Anal. Calcd. for $C_{15}H_{22}N_2O_3$: C, 64.80; H, 7.97; N, 10.07. Found: C, 64.89; H, 7.52; N, 10.36.

4-Benzyl-*cis*-2,6-dimethyl-3,5-diketopiperazine (VIII).—VII (75 g.) was heated at 200–205° for 3 hr. under atmospheric pressure, and the ethyl alcohol formed was collected. The residual viscous oil was distilled, collecting the fraction (65 g.) boiling at 150–170° (0.6 mm.). The crude product was dissolved in ethanol, and an ether solution of dry HCl was added to precipitate the hydrochloride of VII which was filtered and suspended in sodium carbonate solution. The liberated base was extracted with ether, the solvent was evaporated, and the residue was distilled to yield 53.4 g. (85%) of VIII, b.p. 150–155° (0.6 mm.). On standing, the product solidified, m.p. 62–63° (petroleum ether).

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.21; H, 6.94; N, 12.06. Found: C, 67.18; H, 7.12; N, 12.07.

The hydrochloride crystallized from ethanol, m.p. 212–214°.

Anal. Calcd. for $C_{13}H_{17}ClN_2O$: C, 58.10; H, 6.37; Cl, 13.19; N, 10.42. Found: C, 57.95; H, 6.57; Cl, 13.54; N, 10.32.

The infrared spectrum of VIII showed bands at 3280 $m.^{-1}$ (>NH stretching), 1730–1675 $cm.^{-1}$ (>CO of imidic group), and 740–700 $cm.^{-1}$ (CH out of plane of phenyl group). The *cis* configuration of VIII was demonstrated by the n.m.r. spectrum[8] which showed absorption at 1.41 δ (doublet, 6H, methyl hydrogens), 1.58 δ (singlet, 1H, hydrogen attached to nitrogen), 3.57 δ (quartet, 2H, hydrogens bonded to the carbons of the ring), 4.90 δ (singlet, 2H, methylene hydrogens), and 7.27 δ (multiplet, 5H, aromatic hydrogens). The presence of a doublet at 1.41 δ and of a quartet at 3.57 δ is consistent with an identical orientation of the 2,6-C–H bonds.

4-Benzyl-*cis*-2,6-dimethylpiperazine (III).—A solution of 44.5 g. of VIII in 500 ml. of anhydrous ether was added with stirring to a suspension of 44 g. of lithium aluminum hydride in 500 ml. of ether, and the mixture was refluxed for 6 hr. On cooling, the reaction mixture was decomposed by adding dropwise 135 ml. of water and by stirring the mass for 1 hr. at room temperature. The inorganic salts were filtered, thoroughly washed with ether, and the filtrates were dried over sodium sulfate. After removing the solvent, the oily residue was distilled and the fraction, b.p. 85–86° (0.6 mm.), was collected, yield 38 g. (95%), $n^{20}D$ 1.5363.

Anal. Calcd. for $C_{13}H_{20}N_2$: C, 76.42; H, 9.86; N, 13.71. Found: C, 76.63; H, 10.04; N, 13.61.

The dipicrate crystallized from 70% ethanol, m.p. 245–247°.

Anal. Calcd. for $C_{25}H_{26}N_8O_{14}$: C, 45.31; H, 3.95; N, 16.91. Found: C, 44.95; H, 4.10; N, 17.17.

1-Benzyl-*cis*-2,6-dimethylpiperazine (IV).—A solution of 30 g. of 1-benzoyl-*cis*-2,6-dimethylpiperazine (X) in 300 ml. of ether was added dropwise with stirring to a cooled suspension of 30 g. of lithium aluminum hydride in 300 ml. of ether. The mixture was refluxed for 6 hr., then cooled at −5° and cautiously decomposed with 90 ml. of water. The mass was stirred for 1 hr. at room temperature, the inorganic salts were filtered and washed with ether. The filtrate was collected and dried over sodium sulfate; the solvent was evaporated, and the residue was distilled to yield 25.8 g. (92%) of IV, b.p. 97–98° (0.6 mm.), $n^{20}D$ 1.5473.

