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

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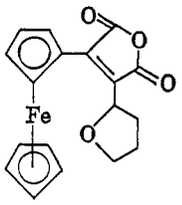
In connection with other studies, we had occasion to prepare a solution of ferrocene and maleic anhydride in tetrahydrofuran. Surprisingly, a gradual discoloration took place indicating a reaction. The inertness of ferrocene to the action of maleic anhydride in the Diels–Alder reaction is well known[2] 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

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(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.

maleic anhydride and 2.0 g. (10.7 mmoles) of ferrocene in 100 ml. of tetrahydrofuran was added 3 ml. of a 30% aqueous solution of hydrogen peroxide. The solution was then allowed to stand at room temperature for 60 hr. during which time it darkened and deposited a brown sludge. Next, 3 g. of anhydrous magnesium sulfate was added, and the resultant mixture was allowed to stand several hours. It was then filtered and evaporated to dryness on a rotary evaporator to yield 3.1 g. of a deep orange-blue solid. This material was transferred to a sublimator, unchanged ferrocene and maleic anhydride were sublimed, and a residue of 0.5 g. remained (27% yield based on maleic anhydride).

A benzene solution of the residue was chromatographed on deactivated silica gel. Ether–petroleum ether (b.p. 30–60°) (1:3) eluted a blue band which was evaporated to dryness to yield 0.2 g. (10%) of I as blue needles, m.p. 138–139.2° (recrystallized from hexane).

Anal. Calcd. for $C_{18}H_{16}FeO_4$: C, 61.4; H, 4.6; Fe, 15.8; mol. wt., 352. Found: C, 61.4; H, 4.6; Fe, 15.4; mol. wt., 360 ± 10 (ebullioscopic in benzene).

Methyl 6-*S*-Methyl-6-thiohexopyranosides. Effect of the Methylthio Group at C-6 on Rates of Enzymic and Nonenzymic Hydrolysis[1]

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We report the synthesis and certain properties of methyl 6-*S*-methyl-6-thio-β-D-glucopyranoside (I) and methyl 6-*S*-methyl-6-thio-α-D-galactopyranoside (II). These substances were prepared as glycosidase substrates and model compounds during an investigation of the mechanism of glycosidase–glycosyltransferase action.

Both syntheses involved conventional reactions. Compound I was prepared by the following scheme.

1,2-*O*-isopropylidene-6-*O*-*p*-tolylsulfonyl-D-glucofuranose
↓ NaSMe
1,2-*O*-isopropylidene-6-*S*-methyl-6-thio-α-D-glucofuranose
MeOH ↓ HCl
I

Compound II was prepared by the sequence following.

1,2:3,4-di-*O*-isopropylidene-6-*O*-*p*-tolylsulfonyl-α-D-galactose
↓ NaSMe
1,2:3,4-di-*O*-isopropylidene-6-*S*-methyl-6-thio-α-D-galactose
MeOH ↓ HCl
II

Configurations at the anomeric carbon of these glycosides were assigned on the basis of rotational data; the assignment of pyranoside structures was based on formic acid yields from periodate oxidation.

One objective in our general investigation of the mechanism of glycosidase–glycosyltransferase action has been to determine whether or not methylthio and other nucleophilic groups augment the rates of glycoside hydrolysis by neighboring-group assistance. Since the 1C and certain flexible conformations of methyl 6-*S*-methyl-6-thio-α-D-galactopyranoside allow proper orientation of the methylthio group for possible nucleophilic participation during hydrolysis,[3] the nonenzymic hydrolysis rate for this glycoside was determined. Hydrolysis rates for methyl 6-*O*-methyl-α-D-galactopyranoside and methyl α-D-galactopyranoside were determined under identical conditions for purposes of comparison. These rate determinations, although carried out by observing both the change in rotation of the reaction mixtures and the formation of reducing substances, leave something to be desired, since the vigorous conditions necessary to produce reasonable rates bring about some degradation of the reducing sugars. The hydrolysis data (shown in Table I)

TABLE I

RATES OF ACID-CATALYZED HYDROLYSIS OF GLYCOSIDES

Glycoside	Method	Temp., °C.	k_2, l. mole^{-1} sec.$^{-1}$
Methyl α-D-galactopyranoside	I[a]	60.0	1.0×10^{-5}
Methyl 6-*O*-methyl-α-D-galactopyranoside	I	60.0	5.4×10^{-6}
Methyl 6-*O*-methyl-α-D-galactopyranoside	II[b]	85.0	1.2×10^{-4}
Methyl 6-*S*-methyl-6-thio-α-D-galactopyranoside	I	60.0	6.7×10^{-6}
Methyl 6-*S*-methyl-6-thio-α-D-galactopyranoside	II	85.0	1.4×10^{-4}

[a] Polarimetric. [b] Colorimetric.

indicate no increase in rate on substituting a methylthio group for a hydroxyl group at C-6. Instead, the methyl 6-*S*-methyl-6-thio-α-D-galactopyranoside and methyl 6-*O*-methyl-α-D-galactopyranoside hydrolysis rates, which were nearly the same, appear to be significantly smaller than that for methyl α-D-galactopyranoside. Similar slowing of acetal and ketal hydrolysis on substituting methoxyl or methylthio at the γ-position (with respect to the potential carbonyl group) has been observed and attributed to a field effect.[4]

It is difficult to estimate—other than very roughly—the relative magnitudes of field effects by different C-6 substituents on these glycoside hydrolysis reactions. It seems reasonable to assume, however, that such an effect by a C-6 hydroxyl should be smaller than that by a methoxyl at this position; further, the effect by methoxyl should be somewhat smaller than that by methylthio—as has been observed in hydrolysis of 5-substituted 2-pentanone diethyl ketals.[4] The hydrolysis rate observed for compound II is slightly higher than that for the corresponding methoxy compound, but this may be a consequence of experimental error.

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(3) Although the C1 conformation is probably a lower energy conformation for α-D-galactopyranosides in solution, it is clear that the intermediacy of other conformations during reactions of these substances is by no means excluded. Pertinent to this matter is the alkaline degradation of phenyl β-D-galactopyranoside (presumably more stable in the C1 conformation than are the α-D-galactopyranosides), which proceeds by participation of oxygen at C-2 through either a half-chair or an approximately half-chair conformation to give phenoxide ion and 1,6-anhydro-β-D-galactopyranose as final products; pertinent also is the thermal degradation of D-lactose to 1,6-anhydro-β-D-galactopyranose.

(4) J. C. Speck, Jr., D. J. Rynbrandt, and I. H. Kochevar, *J. Am. Chem. Soc.*, **87**, 4979 (1965).

(5) *Cf.* H. Holtz and L. M. Stock, *ibid.*, **86**, 5188 (1964).