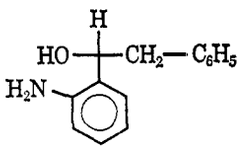
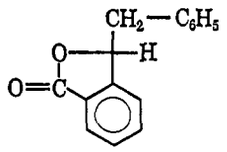
II, which, therefore, corresponds to the Fischer projection VII. Furthermore, if the hypothesis of configurational retention in the transformation of II into V is right, (+) V has the (*R*) configuration (VIII).



VII



VIII

Experimental Section

Melting points were determined on the Kofler apparatus. Specific rotations were determined on a Perkin-Elmer photoelectric polarimeter, Model 141.

1-(*o*-Aminophenyl)-2-phenylethanol (II).—A solution of 5.28 g. (25 mmole) of 2′-amino-2-phenylacetophenone (I)[3] in 100 ml. of methanol was treated slowly, under stirring, with 1.73 g. (32 mmoles) of potassium borohydride in 18 ml. of 0.001 *N* sodium hydroxide. Water was added after 15 hr. and the precipitate was crystallized from hexane, to give 4.90 g. of II, white plates, m.p. 129–130°.

Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.84; H, 7.09. Found: C, 79.05; H, 7.04.

Resolution of II.—A solution of 2.13 g. (10 mmoles) of (±) II and 3.76 g. (10 mmoles) of (−)-dibenzoyltartaric acid monohydrate in 25 ml. of ethyl acetate was diluted with 20 ml. of benzene and set aside at 0° for 15 hr. The precipitated salt (2.6 g.) was crystallized from ethyl acetate–benzene to give 1.3 g. of a product, m.p. 108–109° (A), $[\alpha]^{20}D$ −48.5° (*c* 1.1, ethyl acetate).

Anal. Calcd. for $C_{14}H_{15}NO \cdot C_{18}H_{14}O_8$: N, 2.45. Found: N, 2.65.

The combined mother liquors were evaporated almost to dryness *in vacuo* and diluted with benzene, to give 1.6 g. of a salt, m.p. 110–115° (B), $[\alpha]^{20}D$ −85.5° (*c* 0.9, ethyl acetate). A more extensive purification of the diastereoisomeric salts was not convenient, because of their tendency to decompose.

The free bases were obtained from the salts by heating them 15 min. on a steam bath with 2 *N* sodium carbonate. The precipitates were crystallized from chloroform, in which the enantiomeric bases are much less soluble than the racemate, a fact which facilitates the achievement of a high optical purity. The salt A gave 0.3 g. of (*S*) II, m.p. 150–151°, $[\alpha]^{20}D$ +29°. The salt B yielded 0.3 g. of (*R*) II, m.p. 149–150°, $[\alpha]^{20}D$ −28.6°; a second crystallization from chloroform gave a product with m.p. 150–151°, $[\alpha]^{20}D$ −30°, $[\alpha]^{20}_{546}$ −36°, $[\alpha]^{20}_{436}$ −90°, $[\alpha]^{20}_{365}$ −242° (*c* 0.52, chloroform).

Deamination of II.—A solution of 250 mg. (1.17 mmoles) of II, $[\alpha]^{20}D$ +29°, in 1.5 ml. of 2 *N* hydrochloric acid was cooled at 0° and treated dropwise with 82 mg. (1.18 mmoles) of sodium nitrite in 0.5 ml. of water. After 20 min. at 0°, 1.6 ml. of 50% hypophosphorous acid was added, the solution was left 15 min. at 0° and 4 hr. at room temperature and then extracted with ether, and the ether layer was washed with 2 *N* sodium hydroxide, dried over magnesium sulfate, and evaporated. The residue was taken up in petroleum ether (b.p. 30–50°) and chromatographed over neutral alumina (activity II). Petroleum ether eluted 25 mg. of phenanthrene, m.p. 98–99°; ethyl ether eluted 75 mg. of 1,2-diphenylethanol (VI), m.p. 64–65°, $[\alpha]^{20}D$ + 53.0° (*c* 0.9, ethanol), optical purity about 95%, whose infrared spectrum was identical with that of an authentic sample.[5] When the reduction of the diazo compound was carried out with 1 g. of sodium hypophosphite in 8 ml. of concentrated hydrochloric acid, phenanthrene was the main product, while only a very small amount of VI was isolated.

