(0°) for 48 hr and the olive green crystals were collected by filtration, washed with a little ice–water, and air-dried, yielding 504 mg (77%): mp 203–205° dec; faint yellow Ehrlich test; insoluble in water and common organic solvents; ir (KBr) 1710, 1675 (vs), 1625 cm^{-1} (s); nmr (D_2O/NaOD, TSPS external standard) δ 6.43 (1 H, d, J = 1.6 Hz), 6.72 (1 H, d, J = 1.6 Hz). Because of its insolubility this material was used without further purification.

3-Guanidinopyrrole Acetate (6).—To anhydrous barium acetate (127.8 mg, 0.50 mmol) in 5% aqueous acetic acid (15 ml) was added 2-carboxy-4-guanidinopyrrole sulfate (9) (217 mg, 0.50 mmol) followed by mercuric acetate (175 mg, 0.55 mmol). The heterogeneous mixture was heated at 93° (oil bath) with stirring for 3 hr (the reaction mixture darkened quickly and within 15 min gave a violet color with Ehrlich reagent). The reaction mixture was cooled and filtered and the filtrate treated with hydrogen sulfide. The small amount of mercuric sulfide precipitate was filtered off and the filtrate taken to dryness *in vacuo*. Crystallization and recrystallization from methanol–ethyl ether gave 119 mg of crystalline 3-guanidinopyrrole acetate: mp 170–178° dec; ir (KBr) 1680, 1640, 1535 cm^{-1}. The synthetic product was homogeneous and identical with material obtained by oxidation of viomycidine (tlc on cellulose powder, solvent C, Ehrlich reagent, and ir spectrum).

Anal. Calcd for $C_7H_{12}N_4O_2$: C, 45.64; H, 6.57. Found: C, 45.69; H, 6.64.

2-Carboxy-4-guanidinopyrrole Hydrochloride (9).—A saturated barium hydroxide solution was added with vigorous mixing to 2-carboxy-4-guanidinopyrrole sulfate (245 mg) suspended in 10 ml of distilled water until a pH of 8–9 (Hydrion pH paper) was attained. The precipitated barium sulfate was centrifuged down and the supernatant liquid drawn off. The barium sulfate was washed with a few milliliters of distilled water and the wash combined with the supernatant liquid; the combination was acidified (carefully with dilute hydrochloric acid) and taken to dryness *in vacuo*. The residue was extracted with boiling methanol (three 3-ml portions), the extract taken to dryness *in vacuo*, and the residue recrystallized from methanol–ethyl ether. The first recrystallization gave 65 mg of impure hydrochloride. Further recrystallization from methanol–ethyl ether gave 40 mg of pure 2-carboxy-4-guanidinopyrrole hydrochloride as granular crystals: mp 179–180° dec; homogeneous upon tlc (cellulose powder, solvent C); extremely weak Ehrlich test (yellow color); ir (KBr) 3460, 3325, 3165, 1690, 1670, 1604 cm^{-1}; nmr (D_2O, TSPS external standard) δ 6.61 (1 H, d, J = 1.7 Hz), 6.89 (1 H, d, J = 1.7 Hz).

2-Carbomethoxy-4-guanidinopyrrole Hydrochloride (10).—A solution of 2-carboxy-4-guanidinopyrrole hydrochloride (9) (40 mg) in 5 ml of absolute methanol was saturated with hydrogen chloride gas. After 12 hr at room temperature in a sealed flask the methanolic solution was taken to dryness *in vacuo*, and the residual hydrogen chloride removed by repeated evaporations with methanol. The final residue was recrystallized from methanol–ethyl ether to give 24 mg of hydroscopic granular crystals: mp 103–107°; homogeneous by tlc (silica gel G, solvent A); ir (KBr) 1700, 1675, 1635, 1600, 1510 cm^{-1}; nmr (D_2O, TSPS external standard) δ 3.83 (3 H, s), 6.87 (1 H, d, J = 1.8 Hz), 7.12 (1 H, d, J = 1.8 Hz). The extremely hydroscopic nature of this compound prevented a satisfactory elemental analysis.

Anal. Calcd for $C_7H_{11}N_4O_2Cl$: C, 38.45; H, 5.07; N, 25.63. Found: C, 37.93; H, 5.38; N, 24.89.

Registry No.—**4**, 24250-74-6; **4** 2HCl, 27557-44-4; **4** Me ester 2HCl, 27557-45-5; **6** acetate, 27557-46-6; **7** HCl, 27557-47-7; **9** sulfate, 27557-48-8; **9** HCl, 27617-87-4; **10** HCl, 27557-49-9.

Acknowledgment.—We are indebted to the National Institutes of Health for generous financial support and to Dr. F. A. Hochstein, Chas. Pfizer Inc., Groton, Conn., for a supply of viomycin sulfate.

The Stereoselective Total Synthesis of Racemic Fukinone

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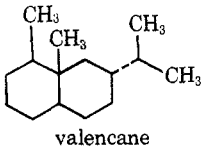
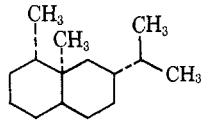
Two synthetic approaches to racemic fukinone, a sesquiterpene ketone of the eremophilane–valencane type, are described. Both utilize a decalone intermediate **12** synthesized from the known unsaturated alcohol **7** *via* acetylation, allylic oxidation, conjugate methylation, Wolff–Kishner reduction, and oxidation. The stereochemically crucial step of this sequence, conjugate methylation of enone **9**, was effected cleanly with lithium dimethylcopper(I). A reaction sequence involving a novel reduction–fragmentation of a β,γ-epoxynitrile (**15** → **16**) failed for lack of a suitable method for oxidizing the resulting allylic alcohol **16**. An alternative route involving addition of isopropenyllithium to the acetoxy ketone **20** and hydrogenolysis of the derived α-acetoxy ketone **23** was accordingly examined. This route led to a mixture of unsaturated ketones which isomerized to racemic fukinone (**17**) upon chromatography.

