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).

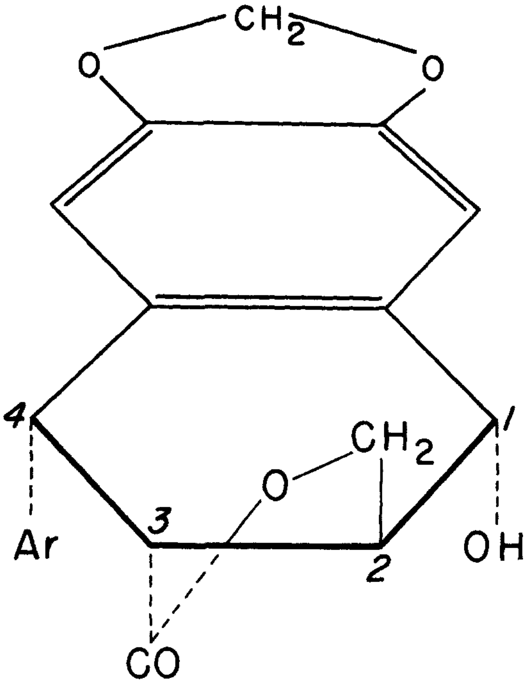
[3] Elson, Gibson, and Johnson, *J. Chem. Soc.*, 1128 (1930).

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).

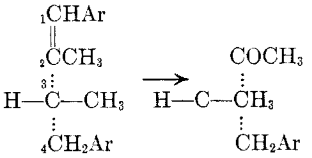
[3] Schrecker and Hartwell, *J. Am. Chem. Soc.*, 75, 5916 (1953); 77, 432 (1955).

[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).

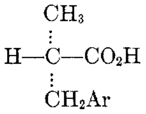
[6] Formulas conform to the Fischer convention and represent absolute configurations; *cf.* W. Klyne, "*Progress in Stereochemistry*," Academic Press Inc., New York, 1954, p. 178; W. Klyne in Braude and Nachod "*Determination of Organic Structures by Physical Methods*," Academic Press Inc., New York,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

Hydroxylation of II with osmium tetroxide,[7] periodate oxidation of the oily diol, and treatment with Girard's reagent P gave 4-(3,4-dimethoxyphenyl)-3-methyl-2-butanone (III), isolated as the semicarbazone (75% yield from II), m.p. 158.7–159.3°, $[\alpha]_D^{20}$ −48.0° (chloroform) (Found: C, 60.05; H, 7.57; N, 15.08). (+)-3,4-Dimethoxy-α-methylhydrocinnamic acid (IV), b.p.$_{0.01}$ 130° (bath temperature), $[\alpha]_D^{21}$ +27.5° (chloroform) (Found: C, 63.84; H, 7.16), obtained by resolving the racemate[8] with quinine, was converted with oxalyl chloride to the chloride, b.p.$_{0.015}$ 90° (bath temperature), $[\alpha]_D^{20}$ +20.5° (benzene), which with ethereal methylmagnesium bromide at −74° afforded the optical antipode of III, again isolated as the semicarbazone (17% yield[9]), m.p. 156.5–157.5°, $[\alpha]_D^{21}$ +46.7° (chloroform).



$$\begin{array}{c} {}_1\text{CHAr} \\ \| \\ {}_2\text{CCH}_3 \\ {}_3\vdots \\ \text{H—C—CH}_3 \\ \vdots \\ {}_4\text{CH}_2\text{Ar} \end{array} \longrightarrow \begin{array}{c} \text{COCH}_3 \\ \vdots \\ \text{H—C—CH}_3 \\ \vdots \\ \text{CH}_2\text{Ar} \end{array}$$

II III

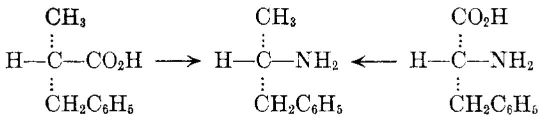


$$\begin{array}{c} \text{CH}_3 \\ \vdots \\ \text{H—C—CO}_2\text{H} \\ \vdots \\ \text{CH}_2\text{Ar} \end{array}$$