(+)-(*R*)-3-Benzylphthalide (VIII).—A solution of 300 mg. (1.4 mmoles) of II, $[\alpha]^{20}D$ −28.6°, in 1.4 ml. of 2 *N* hydrochloric acid was diazotized with 98 mg. (1.4 mmoles) of sodium nitrite at 0°, then brought to pH 6.5 with sodium bicarbonate, poured into a solution prepared from 250 mg. of potassium cyanide and 170 mg. of cuprous cyanide in 4 ml. of water, heated 1 hr. at 50°, and then extracted with ether. The ether layer was washed with 2 *N* sodium hydroxide, dried over magnesium sulfate, and evaporated. The viscous red residue could not be purified; it showed strong infrared bands at 2.95 (OH) and 4.50 μ (CN), but no carbonyl bands. It was taken up in benzene and passed through a column of neutral alumina (activity II). Elution with benzene gave 100 mg. of a colorless solid, which was crystallized from hexane to give 3-benzylphthalide, m.p. 93–95°, $[\alpha]^{20}D$ +53°, $[\alpha]^{20}_{546}$ +58°, $[\alpha]^{20}_{436}$ +93°. The infrared spectrum showed slight differences from that of racemic V in Nujol mull, but not in chloroform solution.

Acknowledgment.—This work was supported by a grant from the Consiglio Nazionale delle Ricerche.

Buxus Alkaloids. X.[1] The Isolation and Constitution of Cyclovirobuxeine-B[2]

S. MORRIS KUPCHAN AND G. OHTA

Department of Pharmaceutical Chemistry, University of Wisconsin, Madison, Wisconsin 53706

Received August 13, 1965

The elucidation of the structure[3] and configuration[4] of cyclobuxine-D (I), an alkaloid isolated from *Buxus sempervirens* L.,[5] was first reported in 1962. Cyclobuxine-D was shown to be the prototype of a new class of steroidal alkaloids which contain a cyclopropane ring and which have a substitution pattern at C-4 and C-14 which is intermediate in the biogenetic scheme, between lanosterol- and cholesterol-type steroids. Subsequent studies have characterized the following structurally related alkaloids: cyclomicrophylline-A (II, $R^1 = R^2 = CH_3$)[6]; cyclomicrophylline-B (II, $R^1 = CH_3$; $R^2 = H$)[6,7]; cyclomicrophylline-C (II, $R^1 = H$; $R^2 = CH_3$)[6]; cyclobuxamine-H (III, $R^1 = R^2 = R^3 = R^4 = H$)[8]; cyclovirobuxine-D (III, $R^1 = R^4 = CH_3$; $R^2 = R^3 = H$)[9]; cycloprotobuxine-C (IV, $R^1 = H$; $R^2 = CH_3$)[10,11]; cycloprotobuxine-D (IV, $R^1 = R^2 = H$)[12]; cycloprotobuxine-A (IV, $R^1 = R^2 = CH_3$)[7]; baleabuxine[7]; and cyclobuxoxine.[1] In addition, several new alkaloids containing a novel 9(10→19)abeo steroidal diene system[13,14] and irehine (20α-dimethylamino-Δ⁵-pregnen-3β-ol)[15] have recently been isolated from *Buxus sempervirens* L. The isolation from *Buxus sempervirens* L. and elucidation of the structure of an additional new alkaloid, cyclovirobuxeine-B (V), is described in the present report.

Cyclovirobuxeine-B was isolated from the "moderate bases" obtained by the fractionation procedure de-

(1) Part IX: S. M. Kupchan and E. Abushanab, *J. Org. Chem.*, **30**, 3931 (1965).

(2) This investigation was supported in part by research grants from the National Institutes of Health (HE-02952 and HE-02275).

(3) (a) K. S. Brown, Jr., and S. M. Kupchan, *J. Am. Chem. Soc.*, **84**, 4590 (1962); (b) *ibid.*, **86**, 4414 (1964).

(4) K. S. Brown, Jr., and S. M. Kupchan, *ibid.*, **84**, 4592 (1962); **86**, 4424 (1964).

(5) K. Heusler and E. Schlittler, *Helv. Chim. Acta*, **32**, 2226 (1949).

(6) T. Nakano and S. Terao, *Tetrahedron Letters*, 1035, 1045 (1964).

(7) D. Herlem-Gaulier, F. Khuong-Huu-Lainé, E. Stanislas, and R. Goutarel, *Bull. soc. chim. France*, 657 (1965).