Considerable effort has been invested over the past several years in the development of rational schemes for the synthesis of sesquiterpenes related to the valencane–eremophilane family.[1] One of the difficulties in designing a synthetic approach to such compounds stems from the need for stereochemically selective methods for introducing the distinctive cis-related vicinal methyl substituents. In the case of fukinone (**17**), a sesquiterpene ketone isolated from the flower stalks of a cultivated variety of *Petasites japonicus* Maxim,[2] the presence of a cis-fused decalin system led us to consider the application of lithium dimethylcopper 1,4 addition[3] to an angularly methylated 1-octal-3-one (*e.g.*, **9**) as a means for achieving this task.[4] This report details the successful execution of that plan and the subsequent chemical transformations leading to totally synthetic fukinone (**17**).[5]



valencane



eremophilane

(1) *Cf.* J. A. Marshall, H. Faubl, and T. M. Warne, Jr., *Chem. Commun.*, 753 (1967); R. M. Coates and E. J. Shaw, *ibid.*, **47**, 515 (1968); *Tetrahedron Lett.*, 5405 (1968); C. Berger, M. Franck-Neumann, and G. Ourisson, *ibid.*, 3451 (1968); E. Piers and R. J. Keziere, *ibid.*, 583 (1968); S. Murayama, D. Chan, and M. Brown, *ibid.*, 3715 (1968).

(2) K. Naya, I. Takagi, Y. Kawaguchi, Y. Asada, Y. Hirose, and N. Shinoda, *Tetrahedron*, **24**, 5871 (1968).

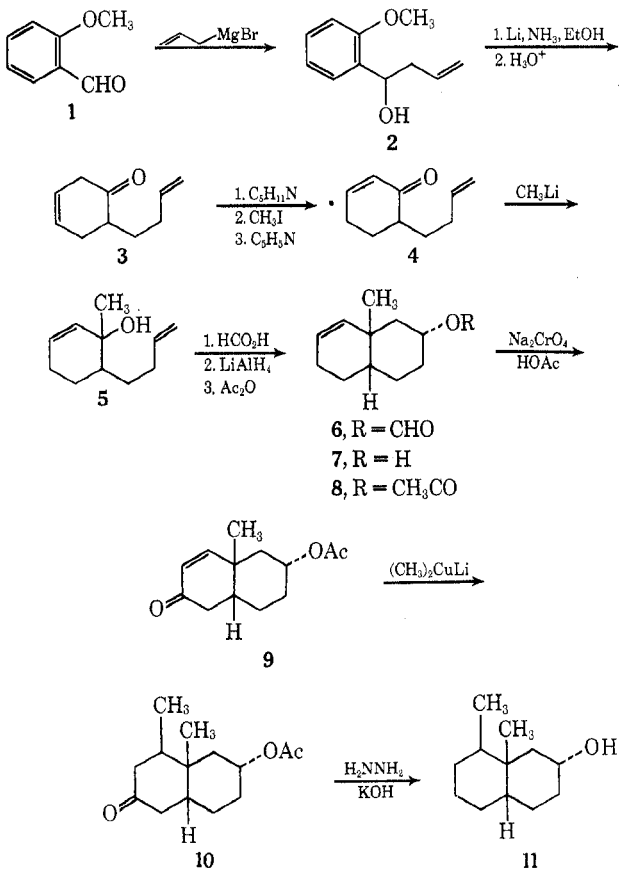
(3) *Cf.* H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966).

(4) Related trans-fused decalin enones undergo 1,4 additions with this reagent to give trans-related methyl groups. *Cf.* M. Pesaro, G. Bozatto, and P. Schudel, *Chem. Commun.*, 1152 (1968).

(5) For a preliminary report of this work, see J. A. Marshall and G. M. Cohen, *Tetrahedron Lett.*, in press.

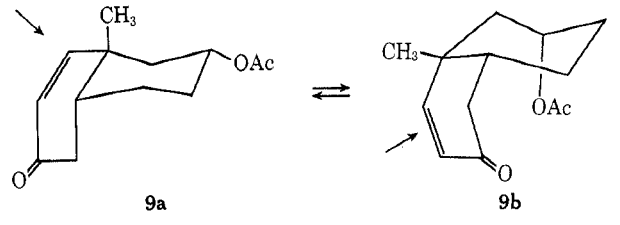
An attractive starting material for this project, the cis-fused octalyl formate **6**, had already been synthesized by Johnson and coworkers through an elegant application of their allyl-cation-initiated olefin cyclization method.[6] We utilized their approach but chose 1-methyl-2-(3-butenyl)-5-cyclohexen-1-ol (**5**) as the allyl cation precursor rather than the isomeric 5-methyl-2-(3-butenyl)-5-cyclohexen-1-ol employed by them in their synthesis. In this way we were able to simplify the reaction sequence leading to formate **6** (Scheme I).

SCHEME I

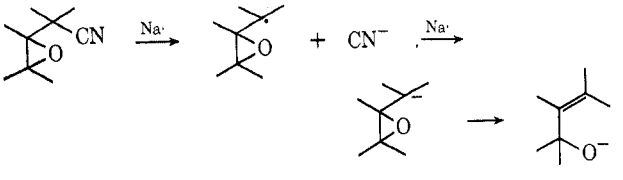


The main complication in our sequence, reduction of the butenyl and cyclohexenyl double bonds in the Birch reduction of the benzylic alcohol **2**, was likewise experienced by Johnson.[6] We employed his method[7] for the separation of cyclohexene-reduced material from enone **4** wherein the piperidine 1,4 adduct of the enone is prepared and separated from the neutral by-product *via* acid extraction. Basic treatment of the corresponding methiodide then affords the enone **4** contaminated only with butenyl-reduced material. The alcohol **7** secured *via* cyclization of allylic alcohol **5** and subsequent cleavage of the formate derivative **6** exhibited the properties reported by Johnson and coworkers[6] for the alcohol obtained through cyclization of the allylic isomer of dienol **5**.