Anal. Calcd. for $C_{13}H_{20}N_2$: C, 76.42; H, 9.86; N, 13.71. Found: C, 76.40; H, 10.09; N, 13.51.

***cis*-2,6-Dimethylpiperazine (V).**—A solution of 10.2 g. of III (or IV) in 50 ml. of ethanol was hydrogenated at atmospheric pressure over 3 g. of 10% palladium-on-carbon. After 5 hr., the theoretical amount of hydrogen had been consumed, and the reduction was stopped. The catalyst was filtered and the filtrate was distilled at atmospheric pressure collecting the fraction (4.8 g.) boiling at 140–145°. The product solidified at room temperature and after crystallization from ether melted at 115–116° (lit.[9] m.p. 110–111°), yield 84%. The n.m.r. spectrum[8] showed absorption at 0.92 δ (doublet, 6H, methyl hydrogens), 1.04 δ (singlet, 3H, hydrogen attached to nitrogen), and 2.30–2.80 δ (multiplet, 6H, hydrogens attached to the carbons of piperazine ring).

1(4)-Benzoyl-4(1)-benzyl-*cis*-2,6-dimethylpiperazine (IX, XI).—To a cooled suspension of 0.1 mole of 4(1)-benzyl-*cis*-2,6-dimethylpiperazine (III, IV) in 300 ml. of 5% sodium hydroxide, 0.12 mole of benzoyl chloride was added with stirring. The reaction mixture was stirred for 2 hr. at room temperature and acidified with hydrochloric acid. The unreacted benzoyl chloride was extracted with ether. The acid layer was made basic with sodium carbonate, and the viscous separated oil was thoroughly extracted with ether. After drying over sodium sulfate, the solvent was evaporated and the residue was distilled by the technique of Ronco, *et al.*,[9] obtaining IX in 86% yield, b.p. 190–195° (1 mm.).

Anal. Calcd. for $C_{20}H_{24}N_2O$: C, 77.87; H, 7.84; N, 9.08. Found: C, 77.52; H, 9.02; N, 9.31.

XI, b.p. 200° (1 mm.) was obtained in 90% yield.

Anal. Calcd. for $C_{20}H_{24}N_2O$: C, 77.87; H, 7.84; N, 9.08. Found: C, 78.11; H, 8.03; N, 8.89.

1(4)-Benzoyl-*cis*-2,6-dimethylpiperazine (X, XII).—A solution of 0.1 mole of IX (XI) in 500 ml. of absolute ethanol was hydrogenated at 60° and 51.65 kg. of initial hydrogen pressure/$cm.^2$ in the presence of 10 g. of 10% palladium-on-carbon. The catalyst was filtered, the solvent was evaporated, and the residue was distilled. X, b.p. 128–130° (0.5 mm.) was isolated in 87% yield. On standing, the product solidified and after two crystallizations from ether melted at 110–112°, (lit.[4] m.p. 109–110° for a hypothetical 1-benzoyl-2,6-dimethylpiperazine to which, however, the structure was assigned without adequate proof).

Anal. Calcd. for $C_{13}H_{18}N_2O$: C, 71.52; H, 8.30; N, 12.83. Found: C, 71.39; H, 8.42; N, 12.66.

Infrared spectrum of X (in $CHCl_3$) showed, besides bands at 3400 (>NH) and 1610 $cm.^{-1}$ (−CON<), strong absorption at 1430 $cm.^{-1}$. The n.m.r. spectrum[8] showed absorption at 1.28 δ (doublet, 6H, methyl hydrogens), 1.45 δ (singlet, 1H, hydrogen bonded to nitrogen), 2.74 δ (doublet, 6H, methylene hydrogens), 4.12 δ (multiplet, 2H, hydrogens bonded to the carbon of the piperazine ring), and 7.29 δ (singlet, 5H, aromatic hydrogens).

The **D-tartrate** was obtained by evaporating to dryness an ethanol solution of equimolar amount of the base and D-tartaric acid. The solid product was purified by crystallization from ethanol, m.p. 198–200°.