(8) K. S. Brown, Jr., and S. M. Kupchan, *J. Am. Chem. Soc.*, **86**, 4430 (1964).

(9) K. S. Brown, Jr., and S. M. Kupchan, *Tetrahedron Letters*, 2895 (1964). The convention on use of letter suffixes to designate substitution pattern at C-3 and C-20 nitrogen functions is described in this reference.

(10) J. P. Calame and D. Arigoni, *Chimia* (Aarau), **18**, 185 (1964).

(11) T. Nakano and M. Hasegawa, *Tetrahedron Letters*, 3679 (1964).

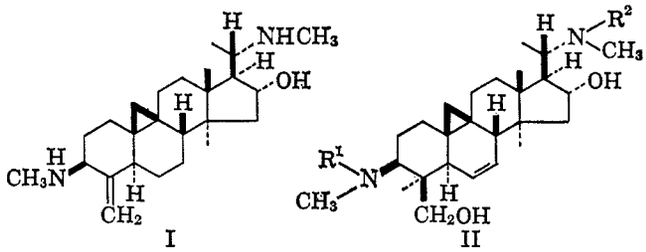
(12) S. M. Kupchan and E. Kurosawa, *J. Org. Chem.*, **30**, 2046 (1965).

(13) S. M. Kupchan and W. L. Asbun, *Tetrahedron Letters*, 3145 (1964).

(14) D. Stauffacher, *Helv. Chim. Acta*, **47**, 968 (1964).

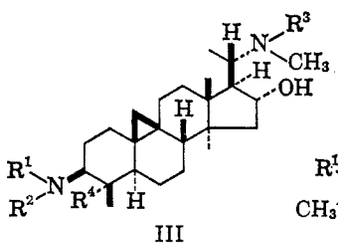
(15) Z. Voticky and J. Tomko, *Collection Czech. Chem. Comm.*, **30**, 348 (1965).

scribed earlier.[3b] Partition chromatography[16] of the hexane–ethylene chloride (10:1) soluble portion of this fraction yielded cyclovirobuxeine-B, $C_{27}H_{46}ON_2$, m.p. 198–200° dec., $[\alpha]^{27}D$ −62° (chloroform), which has an infrared spectrum indicating the presence of a *cis* double bond (6.07 and 14.40 μ). The n.m.r. spectrum shows the presence of two vinyl protons (τ 4.44–

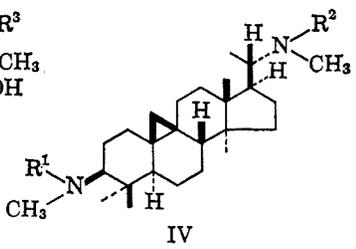


I

II



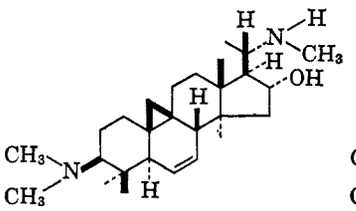
III



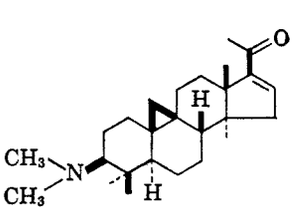
IV

4.65, multiplet), one proton under a hydroxyl group split by several neighboring protons (τ 5.85, octet, J = 2.5, 7, and 8.5 c.p.s.; *cf.* ref. 3b), one N-methyl group (τ 7.56, 3 H), one $N(CH_3)_2$ group (τ 7.71, 6 H), one secondary C-methyl group (τ 8.91, doublet, J = 5.5 c.p.s.), four tertiary C-methyl groups (τ 8.95, 9.06, 9.09, and 9.21), and a cyclopropyl methylene (τ 9.28 and 10.21, AB doublet, J = 4 c.p.s.). Catalytic hydrogenation of cyclovirobuxeine-B in the presence of platinum and acetic acid yielded a dihydro derivative, m.p. 233–234° dec., $[\alpha]^{27}D$ +59° (chloroform), which shows an infrared spectrum similar to that of cyclovirobuxine-D (III, $R^1 = R^4 = CH_3$; $R^2 = R^3 = H$). The foregoing infrared and n.m.r. data led to the preliminary formulation of cyclovirobuxeine-B as a methyldehydrocyclovirobuxine-D. Furthermore, the n.m.r. data best accord with the structure possessing the *cis* double bond between C-6 and C-7, previously demonstrated to occur in cyclomicrophylline-A (II, $R^1 = R^2 = CH_3$) and cyclomicrophylline-B (II, $R^1 = CH_3$; $R^2 = H$). Thus, the splitting pattern in the vinyl region (τ 4.44–4.65) closely resembles that of cyclomicrophylline-B,[7] and the signal for one proton of the cyclopropyl methylene shows the previously noted unusual high field chemical shift. In the dihydro derivative, the cyclopropyl methylene protons show normal signals, *i.e.*, τ 9.47 and 9.73, AB doublet, J = 4 c.p.s. The large negative molecular rotation increment from the dihydro derivative (ΔM_D −502°) parallels those for the related $\Delta^{6,7}$ alkaloids.[17]