Oxidation of the unsaturated acetate **8** with sodium chromate in acetic acid–acetic anhydride[8] afforded the crystalline enone **9** in high yield. Conformational analysis of this enone suggests that the steroid conformation **9a** should be favored over the nonsteroid conformation **9b** by an energy of 0.6 kcal/mol plus an additional increment arising from interaction of the acetoxyl grouping with the C-1 vinylic carbon. These interactions would be present to perhaps an even greater extent in the transition state for the conjugate addition of lithium dimethylcopper(I) to enone **9**.[9] Previous studies have shown that steric and stereoelectronic factors control the stereochemical outcome of this reaction.[10] In the case of conformer **9a** both factors favor formation of the cis adduct **10**. In conformer **9b** the stereoelectronically favored antiparallel attack[11] appears effectively blocked by the acetoxyl grouping and the concave cis-fused bicyclic geometry. Hence the cis adduct **10** might likewise be expected to predominate in 1,4 additions whose transition state geometry resembles this conformer. In any case, only a single stereoisomer was obtained upon treatment of enone **9** with lithium dimethylcopper(I). This product was assigned the cis stereochemistry in consideration of the foregoing arguments.



With a solution to the stereochemical problem of fukinone in hand we were able to attack the second synthetic problem presented by this molecule, introduction of the α-isopropylidene ketone functionality. For this task the ketone **12**, secured *via* Wolff–Kishner reduction of keto acetate **10** and oxidation of the resulting alcohol **11**, seemed like a promising intermediate. Our initial plan called for the application of an interesting reduction–fragmentation reaction of the β,γ-epoxynitrile **15**. The expected formation of allylic alcohol **16** by this route was based on the finding of Arapakos, Scott, and Hubert that tertiary nitriles readily undergo reductive decyanation upon treatment with sodium in ammonia.[12] The following sequence illustrates the basis for our proposed fragmentation reaction.



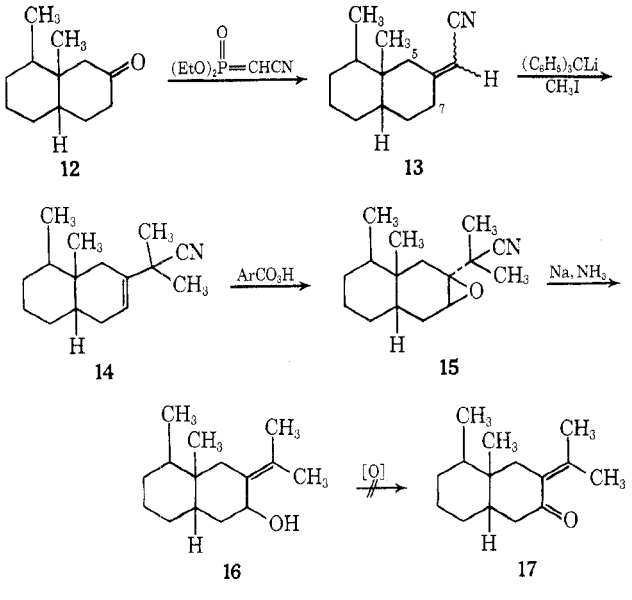
Ketone **12** yielded a 1:1 mixture of geometrically isomeric unsaturated nitriles **13** upon condensation with diethyl cyanomethylphosphonate. Alkylation of this mixture with methyl iodide using triphenylmethyllithium as the base afforded the dimethylated nitrile **14** as the major product. The major by-product of this reaction appeared to be the monomethylated

(6) W. S. Johnson and K. E. Harding, *J. Org. Chem.*, **32**, 478 (1967).
(7) The method was developed by G. Stork and W. N. White, *J. Amer. Chem. Soc.*, **78**, 4604 (1956).
(8) *Cf.* W. G. Dauben and A. C. Ashcraft, *ibid.*, **85**, 3673 (1963).
(9) *Cf.* J. A. Marshall, W. I. Fanta, and H. Roebke, *J. Org. Chem.*, **31**, 1016 (1966).
(10) *Cf.* J. A. Marshall and N. H. Andersen, *ibid.*, **31**, 667 (1966); H. O. House and W. F. Fischer, Jr., *ibid.*, **33**, 949 (1968).
(11) *Cf.* E. Toromanoff, *Bull. Soc. Chim. Fr.*, 708 (1962).
(12) P. G. Arapakos, M. K. Scott, and F. E. Hubert, Jr., *J. Amer. Chem. Soc.*, **91**, 2059 (1969).

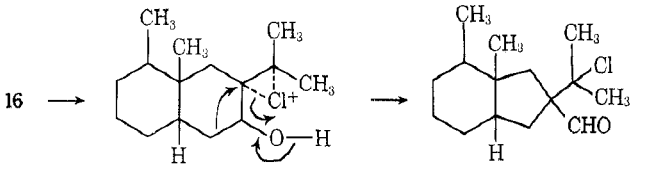
counterpart of nitrile **14**. We could find no indication that the *a priori* possible double bond isomer of nitrile **14** was formed to any extent. Our selection of a bulky base for the methylation reaction was made with this outcome in mind on the premise that proton abstraction from C-5 would involve appreciably greater steric interactions than abstraction at C-7. The use of potassium *tert*-butoxide in *tert*-butyl alcohol for this reaction led only to recovered starting material.

Expoxidation of the unsaturated nitrile **14** with *m*-chloroperoxybenzoic acid afforded material consisting largely of an isomer assigned structure **15** on the basis of spectral evidence and conformational considerations (attack of peroxy acid on the less hindered face of the double bond of olefin **14** in the steroid conformation). Treatment of the epoxynitrile **15** with sodium in ammonia gave the unsaturated alcohol **16** in 94% yield. Consideration of a probable mechanism for this cleavage (see Scheme II) leads to the indicated stereochemical assignment for this product.

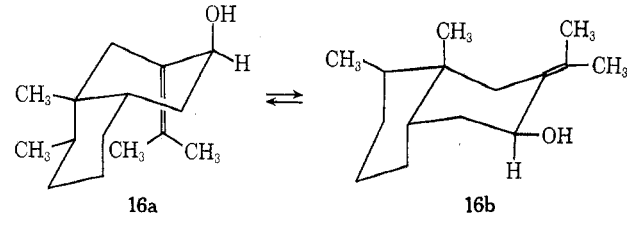
SCHEME II



Unfortunately, the seemingly trivial final step of this synthetic sequence, oxidation of alcohol **16** to racemic fukinone (**17**), could not be effected in our hands despite a considerable effort. The following reagents gave the results indicated: manganese dioxide[13] and Oppenauer oxidation[14] (recovered starting material); Collins reagent[15] (epoxide and epoxy ketone formation); Jones reagent,[16] ceric ammonium nitrate,[17] silver(II) picolinate,[18] dimethyl sulfoxide–acetic anhydride[19] (dehydration); chlorobenzotriazole[20] (rearrangement). This last reaction was of some interest as it afforded an aldehyde whose formation can be envisioned as follows.