Anal. Calcd. for $C_{13}H_{18}N_2O \cdot C_4H_6O_6$: C, 55.42; H, 6.57; N, 7.60. Found: C, 55.21; H, 6.67; N, 7.63.

XII, b.p. 160° (1 mm.), was isolated in 82% yield. On standing, the product solidified and was crystallized from ether, m.p. 117–119° (lit.[4] m.p. 117° for the hypothetical 4-benzoyl-2,6-dimethylpiperazine). Infrared spectrum (in $CHCl_3$) showed bands at 3400 $cm.^{-1}$ (>NH), 1620 $cm.^{-1}$ (−CON<), and characteristic strong bands at 1430–1450, 1275, and 1085 $cm.^{-1}$. The n.m.r. spectrum[8] showed absorption at 0.97 δ (doublet, 6H, methyl hydrogens), 1.32 δ (singlet, 1H, hydrogen attached to nitrogen), 2.65 δ (multiplet, 6H, methylene hydrogens), 4.00 δ (multiplet, 2H, hydrogens bonded to the carbon of the piperazine ring), and 7.31 δ (singlet, 5H, aromatic hydrogens).

By evaporating to dryness an equimolar amount of the base and D-tartaric acid, a gummy residue was obtained which, after boiling in acetone-ethanol, separated a **di-D-tartrate**, m.p. 223–225°.[10] The product crystallized from ethanol, m.p. 228–229°.

Anal. Calcd. for $C_{13}H_{18}N_2O \cdot 2C_4H_6O_6$: C, 61.41; H, 7.21; N, 9.55. Found: C, 61.43; H, 7.28; N, 9.42.

(8) The n.m.r. spectrum was obtained using a Varian-A-60 spectrometer operating at 60 Mc., in carbon tetrachloride with tetramethylsilane as internal reference; the chemical shifts are reported as δ values.

(9) K. Ronco, B. Prijs, and H. Erlenmeyer, *Helv. Chim. Acta*, **39**, 2088 (1957).

(10) By this procedure, Pope and Read[4] isolated a D-tartrate, m.p. 227–228°. However, these authors erroneously attributed to it the formula of a *mono* salt.

p-Vinylphenyl Glycosides of Cellobiose and Maltose

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During the course of an immunochemical investigation currently being undertaken in this Laboratory, it became desirable to synthesize glycosides derived from *p*-vinylphenol and certain

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disaccharide sugars, for use in the preparation of synthetic polymers. Such polymers with terminal carbohydrate determinant groups might then display antigenic properties.[2,3]

p-Ethylphenyl β-maltoside heptaacetate[4,5] and *p*-ethylphenyl β-cellobioside heptaacetate[6] were converted into the corresponding *p*-vinylphenyl disaccharide heptaacetates by the method that Helferich and Hofmann[7] used for the synthesis of the tetraacetate of *p*-vinylphenyl β-D-glucoside. The *p*-vinylphenyl cellobioside heptaacetate was also prepared directly from *p*-acetoxystyrene and acetobromocellobiose in aqueous acetone in the presence of alkali.[8] *O*-Deacetylations were effected with barium methoxide in methanol.

Experimental

Melting points were determined on a Koffler hot stage. All solvent distillations were carried out at 40° (bath temperature) and 20 mm. Microanalyses are by the Analytical Services Unit of this Institute, Harold C. McCann, director.

***p*-Ethylphenyl β-Maltoside Heptaacetate.**—β-Maltose octaacetate (48 g.) and 2.5 ml. of acetic anhydride were added to a molten mixture of 0.7 g. of *p*-toluenesulfonic acid and 65 g. of *p*-ethylphenol. The mixture was heated at 100° (20 mm.) for 1 hr. and dissolved in 400 ml. of benzene. The solution was washed with water, 2 *N* sodium hydroxide, and water and dried ($CaCl_2$). The residue obtained after distillation of the benzene was crystallized and recrystallized from methanol to give white needles (21.7 g., 41%), m.p. 129–130°, $[\alpha]^{20}D$ +44.6° (*c* 1.15, $CHCl_3$).