Strong support for assignment of constitution V to cyclovirobuxeine-B was adduced by interrelation of the dihydro derivative III ($R^1 = R^2 = R^4 = CH_3$; $R^3 = H$) with cyclovirobuxine-D and by Ruschig degradation of the dihydro derivative to an α,β-unsaturated methyl ketone. Methylation of dihydrocyclovirobuxeine-B with formaldehyde and formic acid yielded methyldihydrocyclovirobuxeine-B (III, $R^1 = R^2 = R^3 = R^4 = CH_3$) and the latter compound was shown to be identical with dimethylcyclovirobuxine-D.[9] Ruschig degradation of dihydrocyclovirobuxeine-B yielded the conjugated enone VI, m.p. 149–151°, λ_{max}^{KBr} 6.02 (vs) and 6.28 (m), λ_{max}^{EtOH} 242 mμ (ε 10,500). The structure of the Ruschig degradation product showed that the methylamino group in cyclovirobuxeine-B is at C-20 and that the dimethylamino group consequently could be assigned to C-3.



V



VI

Calame and Arigoni independently have isolated and elucidated the structure of cyclovirobuxeine-B.[18] Direct comparison of our alkaloid (mixture melting point, t.l.c.) with a sample kindly provided by Professor Arigoni has confirmed the identity of the respective materials.

Experimental Section[19,20]

Separation of the Hexane–Ethylene Chloride (10:1) Soluble Moderate Bases by Partition Chromatography.—The crude moderate base fraction[3b] (100 g.) was dissolved in 2 *N* acetic acid (800 ml.) and extracted with chloroform (three 500-ml. portions), and the chloroform solutions were back washed successively with 2 *N* acetic acid (250 ml.), water, 2 *N* ammonium hydroxide (400 ml.), and water. Evaporation of the combined chloroform solution gave the weak bases (50 g.). The combined acetic acid solution was neutralized (red to phenol red) with ammonium hydroxide and extracted with chloroform (three 250-ml. portions). Evaporation of the chloroform extract gave the purified moderate bases (47.5 g.). The purified moderate base fraction (175 g.) was dissolved in 90% methanol (350 ml.) and extracted with hexane–ethylene chloride (10:1; two 700-ml. portions). The hexane–ethylene chloride solutions were back washed with 90% methanol (350 ml.), combined, and evaporated to give the hexane–ethylene chloride (10:1) soluble portion (73.5 g). Evaporation of the combined methanolic solution gave a residue (95.0 g) which was reserved for further separation.

The hexane–ethylene chloride soluble portion (1.936 g.) was dissolved in the upper phase of the system hexane–ethylene chloride–methanol–water (50:5:15:1) and chromatographed on a column of Celite 545 impregnated with phenol red and lower phase of the solvent system.[16] Seven red bands were visible on the column, at R_f 0.95, 0.77, 0.64, 0.55, 0.45, 0.27, and 0.15. The R_f 0.77 band was eluted and the solution was evaporated to dryness. The residue was dissolved in chloroform and extracted with 1.4 *N* hydrochloric acid solution. The acid solution was made alkaline with ammonium hydroxide and extracted with chloroform and the chloroform extract was evaporated to give a yellow semisolid material (0.473 g.). In the same way, a total of 83.3 g. of the base was chromatographed in 5-g. portions. Rechromatography of the crude product, using the same solvent system, gave the R_f 0.77 base (15.5 g.) which was treated with acetone. An insoluble material (0.641 g.) was removed by filtration and the filtrate was concentrated and kept

(16) K. S. Brown, Jr., and S. M. Kupchan, *J. Chromatog.*, **9**, 71 (1962).