Of the two major conformations **16a** and **16b** available to alcohol **16** the former should be of substantially lower energy. In addition to an axially oriented secondary methyl group (1.8 kcal/mol)[21] the latter also suffers from an $A^{(1,3)}$ interaction between the equatorial hydroxyl group and a vinyl methyl group.[22] Conformer **16a** suffers from two major drawbacks with regard to oxidation reactions: (1) acidic reagents should readily promote dehydration of the axial allylic hydroxy group, and (2) abstraction of the carbinyl hydrogen should be difficult owing to steric hindrance by the *syn*-vinyl methyl group.



Finding no way to effect the oxidation of alcohol **16**, we turned to an alternative plan for introducing the isopropylidene ketone grouping of fukinone. To this end, ketone **17** was treated first with triphenylmethyllithium and then acetic anhydride to give the enol acetate **18**. The use of a bulky base in this reaction to direct enolate formation in the desired direction was decided by consideration of steric factors as discussed above for the unsaturated nitrile **7**. Acid-catalyzed enol acetylation[23] led to a mixture of double bond isomers.

Epoxidation of the enol acetate **18** with *m*-chloroperoxybenzoic acid followed by thermal rearrangement[24] of the resulting epoxy acetate **19** afforded the acetoxy ketone **20**, an apparent mixture of epimers. Addition of isopropenyllithium gave the acid-labile diol **21** which was oxidized directly by the dimethyl sulfoxide–pyridine–sulfur trioxide method.[25] Acetylation then afforded the acetoxy ketone **23** as a mixture of epimers. Reduction with calcium in ammonia removed the acetoxy function from this compound and led to a mixture of α,β- and β,γ-unsaturated ketones **24**. Isomerization of the latter to racemic fukinone was effected upon chromatography of the mixture on alkaline alumina. Material thus secured was spectroscopically and chromatographically identical with natural fukinone[1,26] (Scheme III).

(13) *Cf.* P. J. Neustaedter in "Steroid Reactions," C. Djerassi, Ed., Holden-Day, San Francisco, Calif., 1963, pp 104–110.

(14) Reference 13, pp 92–104; C. Djerassi, *Org. React.*, **6**, 235 (1951); R. B. Woodward, N. L. Wendler, and F. J. Brutschy, *J. Amer. Chem. Soc.*, **67**, 1425 (1945).

(15) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

(16) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, **39** (1946).

(17) W. S. Trahanovsky, L. B. Young, and G. L. Brown, *J. Org. Chem.*, **32**, 3865 (1967).

(18) J. B. Lee and T. G. Clarke, *Tetrahedron Lett.*, 415 (1967).

(19) J. D. Albright and L. Goldman, *J. Amer. Chem. Soc.*, **87**, 4214 (1965).

(20) C. W. Rees and R. C. Storr, *Chem. Commun.*, 1305 (1968).

(21) *Cf.* E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformationl Analysis," Interscience, New York, N. Y., 1965, p 44.

(22) F. Johnson and S. K. Malhotra, *J. Amer. Chem. Soc.*, **87**, 5492 (1965).

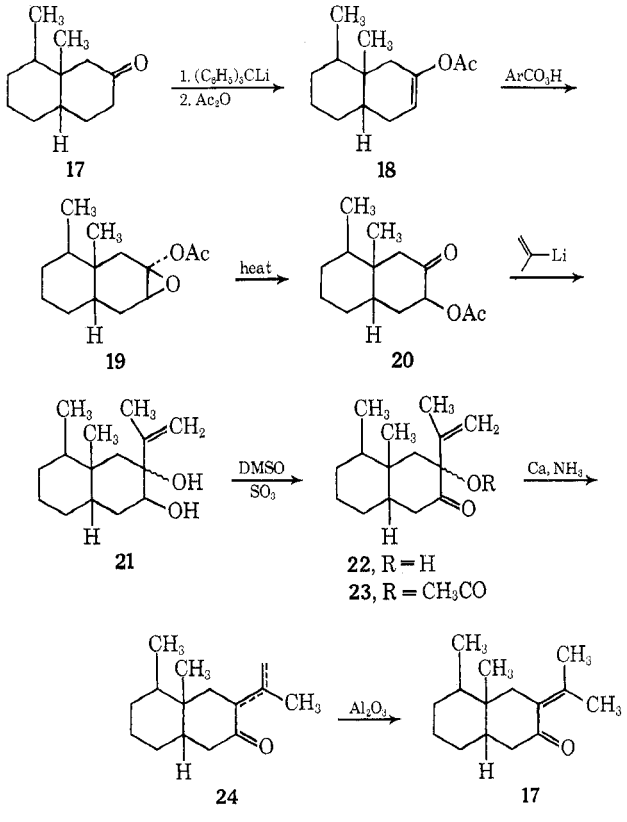
(23) B. E. Edwards and P. N. Rao, *J. Org. Chem.*, **31**, 324 (1966).

(24) *Cf.* K. L. Williamson and W. S. Johnson, *ibid.*, **26**, 4563 (1961).

(25) J. R. Parikh and W. von E. Doering, *J. Amer. Chem. Soc.*, **89**, 5505 (1967).

(26) We are indebted to Dr. K. Naya and Dr. Y. Hirose for a sample of natural fukinone.

SCHEME III



Experimental Section[27]

1-(*o*-Methoxyphenyl)-3-buten-1-ol (2).—To a solution of allylmagnesium bromide (prepared from 30.0 g of Mg and 57.1 g of allyl bromide in 370 ml of ether)[28] at 0° was added, with stirring, 55.8 g of *o*-anisaldehyde in 200 ml of ether over a period of 1.5 hr. Stirring was continued for 20 min and aqueous ammonium chloride and 1:1 aqueous HCl were added to dissolve the precipitated salts. The product was isolated with ether[27] and distilled affording 57.8 g (78%) of alcohol **2**: bp 80–92° (0.02 mm); λ_{max}^{film} 6.09, 6.24, 8.08, 9.02, 10.89, and 13.18 μm; $\delta_{TMS}^{CCl_4}$ 2.34 (CH_2, broad triplet, J = 6 Hz), 2.75 (OH), 3.63 (OCH_3), 4.7–5.1 (=CH_2 and CHOH), 5.3–5.9 (CH=), and 6.5–7.3 ppm (aryl CH).

