arylation reaction. Equations (1) through (6) are applicable to the Sandmeyer reaction in aqueous acetone. Waters' proposal[4] concerning the electron transfer ability of cuprous salts and the kinetic work of Cowdrey and Davies[5] have been followed in formulating equation (2).

$$\mathrm{CH_3COCH_3 + 2CuCl_2 \longrightarrow 2CuCl + ClCH_2COCH_3 + HCl} \tag{1}$$

$$\mathrm{ArN_2^+ + CuCl_2^- \longrightarrow ArN{=}N\cdot + CuCl_2} \tag{2}$$

$$\mathrm{ArN{=}N\cdot \longrightarrow Ar\cdot + N_2} \tag{3}$$

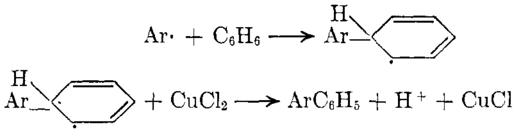
$$\mathrm{Ar\cdot + CuCl_2 \longrightarrow ArCl + CuCl} \tag{4}$$

$$\mathrm{Ar\cdot + CH_3COCH_3 \longrightarrow ArH + \cdot CH_2COCH_3} \tag{5}$$

$$\mathrm{\cdot CH_2COCH_3 + CuCl_2 \longrightarrow ClCH_2COCH_3 + CuCl} \tag{6}$$

$$\mathrm{Ar\cdot + -\overset{|}{C}{=}\overset{|}{C}- \longrightarrow Ar-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}\cdot} \tag{7}$$

$$\mathrm{Ar-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}\cdot + CuCl_2 \longrightarrow Ar-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}\,Cl + CuCl} \tag{8}$$



$\mathrm{Ar\cdot + C_6H_6 \longrightarrow}$ (7′)

$\mathrm{+ CuCl_2 \longrightarrow ArC_6H_5 + H^+ + CuCl}$ (8′)

Vogl and Rondestvedt[6] have suggested an intermediate complex type of "radicaloid" mechanism for the Meerwein reaction. Although complexing of cupric and or cuprous chloride with the unsaturate may explain the observed[3,7] dependence of the rate of evolution of nitrogen on the nature of the unsaturate, it does not appear to be important in the aromatic arylation reaction. This conclusion is based on our observation that, under essentially the same conditions as previously described, the phenylation of chlorobenzene occurred to the extent of only 2%. We interpret this variation in terms of the electrophilic[8] character of the aryl radical and the

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(1) H. Meerwein, E. Buchner, and K. van Emster, *J. prakt. Chem.*, **152**, 237 (1939).

(2) J. K. Kochi, *J. Am. Chem. Soc.*, **77**, 5274 (1955).

(3) C. F. Koelsch and V. Boekelheide, *J. Am. Chem. Soc.*, **66**, 412 (1944).

(4) W. A. Waters, *J. Chem. Soc.*, 266 (1942).

(5) W. A. Cowdrey and D. S. Davies, *J. Chem. Soc.*, S 48 (1949).

(6) O. Vogl and C. S. Rondestvedt, Jr., *J. Am. Chem. Soc.*, **77**, 3067 (1955).

(7) S. C. Dickerman and K. Weiss, unpublished results.

(8) R. L. Dannley and M. Sternfeld, *J. Am. Chem. Soc.*, **76**, 4543 (1954).

stability of the diazonium ion toward ionic decomposition to phenol.

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The Swamping Catalyst Effect in Bromination of Acetophenone

Sir:

We have obtained a 60% yield of *m*-bromoacetophenone, uncontaminated with phenacyl bromide, by the bromination of acetophenone mixed with a large excess of aluminum chloride catalyst. With catalytic quantities of aluminum chloride the bromination of acetophenone yields phenacyl bromide apparently unaccompanied by nuclear substitution products.[1] We attribute this rather dramatic change in orientation of the bromine atom to (a) suppression of "active methylene" activity by complex formation between the carbonyl group and the catalyst[2] and (b) the increase in substitution activity of bromine as it exists in complex formation with the catalyst. The synthesis of *m*-bromoacetophenone was as follows: acetophenone (0.28 mole) was added dropwise to anhydrous aluminum chloride (0.84 mole) contained in a flask equipped with a stirrer, gas outlet, and drying tubes. Bromine (0.28 mole) then was added to the fluid mass at room temperature within 10 minutes. After being stirred an additional hour and becoming semi-solid, the mixture was quenched in a slurry of ice and acid. After the usual extraction, washing, and drying of the oil in ether, the oil was concentrated and stripped from the residue (5.6 g.) by distillation at 2 mm. pressure; yield, 42.7 g. Fractionation of the distillate at 2 mm. yielded crude acetophenone (b.p. 57–94°, 3.4 g., 10%) and *m*-bromoacetophenone (b.p. 94–95°, n_{D}^{25} 1.5740; m.p. and reported[3] m.p. 7–8°; 33.1 g., 59.4%; *oxime* m.p. and mixture m.p. with an authentic sample 100–101°). Larger amounts of bromine relative to ketone gave a product contaminated with a lachrymatory substance.

Continuing studies of the swamping catalyst effect in substitution behavior of ketones and of other substances will be reported at a later date.

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[1] *Org. Syntheses*, Coll. Vol. II, 480 (1944).

[2] Baddeley, *J. Chem. Soc.*, 232 (1944).

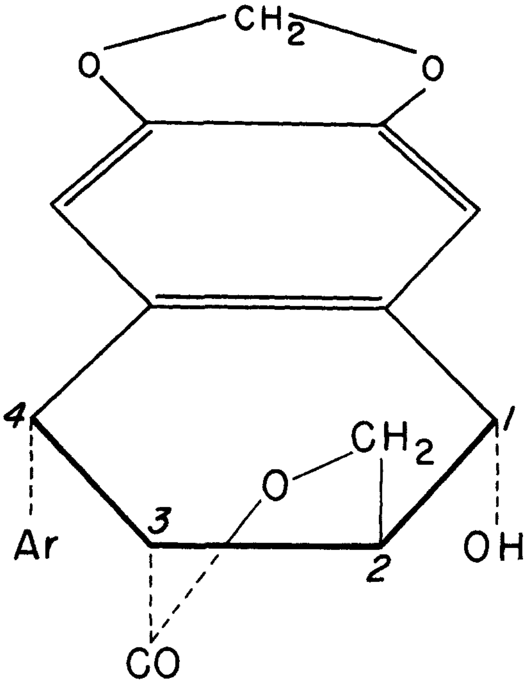
[3] Elson, Gibson, and Johnson, *J. Chem. Soc.*, 1128 (1930).

Components of Podophyllin. XX.[1] The Absolute Configuration of Podophyllotoxin and Related Lignans

Sir:

Since the tumor-damaging potency of podophyllotoxin (I) and related compounds is closely associated with their stereochemistry,[2] a determination of their absolute configuration might shed further light on the mechanism of their action, a question of importance in the search for effective chemotherapeutic agents.

Previous research[3] has demonstrated the *trans*-(1:2)-*trans*(2:3)-*cis*(3:4) arrangement[4] of I and its configurational identity at C_3 with (−)-guaiaretic acid dimethyl ether[5] (II).[6] We now wish to report the stereochemical correlation of II with a natural α-amino acid; this *ipso facto* proves the absolute configuration of I.



Ar = *3,4,5*-$(MeO)_3C_6H_2$
I

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[1] Paper XIX, Schrecker, Trail, and Hartwell, *J. Org. Chem.*, **21**, 292 (1956).

[2] Hartwell, Schrecker, and Leiter, *Proc. Am. Assoc. Cancer Research*, **1** (No. 2), 19 (1954).

[3] Schrecker and Hartwell, *J. Am. Chem. Soc.*, **75**, 5916 (1953); **77**, 432 (1955).

[4] The numbering of I was chosen to conform with the one appropriate for the majority of lignans.

[5] Schroeter, Lichtenstadt, and Ireneu, *Ber.*, **51**, 1587 (1918).

[6] Formulas conform to the Fischer convention and represent absolute configurations; *cf.* W. Klyne, "*Progress in Stereochemistry*," Academic Press Inc., New York, 1954, p. 178; W. Klyne in Braude and Nachod "*Determination of Organic Structures by Physical Methods*," Academic Press Inc., New York, 1955, p. 74.