(17) The ΔM_D in the case of cyclomicrophylline-A is −598° and that for cyclomicrophylline-B is −536°, according to the data in ref. 6 and 7.

(18) J. P. Calame and D. Arigoni, *Helv. Chim. Acta*, in press. We thank Professor Arigoni cordially for informing us of these results prior to publication.

(19) Melting points are corrected to the nearest degree. Infrared spectra were measured on a Beckman Model IR-5A spectrophotometer. Rotations have been approximated to the nearest degree. N.m.r. spectra were determined in deuteriochloroform solution on a Varian A-60 spectrometer. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(20) We are grateful to CIBA Pharmaceutical Co. for procurement and large-scale extraction of plant material, and we especially thank Dr. E. Schlittler, Dr. D. Dickel, and Dr. K. Heusler for their kind interest and cooperation in this project.

in the refrigerator to allow separation of a crystalline material (1.704 g.). Repeated recrystallization from acetone yielded cyclovirobuxeine-B as plates (236 mg.), m.p. 198–200° dec., $[\alpha]^{27}D$ −62° (*c* 0.99, chloroform). *Anal.* Calcd. for $C_{27}H_{46}N_2O$: C, 78.20; H, 11.18; N, 6.76; O, 3.86. Found: C, 78.15; H, 11.24; N, 6.64; O, 3.80.

Dihydrocyclovirobuxeine-B (III, $R^1 = R^2 = R^4 = CH_3$; $R^3 = H$).—Cyclovirobuxeine-B (81 mg.) was hydrogenated in acetic acid (12 ml.) with prereduced platinum catalyst (62 mg.) for 23 hr. The hydrogen uptake was 1.13 mole equiv. The catalyst was removed by filtration and the filtrate was evaporated under reduced pressure. The residue was dissolved in water, washed with ether, basified with ammonium hydroxide, and extracted with methylene dichloride. Evaporation of the extract and recrystallization of the residue from acetone–methylene dichloride yielded needles (68 mg.), m.p. 233–234° dec., $[\alpha]^{27}D$ +59° (*c* 1.28, chloroform). The infrared spectrum showed no absorption at 6.07 and 14.40 μ. *Anal.* Calcd. for $C_{27}H_{48}N_2O$: C, 77.83; H, 11.61; N, 6.72. Found: C, 77.98; H, 11.35; N, 6.68.

N-Methyldihydrocyclovirobuxeine-B (III, $R^1 = R^2 = R^3 = R^4 = CH_3$).—A solution of dihydrocyclovirobuxeine-B (15 mg.) in 40% formaldehyde (37 mg.) and 88% formic acid (60 mg.) was heated under reflux for 16 hr. The reaction mixture was poured into 0.5 *N* hydrochloric acid solution; the acid solution was washed with ether, made alkaline with ammonium hydroxide, and extracted with methylene dichloride. Evaporation to dryness gave a residue which was chromatographed on a column of Celite 545 using the same partition system as described above; one band was visible at R_f 0.76. The product (15 mg.) was crystallized from acetone to yield plates (6.6 mg.), m.p. 236–237° dec. The infrared spectrum was superimposable upon that of an authentic sample of N,N-dimethylcyclovirobuxine-D (III, $R^1 = R^2 = R^3 = R^4 = CH_3$)[9] and the melting point was not depressed upon admixture with the authentic sample.

Ruschig Degradation of Dihydrocyclovirobuxeine-B.—A solution of dihydrocyclovirobuxeine-B (42 mg.) in methylene dichloride (6 ml.) was cooled to 0° and treated with stirring with a solution of N-chlorosuccinimide (15 mg.) in methylene dichloride (2 ml.). After stirring for 10 min. at 0°, the solution was kept at room temperature for 1 hr., washed with water, and evaporated. The residue (45 mg.) was treated with a solution of sodium methoxide (480 mg.) in methanol (10 ml.) and the mixture was heated under reflux for 2 hr. After evaporation to dryness, the residue was treated with water and chloroform. The chloroform solution was evaporated, the residue (40 mg.) was dissolved in methanol (5 ml.) and 3 *N* sulfuric acid (10 ml.), and the solution was heated under gentle reflux for 4 hr. The mixture was diluted with water, basified with ammonium hydroxide, and extracted with chloroform, and the chloroform extract was evaporated to dryness. The residue (37 mg.) was chromatographed on Woelm alkaline alumina (4 g.), using 10% ether in benzene (20 ml.) and 50% ether in benzene (20 ml.) as eluents. The latter solvent mixture yielded a residue (25 mg.) which was rechromatographed on Woelm alkaline alumina (6 g.) using 10% ether in benzene as eluents. The fractions (30 ml.) eluted after a 20-ml. forerun gave a residue which was crystallized from acetone–methanol to yield 3β-dimethylamino-4,4,14α-trimethyl-9,19-cyclo-Δ[16]-pregnen-20-one (VI) as clumps of needles (6 mg), m.p. 149–151°, λ_{max}^{EtOH} 242 mμ (ε 10,500), λ_{max}^{KBr} 6.02 and 6.28 μ. *Anal.* Calcd. for $C_{26}H_{41}NO$: C, 81.40; H, 10.77. Found: C, 81.17; H, 10.83.