The analytical sample was secured by preparative gas chromatography on a 13.5 ft by 0.5 in. column of DC-550 silicone oil on 70–80 mesh Chromosorb G (AW-DMCS).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.1; H, 7.7.

Conversion of Alcohol 2 to Octalol 7.—The following sequence was patterned after an analogous conversion reported by Johnson.[6] A solution of 62.2 g of alcohol **2** in 800 ml of 1,2-dimethoxyethane and 1600 ml of ammonia cooled in a Dry Ice–acetone bath was treated with 13.8 g of Li wire in small pieces over a period of 0.5 hr. Ethanol (40.7 ml) was added dropwise to the efficiently stirred solution over a period of 0.5 hr and, 10 min after complete addition, excess ammonium chloride was added to discharge the blue color. The ammonia was allowed to evaporate and the product was isolated with ether affording 51.9 g (89%) of material comprised chiefly of the enol ether but containing considerable (~20–30%) amounts of material with reduced vinyl and cyclohexene double bonds.

A solution of 26.6 g of the above material and 3.3 g of oxalic acid dihydrate in 25 ml of 1,2-dimethoxyethane and 40 ml of water was stirred briskly for 22 hr. The product was isolated with ether affording 16.7 g (69%) of β,γ-unsaturated ketone **3** contaminated with saturated ketone and butenyl-reduced material according to the nmr spectrum.

A solution of 30.4 g of enone, comparable to that described above, in 125 ml of piperidine was stirred at reflux for 4 hr. The cooled solution was poured into 440 ml of 10% HCl and washed with ether. The aqueous phase was made basic with 220 ml of 20% NaOH and extracted with ether affording 33.3 g of β-amino ketone: λ_{max}^{film} 5.84 μm; $\delta_{TMS}^{CCl_4}$ 4.8–5.2 (=CH_2) and 5.4–6.1 ppm (CH=).

The above amino ketone was cooled in an ice bath during the careful addition of 67 ml of methyl iodide. The mixture was allowed to reach room temperature over 3 hr and excess methyl iodide was removed from the crushed mass under vacuum.

The above methiodide in 50 ml of pyridine was heated on a steam bath for 1.7 hr and the cooled solution was poured into 430 ml of 10% HCl. The product was isolated with ether and treated with activated charcoal to remove colored impurities. Distillation at 87–89° (1.7 mm) afforded 17.0 g (74%) of enone **4** contaminated with 30% of the butenyl-reduced enone according to gas chromatography: λ_{max}^{film} 5.96, 6.08, and 10.92 μm; $\delta_{TMS}^{CCl_4}$ 4.7–5.3 (=CH_2), 5.4–6.2 (CH=), 5.88 (t of d, CH=CHC=O, J = 1 and 10 Hz), and 6.86 ppm (t of d, CH=CHC=O, J = 7 and 10 Hz).

A solution of 17.0 g of the above enone in 110 ml of ether was added to 150 ml of 1.37 *M* methyllithium in ether at 0° with stirring. After 2.5 hr the ice bath was removed and the product was isolated with ether. The crude alcohol **5** thus secured was poured into 300 ml of rapidly stirred formic acid. After several minutes, the product was isolated with hexane affording 14.2 g (65% based on enone **4**) of formate **6**: λ_{max}^{film} 5.80, 6.02, and 8.47 μm.

A mixture of 10.2 g of the above formate and 3.22 g of lithium aluminum hydride in 350 ml of ether was stirred at 0° for 0.5 hr and at room temperature for 0.5 hr. The mixture was cooled to 0° and 6.4 ml of water and 5.1 ml of 10% NaOH were added carefully with stirring. After 4 hr the mixture was filtered and the solvent was removed *in vacuo* affording 9.30 g (100%) of alcohol **7**: λ_{max}^{film} 3.1, 6.05, and 9.55 μm. The 3,5-dinitrobenzoate had mp 127–128° (lit.[6] mp 128–129°) after recrystallization from ethanol.

***cis*-10β-Methyl-3-octal-6α-yl Acetate (8).**—A solution of 3.22 g of alcohol **7**, 6 ml of acetic anhydride, and 23 ml of pyridine was stirred for 23 hr at room temperature. The solution was poured into 100 ml of cold 10% sulfuric acid and the product was isolated with ether affording 3.67 g (91%) of acetate **8**: bp 50–60° (0.03 mm); λ_{max}^{film} 5.87, 6.05, 8.02, 8.12, and 9.72 μm; $\delta_{TMS}^{CCl_4}$ 1.08 (CH_3), 1.90 (CH_3CO), 4.5–5.0 (H-6), and 5.1–5.7 ppm (vinyl H multiplet). The analytical sample was secured *via* preparative gas chromatography on an 18 ft by 0.25 in. column of 5% Carbowax 20M on Chromosorb W.

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.0; H, 9.7.

***cis*-10β-Methyl-6α-acetoxy-3-octal-2-one (9).**—The procedure of Dauben[8] was modified. To a solution of 7.77 g of octalin **8** in 92 ml of acetic acid and 64 ml of acetic anhydride was slowly added, with mechanical stirring and intermittent cooling, 44 g of anhydrous sodium chromate. After 7 hr of heating at 60°, 30 ml of water was added, the solution was cooled, and the product was isolated with ether affording 6.68 g (81%) of an oil which crystallized upon cooling. Recrystallization from hexane–ether afforded the analytical sample: mp 63.5–65.5°; λ_{max}^{KBr} 5.78, 5.96, 6.19, 8.18, 9.69, 13.28, and 13.99 μm; $\delta_{TMS}^{CCl_4}$ 1.23 (CH_3), 1.93 (CH_3CO), 2.2–2.5 (H-1), 4.7–5.7 (H-6), 5.72 (H-3 doublet, J = 10 Hz), and 6.48 ppm (H-4 doublet, J = 10 Hz).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.5; H, 8.3.