Anal. Calcd. for $C_{34}H_{44}O_{18}$: C, 55.1, H, 6.0; acetyl, 40.7. Found: C, 55.2; H, 5.8; acetyl, 40.6.

***p*-(1-Bromoethyl) Phenyl β-Maltoside Heptaacetate.**—*p*-Ethylphenyl β-maltoside heptaacetate (7.4 g.), 50 ml. of chloroform, and 4.2 g. of anhydrous sodium bicarbonate in a quartz flask were irradiated with ultraviolet light and stirred at 25° while adding dropwise 1.6 g. of bromine in 16 ml. of chloroform. The colorless mixture was filtered from salts, concentrated to dryness, and crystallized and recrystallized from ether to give small white needles (6.2 g., 75%), m.p. 114–117°. Further recrystallization from ether gave 3.9 g. of white needles, m.p. 118–120°, $[\alpha]^{20}D$ +43.7° (*c* 1.0, $CHCl_3$).

Anal. Calcd. for $C_{34}H_{43}O_{18}Br$: C, 49.8; H, 5.3; Br, 9.75; acetyl, 36.8. Found: C, 50.8; H, 5.5; Br, 8.4; acetyl, 35.7.

The compound was unstable and no attempt was made to purify it further.

***p*-Vinylphenyl β-Maltoside Heptaacetate.**—To a refluxing mixture of 117 g. of anhydrous sodium acetate and 188 ml. of glacial acetic acid was added 18.1 g. of *p*-(1-bromoethyl) phenyl β-maltoside heptaacetate. Refluxing was continued for 6 hr. The hot mixture was poured with stirring into 2 l. of ice-water and the precipitate left to settle. The crude product (13.5 g.) was filtered, washed with water, and dried. The material (13.0 g.) in 300 ml. of dry methanol was deacetylated with 12.5 ml. 0.4 *N* barium methoxide in methanol and left at 5° for 24 hr. The solution was neutralized with dilute sulfuric acid, centrifuged, and the clear solution concentrated to dryness. The dry material was acetylated with 100 ml. of pyridine and 100 ml. of acetic anhydride over 2 days. The solution was poured into 1 l. of ice-water and the crystalline product was recrystallized from ethanol (charcoal) to give off-white needles (8.5 g., 52%), m.p. 150.5–151.5°, $[\alpha]^{20}D$ +49.3° (*c* 0.7, $CHCl_3$), λ_{max}^{MeOH} 253.5 mμ (ε 19,300).

Anal. Calcd. for $C_{34}H_{42}O_{18}$: C, 55.3; H, 5.7; acetyl, 40.8. Found: C, 55.4; H, 6.0; acetyl, 41.3.

***p*-Ethylphenyl β-Cellobioside Heptaacetate.**—*p*-Ethylphenol (40.3 g., 0.3 mole) and potassium hydroxide (3.2 g., 0.06 mole) in 40 ml. of water were added to a solution of acetobromocellobiose[9] (21 g., 0.03 mole) in 60 ml. of acetone and the mixture was left in a shaking machine at 25° for 25 hr. Acetone was distilled, and the remaining solution was extracted with 100 ml. of benzene. The benzene layer was washed with 2 *N* sodium hydroxide and with water, dried ($CaCl_2$), and concentrated to a sirupy residue (22.6 g.). Addition of ether induced crystallization. Recrystallization was effected with ethanol to give white needles (14.2 g., 33%), m.p. 214–216°, $[\alpha]^{20}D$ −27.8° (*c* 0.5, $CHCl_3$).

Anal. Calcd. for $C_{34}H_{44}O_{18}$: C, 55.1; H, 6.0; acetyl, 40.7. Found: C, 55.3; H, 5.9; acetyl, 40.45.