IV

Ar = *3,4*-$(MeO)_2C_6H_3$

IV and (+)-α-methylhydrocinnamic acid (V), $[\alpha]_D$ +27.7° (chloroform),[10] have identical rotations; hence they most certainly[11] belong to the same configurational series. Curtius degradation of V[12] gave (+)-α-methylphenethylamine (VI), identical in rotatory sign with the product obtained from D-phenylalanine (VII) by Karrer and Ehrhardt.[13] It follows that II possesses the D-configuration and that I is 1D, 2L, 3D, 4D.[14] These findings also indicate the absolute configurations of other lignans, insofar as they have been previously correlated[3,15] with I or II.



$$\begin{array}{c} \text{CH}_3 \\ \vdots \\ \text{H—C—CO}_2\text{H} \\ \vdots \\ \text{CH}_2\text{C}_6\text{H}_5 \end{array} \longrightarrow \begin{array}{c} \text{CH}_3 \\ \vdots \\ \text{H—C—NH}_2 \\ \vdots \\ \text{CH}_2\text{C}_6\text{H}_5 \end{array} \longleftarrow \begin{array}{c} \text{CO}_2\text{H} \\ \vdots \\ \text{H—C—NH}_2 \\ \vdots \\ \text{CH}_2\text{C}_6\text{H}_5 \end{array}$$

V VI VII

We are greatly indebted to Dr. W. Klyne for very stimulating discussions and extremely helpful suggestions. Miss Mary M. Trail performed a large portion of the experimental procedures.

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[7] Criegee, Marchand, and Wannowius, *Ann.*, **550**, 99 (1942).

[8] Haworth, Mavin, and Sheldrick, *J. Chem. Soc.*, 1423 (1934).

[9] Dimethylcadmium yielded 46% partly racemized semicarbazone, m.p. 155–156°, $[\alpha]_D^{21}$ +36°.

[10] Pickard and Yates, *J. Chem. Soc.*, **95**, 1011 (1909); *cf.* Kipping and Hunter, *J. Chem. Soc.*, **83**, 1005 (1903).

[11] See Klyne, ref. 6, pp. 204 and 78, respectively.

[12] Jones and Wallis, *J. Am. Chem. Soc.*, **48**, 169 (1926); *cf.* Wallis and Nagel, *J. Am. Chem. Soc.*, **53**, 2787 (1931).

[13] Karrer and Ehrhardt, *Helv. Chim. Acta*, **34**, 2202 (1951); *cf.* Leithe, *Ber.*, **65**, 660 (1932).

[14] *Cf.* Klyne, *Chemistry & Industry*, 1022 (1951). These assignments also agree with the McCasland system ("*A New General System for the Naming of Stereoisomers*," *Chemical Abstracts*, Columbus, Ohio, 1953), according to which I is expressed as D(1,3,4)A.

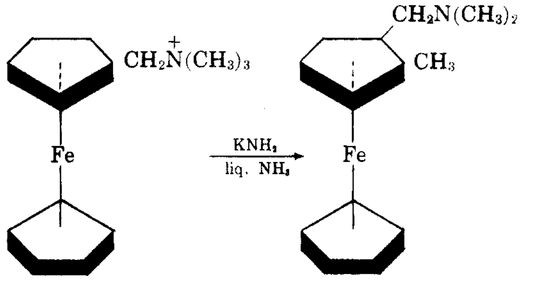
[15] Including the diarylbutanes, lariciresinol, pinoresinol, conidendrin, the peltatins; *cf.* Hartwell, Schrecker, Leiter, and Shilling, *Abstracts of Papers, Am. Chem. Soc.*, 125th Meeting, 11M (1954).

[16] National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare.

Ortho Substitution Type of Rearrangement with Quaternary Ammonium Ions of Dicyclopentadienyliron by Potassium Amide[1]

Sir:

We have simulated the *ortho* substitution type of rearrangement of the benzyltrimethylammonium ion[2] with the ferrocenyltrimethylammonium ion[3] (I) which gave the 2-methyl derivative (II).. This appears to be the first example of an aromatic nucleophylic type of reaction with such an iron compound.



I II

Quaternary ammonium ion I (as the iodide) gave, with potassium amide in liquid ammonia (two hours), a 60% yield of *tertiary amine II*, b.p.

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[1] This work was supported by the Office of Ordnance Research, U. S. Army.

[2] S. W. Kantor and C. R. Hauser, *J. Am. Chem. Soc.*, **73**, 4122 (1951).

[3] The more common electrophilic aromatic character of ferrocene has been noted by Woodward, Rosenblum, and Whiting, *J. Am. Chem. Soc.*, **74**, 3458 (1952).