***cis*-6α-Acetoxy-4β,10β-dimethyl-2-decalone (10).**—The method of House[9] was employed. A solution of lithium dimethylcopper(I) was prepared from 13.6 g of Cu(I) in 300 ml of ether to which 100 ml of 1.36 *M* methyllithium was added at 0°. To this solution was added with stirring a solution of 7.56 g of keto acetate **9** in 100 ml of anhydrous ether. After 0.5 hr, the mixture was poured into 700 ml of saturated ammonium chloride and ammonium hydroxide was added to dissolve the precipitated salts. The product was isolated with ether and distilled, bp 92–132° (0.05 mm). The distilled material was chromatographed on 244 g of Merck alumina. The keto acetate **10** (4.50 g, 55%) was eluted with 1% ether–benzene: λ_{max}^{film} 5.76, 5.82, 8.05, 8.78, 9.60, and 9.79 μm; $\delta_{TMS}^{CCl_4}$ 0.87 (CH_3 doublet, J = 6 Hz), 1.05 (CH_3), 1.92 (CH_3CO), and 4.6–5.1 ppm. The analytical sample

(27) Reactions were conducted under a nitrogen atmosphere using the apparatus described by W. S. Johnson and W. P. Schneider, "Organic Syntheses," Collect Vol. IV, Wiley, New York, N. Y., 1963, p 132. Reaction products were isolated by addition of water and extraction with the specified solvent. The combined extracts were washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was removed from the filtered solutions on a rotary evaporator.

(28) O. Grummitt, E. P. Budewitz, and C. C. Chudd, *ibid.*, p 748.

was secured by preparative gas chromatography on a 7 ft × 0.25 in. column of DC-550 silicone oil on 60–70 mesh Chromosorb G (AW-DMCS).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.4; H, 9.3.

***cis*-4β,10β-Dimethyl-6α-decalol (11).**—A modified Huang-Minlon[29] procedure was used. A solution of 537 mg of keto acetate **10**, 596 mg of KOH, 0.4 ml of 85% hydrazine hydrate, and 20 ml of diethylene glycol was heated at 120° for 18 hr and then at reflux for 3 hr with a Dean–Stark trap. The product was isolated with hexane affording 304 mg (74%) of alcohol **11**. The analytical sample, mp 72–74°, was secured by preparative gas chromatography on a 13.5 ft × 0.5 in. column of 9% DC-550 silicone oil on 70–80 mesh Chromosorb G (AW-DMCS), and sublimation at 70° (0.2 mm): λ_{max}^{KBr} 3.05, 9.59, 9.68, 10.11, 10.48, 10.69, and 10.84 μm; $\delta_{TMS}^{CCl_4}$ 0.85 (CH_3), 0.86 (CH_3 doublet, J = 7 Hz), and 3.90 ppm (H-6).

Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 79.3; H, 12.4.

***cis*-4β,10β-Dimethyl-6-decalone (12).**—The Jones oxidation procedure was used.[16] To a solution of 301 mg of alcohol **11** in 12 ml of acetone at 0° was added dropwise 0.52 ml of Jones reagent.[16] After 3 min isopropyl alcohol was added and the product was isolated with ether affording 274 mg (92%) of ketone **12**: bp 73° (bath temperature) (0.1 mm); λ_{max}^{film} 5.85, 7.62, and 8.01 μm; $\delta_{TMS}^{CCl_4}$ 0.85 (CH_3 doublet, J = 6 Hz) and 0.95 ppm (CH_3).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.0; H, 11.2.

(*Z*)- and (*E*)-(*cis*-4β,10β-Dimethyl-6-decalylidene)cyanoacetate (13).—The method of Wadsworth and Emmons[30] was employed. To 58.5 mg of pentane-washed NaH (from a 53% dispersion in oil) was added 2.0 ml of DME and 259 mg of diethyl cyanomethylphosphonate with stirring and cooling. After hydrogen evolution ceased, 208 mg of ketone **12** and 0.4 ml of DME was added and the solution was allowed to reach room temperature. After 22 hr the product was isolated with ether and chromatographed on silica gel. Elution with 25% benzene–hexane afforded 185 mg (79%) of nitrile **13**: bp 100° (bath temperature) (0.02 mm); λ_{max}^{film} 4.49, 6.12, and 12.12 μm; $\delta_{TMS}^{CCl_4}$ 0.79 (CH_3 doublet, J = 6 Hz), 0.90 and 0.96 (CH_3's of *Z* and *E* isomers), 4.86 and 4.97 ppm (vinyl H's of *Z* and *E* isomers, $W_{h/2}$ = 5 Hz).

***cis*-4β,10β-Dimethyl-6-(dimethylcyanomethyl)-6-octalin (14).**—Triphenylmethyllithium was prepared according to House.[31] The solvent from 2.39 ml of 1.76 *M* methyllithium was removed *in vacuo* and replaced by 4.0 ml of DME. To this solution was added 1.13 g of triphenylmethane. After 3 hr, 188 mg of nitrile **13** was added with stirring and, after 0.5 hr, the solution was cooled in an ice bath and 0.435 ml of methyl iodide was slowly added. After addition was complete the ice bath was removed and after 0.5 hr the product was isolated with ether and chromatographed on 150 g of silica gel. The fractions eluted with 85% hexane–benzene were combined and distilled affording 183 mg (85%) of nitrile **14**: bp 90° (bath temperature) (0.02 mm); λ_{max}^{film} 4.47, 7.26, and 7.35 μm; $\delta_{TMS}^{CCl_4}$ 0.88 (CH_3), 1.23 (gem CH_3's), and 5.67 ppm (H-7, $W_{h/2}$ = 10 Hz). Gas chromatography on a 6 ft × 0.125 in. column of 10% SE-30 silicone gum rubber on 80–100 mesh Diatoport S revealed an 80:20 mixture of nitrile **14** and its monomethylated counterpart.