The Free-Radical Reaction of Ferrocene with Maleic Anhydride

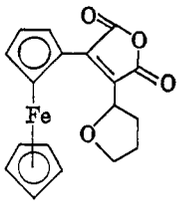
RICHARD E. BOZAK[1]

Shell Development Company, Emeryville, California

Received August 15, 1965

In connection with other studies, we had occasion to prepare a solution of ferrocene and maleic anhydride in tetrahydrofuran. Surprisingly, a gradual discoloration took place indicating a reaction. The inertness of ferrocene to the action of maleic anhydride in the Diels–Alder reaction is well known[2] and, indeed, further investigation suggested a free-radical mechanism for the reaction rather than a Diels–Alder pathway. Ether solvents, such as tetrahydrofuran and dioxane, were essential, and the addition of a small amount of hydrogen peroxide hastened the reaction. Furthermore, no reaction occurred in the absence of hydrogen peroxide when highly purified reactants and solvent were employed in an inert atmosphere.

It proved possible to isolate from the mixture a new compound to which we have assigned structure I.



I

The structure of this material was established on the basis of the following data. (1) Duplicate carbon, hydrogen, and iron analyses coupled with ebullioscopic molecular weight determinations showed the compound to have the formula $C_{18}H_{16}FeO_4$. (2) The absence of a ferricenium ion structure was noted by hydrocarbon solubility, water insolubility, a clearly resolved n.m.r. spectrum, and inertness to reaction with standard ferricenium ion reducing reagents, such as stannous chloride. (3) The presence of a monosubstituted ferrocene moiety was indicated by infrared absorptions at 3090 cm.$^{-1}$, and two stronger bands of almost equal intensity at 1110 and 1000 cm.$^{-1}$. (4) The four homoannular ferrocene ring protons appear in the n.m.r. spectrum as two sets of triplets (J = 4 c.p.s.) centered at 5.0 and 4.70 p.p.m. (relative to TMS). The five heteroannular protons are located at 4.24 p.p.m. The seven tetrahydrofuran protons are located in two regions. The four methylene hydrogens β to the tetrahydrofuryl oxygen are located as a broad multiplet at 2.2 p.p.m. The remaining three are very diffuse at lower field near 4.0 p.p.m. High upfield and low downfield scanning revealed no more proton absorptions. Maleic anhydride protons near 7.1 p.p.m. are quite clearly not present in the compound. (5) Anhydride absorptions are found in the infrared as a pair of doublets centered at 1825 and 1775 cm.$^{-1}$. (6) Cross conjugation of the ferrocene nucleus with the carbon–carbon double bond of the anhydride is indicated by absorptions in the visible and ultraviolet spectra at 557 mμ (broad) (ε 1870), 412 mμ (ε 810), and 327 mμ (ε 8800).

Experimental Section[3]

The Free-Radical Reaction of Ferrocene with Maleic Anhydride in Tetrahydrofuran.—To a solution of 0.5 g. (5.1 mmoles) of

(1) Department of Chemistry, California State College at Hayward, Hayward, Calif.

(2) R. B. Woodward, M. Rosenblum, and M. C. Whiting, *J. Am. Chem. Soc.*, **74**, 3458 (1952).

(3) Melting points were determined on a Fisher-Johns apparatus and are corrected. The ultraviolet and visible absorption spectra were determined in 95% ethanol on a Cary Model 14 recording spectrophotometer, and the infrared spectra on a Perkin-Elmer Model 521. The n.m.r. spectra were obtained in deuteriochloroform solution with a Varian A-60 spectrometer using tetramethylsilane as an internal standard.