***p*-Vinylphenyl β-Cellobioside.**—*p*-Ethylphenyl β-cellobioside heptaacetate (3.7 g.), 30 ml. of chloroform and 2.1 g. of sodium bicarbonate in a quartz flask were stirred and irradiated (25°) with ultraviolet light during the dropwise addition of 0.8 g. of bromine in 10 ml. of chloroform. The colorless solution was filtered and concentrated, and the residue was crystallized from chloroform–petroleum ether. The product, *p*-(1-bromoethyl)-phenyl β-cellobioside heptaacetate (2.4 g., m.p. 190–191.5°), was unstable and no attempt was made further to purify it before carrying out the next step. The heptaacetate (16 g.) was added to a refluxing mixture of 117 g. of anhydrous sodium acetate and 188 ml. of glacial acetic acid. The mixture was then refluxed for 6 hr. and poured hot into 2 l. of ice-water (stirring), when a brown solid was precipitated. The material (9.6 g.) was washed with water and dried before being dissolved in 300 ml. of methanol. To the solution was added 9.0 ml. of 0.4 *N* barium methoxide in methanol. After 24 hr. at 5° the solution was neutralized with dilute sulfuric acid, centrifuged, and the clear supernatant solution concentrated to dryness. The residue (4.3 g., 49.5%) was crystallized and recrystallized from water (charcoal) to give soft, chunky crystals, m.p. 175–176°, $[\alpha]^{20}D$ −65.5° (*c* 0.4, H_2O).

Anal. Calcd. for $C_{20}H_{28}O_{11}$: C, 54.0; H, 6.35. Found: C, 53.6; H, 6.6.

***p*-Vinylphenyl β-Cellobioside Heptaacetate.** (a) **From *p*-Vinylphenyl β-Cellobioside.**—This glycoside (2.5 g.), 20 ml. of acetic anhydride, and 20 ml. of pyridine were kept for 3 days at 25° and poured into 500 ml. of ice-water. The crystalline precipitate was filtered, washed with water, and recrystallized from methanol (charcoal); fine white needles (2.5 g., 59%), m.p. 197–198°, $[\alpha]^{20}D$ −31.1° (*c* 0.8, $CHCl_3$), λ_{max}^{MeOH} 253.5 mμ (ε 19,300).

Anal. Calcd. for $C_{34}H_{42}O_{18}$: C, 55.3; H, 5.7; acetyl, 40.8. Found: C, 55.1; H, 5.9; acetyl, 40.4.

(b) **Direct Method.**—*p*-Acetoxystyrene (6.4 g.) and 5.25 g. of sodium hydroxide in 20 ml. of water were added to a solution of 5 g. of acetobromocellobiose[9] in 30 ml. of acetone and left at 25° for 24 hr. Acetone was distilled and the residual aqueous solution was diluted with an equal volume of water and extracted with four 25-ml. portions of chloroform. The combined chloroform extracts were washed with 2 *N* sodium hydroxide, then water and dried ($CaCl_2$). Concentration of the solution left a sirup which crystallized after addition of ether. Recrystallization from methanol gave fine white needles (0.73 g., 14%), m.p. 197–198°, $[\alpha]^{20}D$ −28.5° (*c* 0.7, $CHCl_3$), identical with the material previously prepared.

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Book Reviews

Advances in Pharmacology. Vol. 2. Edited by SILVIO GARATTINI and PARKHURST A. SHORE. viii + 392 pp. 16 × 24 cm. Academic Press, Inc., New York 3, N. Y. $12.00.

The second volume of this series features six chapters, five of which take the reader from the theoretical background and laboratory pharmacology, to the clinical and therapeutic applications of the topic under discussion. In this way, they represent fine examples of today's medical science. The sixth chapter (by Hans Meier), no less excellent, is excused from clinical consequences: it deals with pharmacological research in genetically controlled mice. Gerhard Zbinden writes on experimental and clinical aspects of drug toxicity, a survey badly needed at this time when drug manufacturers, pharmacologists, clinicians, and government agencies are groping for criteria of toxic and teratogenic phenomena, and for the extrapolation of laboratory data to clinical situations including transplacental toxicities. The classes of toxic interferences with metabolic, immunological, and