***cis*-4β,10β-Dimethyl-6-isopropylidenedecal-7β-ol (16).**—A solution of 150 mg of nitrile **14** and 235 mg of *m*-chloroperoxybenzoic acid (97%) in 10 ml of methylene chloride was stirred at room temperature for 6 hr. The solution was treated with 2.5 ml of 10% aqueous sodium sulfite and the product was isolated with ether affording 159 mg (99%) of epoxynitrile **15**: λ_{max}^{film} 4.46, 7.24 and 7.35 μm; $\delta_{TMS}^{CCl_4}$ 0.86 (CH_3), 1.26 and 1.36 (gem CH_3's), and 3.27 ppm (H-7, $W_{h/2}$ = 11 Hz). The gas chromatogram indicated a purity of 73% and contained minor peaks amounting to 7 and 19% along with trace impurity peaks.

The reduction procedure of Arapakos, Scott, and Hubert was followed.[12] To a solution of 217 mg of Na in 15 ml of liquid ammonia was added a solution of 159 mg of epoxy nitrile **15** in 1.6 ml of ether over a period of 5 min. After 20 min excess ammonium chloride was added to discharge the color, the ammonia was allowed to evaporate, and the product was isolated with ether affording 134 mg (94%) of alcohol **16**: λ_{max}^{film} 3.00 μm; $\delta_{TMS}^{CCl_4}$ 0.90 (CH_3), 1.67 and 1.73 [$(CH_3)_2C$=], and 4.70 ppm (H-7, $W_{h/2}$ = 8 Hz).

***cis*-4β,10β-Dimethyl-6-octal-6-yl Acetate (18).**—The method of House[31] was utilized. Triphenylmethyllithium was prepared as described above from 7.8 ml of 1.08 *M* methyllithium and 2.56 g of triphenylmethane in 10 ml of DME. To this solution was added 949 mg of ketone **17**, a quantity which just discharged the red color of the basic solution. After 0.5 hr this enolate solution was added dropwise to 25 ml of acetic anhydride. The solution was stirred for 0.5 hr, poured into hexane, and treated with aqueous and then solid sodium bicarbonate. The product was isolated with hexane and chromatographed on 140 g of silica gel. Elution with 75% benzene–hexane afforded 669 mg (57%) of enol acetate **18**: bp 68° (bath temperature) (0.02 mm); λ_{max}^{film} 5.70, 5.92, 8.24, 9.15, and 9.93 μm; $\delta_{TMS}^{CCl_4}$ 0.93 (CH_3), 0.91 (CH_3 doublet, J = 6 Hz), 1.98 (CH_3CO), and 5.07 ppm (H-7, $W_{h/2}$ = 17 Hz). The analytical sample was secured by preparative gas chromatography on a 7 ft × 0.25 in. of column of DC-550 silicone oil on 60–70 mesh Chromosorb G (AW-DMCS).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.7; H, 9.9.

***cis*-7-Acetoxy-4β,10β-dimethyl-6-decalone (20).**—A solution of 97.8 mg of enol acetate **18**, 166 mg of *m*-chloroperoxybenzoic acid (97%), and 17.7 mg of 2,6-di-*tert*-butylphenol in 1.55 ml of benzene was stirred at room temperature for 4 hr. The solution was treated with 3.5 ml of 10% aqueous sodium sulfite and the product was isolated with ether, after an initial wash with 10% aqueous NaOH, and distilled affording 94.5 mg of epoxy acetate **19**: bp 75–100° (bath temperature); λ_{max}^{film} 5.72 μm, contaminated with 2,6-di-*tert*-butylphenol.

The above sample of epoxy acetate **19** was heated at 170–180° for 10 min and distilled, 110° (bath temperature) (0.02 mm), to yield 79 mg of an oil that was chromatographed on silica gel. Elution with 2% ether–benzene afforded 50 mg (48%) of keto acetate **20**: λ_{max}^{film} 5.72, 5.82, 8.12, and 9.48 μm; $\delta_{TMS}^{CCl_4}$ 0.90 and 0.96 (CH_3), 2.03 (CH_3CO), and 4.9–5.3 ppm (H-7). The C-4 methyl doublets were partially obscured by the angular methyl signals. The analytical sample, mp 96–104°, was secured by repeated crystallization from hexane of one chromatographic fraction.

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.7; H, 9.4.

***cis*-4β,10β-Dimethyl-6-hydroxy-6-isopropenyl-7-decalone (22).**—A solution of isopropenyllithium was prepared from 401 mg of lithium (1% Na) and 1.42 ml of isopropenyl bromide in 23 ml of ether according to the procedure of Braude and Evans.[32] To this solution at 0° was added with stirring 191 mg of keto acetate **20** and 2 ml of ether. After 1 hr the product was isolated with ether (dried over potassium carbonate) and oxidized by treatment with 1.95 g of sulfur trioxide–pyridine complex in 8.8 ml of dimethyl sulfoxide and 4.15 ml of triethylamine for 4 hr.[25] The product was isolated with hexane and distilled to give 137 mg of ketol **22**. Chromatography on 13 g of silica gel afforded on elution with 2% ether–benzene 84 mg (44%) of product: λ_{max}^{film} 2.90, 5.87, 6.08, and 11.06 μm; $\delta_{TMS}^{CCl_4}$ 0.89 (two overlapping CH_3 doublets, J = 7 Hz), 1.05 (CH_3), 1.83 (vinyl CH_3), and 4.6–4.9 ppm (CH_2=). The analytical sample was secured by distillation, 105° (bath temperature) (0.2 mm).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.3; H, 10.3.

***cis*-6-Acetoxy-4β,10β-dimethyl-6-isopropenyl-7-decalone (23).**—The procedure of Huang-Minlon, Wilson, Wendler, and Tishler was employed.[33] A solution of 83.9 mg of ketol **22** and 64.9 mg of *p*-toluenesulfonic acid monohydrate in 4.7 ml of acetic anhydride was stirred for 19 hr at room temperature. The solution was poured into saturated aqueous sodium bicarbonate and hexane, and solid sodium bicarbonate was added. The product was isolated with hexane and distilled to give 88 mg of keto acetate **23**: bp 90° (bath temperature) (0.02 mm); λ_{max}^{film} 5.74, 5.78, 6.08, 8.10, 9.80, and 10.97 μm; $\delta_{TMS}^{CCl_4}$ 0.80 (CH_3 doublet, J = 6 Hz), 0.93 and 0.96 (CH_3), 1.8 (vinyl CH_3), 1.96 and 2.02 (CH_3CO), and 4.7–5.1 ppm (CH_2=). The analytical sample was eluted from silica gel with 2% ether–benzene and distilled, bp 80° (bath temperature) (0.1 mm).

Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.5; H, 9.6.

(29) Huang-Minlon, *J. Amer. Chem. Soc.*, **71**, 3301 (1949).
(30) W. S. Wadsworth, Jr., and W. D. Emmons, *ibid.*, **83**, 1733 (1961).
(31) H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 1341 (1965).
(32) E. A. Braude and E. A. Evans, *J. Chem. Soc.*, 3333 (1956).
(33) Huang-Minlon, E. Wilson, N. L. Wendler, and M. Tishler, *J. Amer. Chem. Soc.*, **74**, 5394 (1952).

(±)-**Fukinone** (**17**).—A stirred solution of 82.8 mg of Ca in 5 ml of liquid ammonia was treated with a solution of 48 mg of keto acetate **23** in 0.8 ml of ether. After 10 min, excess ammonium chloride was added and the ammonia was allowed to evaporate through a Mercury bubbler. The product was isolated with ether and distilled affording 33 mg of an oil, bp 75° (bath temperature) (0.01 mm). Elution from 10 g of Merck alumina with 50% benzene–hexane afforded 15 mg (39%) of (±)-fukinone: λ_{max}^{film} 5.93, 6.12, 6.93, 7.33, 7.88, 8.21, 8.61, and 9.39 μm; $\delta_{TMS}^{CDCl_3}$ 0.85 (CH_3 doublet, J = 7 Hz), 0.97 (CH_3), 1.79 and 1.94 ppm [$(CH_3)_2C$=].[34] The infrared and nmr spectra matched those of natural fukinone and the gas chromatographic behavior of the two substances was identical on three columns (peak enhancement).[1,26]

(34) This spectrum was secured using a Brucker 90-MHz spectrometer.

Registry No.—**2**, 27693-90-9; **8**, 27755-32-4; **9**, 27693-91-0; **10**, 27693-92-1; **11**, 27755-33-5; **12**, 27693-93-2; (*E*)-**13**, 27693-94-3; (*Z*)-**13**, 27693-95-4; **14**, 27693-96-5; **16**, 27693-97-6; **17**, 25828-19-7; **18**, 27693-99-8; **20**, 27694-00-4; **22**, 27694-01-5; **23**, 27694-02-6.

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The Nature of the Ortho Effect. VIII. Composition of the Ortho Effect as a Function of Side-Chain Structure

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Twenty-two sets of ionization constants, in water, for ortho-substituted compounds of the type XGZY (where X is a substituent; Z, a side chain; Y, the reaction site; and G, a skeletal group to which X and Z are attached) were correlated with the equation $Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + \psi_{V,X} + h$, and 27 sets were correlated with the equation $Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + h$. Significant correlations were obtained in most cases. Steric effects were absent in most of those sets which were of diagnostic value. Examination of the ϵ values obtained shows that the composition of the ortho electrical effect is indeed a function of the side chain. It is shown that this implies the existence of electrical proximity effects. The delocalized electrical proximity effect is found to be a function of the side chain. No conclusion can be reached as to whether or not the localized electrical proximity effect is a function of the side chain. In the majority of the sets studied, the value for the unsubstituted compound does lie on the correlation line.

In a further extension of our work on the nature of the ortho effect,[1-7] we consider here the variation of the composition of the ortho electrical effect as a function of side-chain structure in sets of the type $2XC_6H_4ZY$, in which X is the substituent, Y is the reaction site, and Z is the side chain. For this purpose, it is advisable to consider the composition of the overall effect of an ortho substituent on some reaction site. This overall effect is composed of the normal electrical effect of the substituent at the ortho position and of a proximity effect which results from the nearness of the substituent to the reaction site. This proximity effect can be separated into three possible contributions.

I. Proximity Electrical Effects.—These electrical effects are a property of the proximity effect and are exerted in addition to the normal electrical effects of the substituent. They may be resolved into (1) localized effects, which are a function of the σ_I constants, and (2) delocalized effects, which are a function of the σ_R constants.

II. Steric Effects.—These effects are a function of the size of the substituent. They may consist of (1) steric hindrance to solvation of the substituent and/or the reaction site, (2) steric hindrance of the reaction site to attack by a reagent, (3) steric inhibition of resonance in the substituent and/or the reaction site, and (4) steric control of the reacting conformation.

III. Intramolecular Secondary Bonding Forces.—(1) Hydrogen bonding, (2) Keesom (dipole–dipole), Debye (dipole–induced dipole), and London (induced dipole–induced dipole), and (3) charge transfer interactions comprise this group.

It is readily seen that not all ortho-substituted sets will show a proximity effect. The existence of the proximity effect depends on the closeness in space of the substituent to the reaction site. In sets of the type $2XC_6H_4ZY$, the closeness of X to Y is a function of the size and geometry of the side chain Z. For a sufficiently large Z, X and Y must be far enough apart to exclude the possibility of proximity effects. Furthermore, the magnitude of the proximity effect must be a function of the distance between the reaction site and the substituent. We would predict then a dependence of the overall substituent effect upon the size of Z. We may quantitatively represent the overall substituent effect of an ortho substituent by the expression

$$Q_X = \alpha_{norm}\sigma_{I,X} + \beta_{norm}\sigma_{R,X} + \alpha_{prox}\sigma_{I,X} + \beta_{prox}\sigma_{R,X} + \psi r_{V,X} + \nu\omega_X + d \quad (1)$$

where $\alpha_{norm}\sigma_{I,X} + \beta_{norm}\sigma_{R,X}$ represents the proximity electrical effect, $\psi r_{V,X}$ signifies the steric effect, and $\nu\omega_X$ denotes the contribution due to secondary bonding. Equation 1 simplifies to

$$Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + \psi r_{V,X} + \nu\omega_X + h \quad (2)$$

Of the types of secondary bonding considered above, hydrogen bonding and charge transfer occur only in

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