The Total Synthesis of Quinine

Sir:

Quinine preparations have been known and used for centuries in the treatment of malaria. The pure crystalline alkaloid was isolated in 1820, and the extensive degradative researches of the last century culminated in the proposal of the correct structure in 1908, but the complexity of the molecule has placed hitherto insurmountable difficulties in the way of the total synthesis of the drug. We wish to record the first total synthesis of quinine.

7-Hydroxyisoquinoline was converted through its 8-piperidinomethyl derivative (m. p. 81.5-82.5°; Anal. Calcd. for C_16H_21O_N: C, 69.4; H, 7.8; N, 11.6) into 7-hydroxy-8-methylisoquinoline (m. p. 320-323.5°; Anal. Calcd. for C_16H_20O_N: C, 72.5; H, 8.0; N, 10.5). This compound was converted by reaction with ethyl nitrite and sodium ethoxide to N-acetyl-S-acetic acid, obtained by addition of methyl thioglycolate to methyl acrylate in the presence of piperidine, was cyclized in two ways. With sodium methoxide in toluene at 110°, the main product was N-acetyl-7-hydroxy-8-methyl-1,2,3,4-tetrahydroisoquinolines (m. p. 191-198°; Anal. Calcd. for C_16H_19O_N: C, 74.36; H, 5.51; N, 9.85). Reduction of the uramido group was achieved by hydrogenation over platinum oxide to 7-hydroxy-8-methylisoquinoline (m. p. 189.5-190.0°. Anal. Calcd. for C_16H_13O_N: C, 73.41; H, 7.20; N, 10.02; N, 9.85). Further hydrogenation over Raney nickel led to a mixture of stereoisomeric N-acetyl-7-hydroxy-8-methylisoquinolines (cis, m. p. 126.0-128.0°. Anal. Calcd. for C_16H_20O_N: C, 70.54; H, 7.20; N, 10.02; N, 9.85). The pure cis-isomer, m. p. 126.0-128.0°, Anal. Found: C, 68.34; H, 9.58; N, 6.59) which was oxidized directly to the corresponding N-acetyl-7-keto-8-methyldecahydroisoquinolines. From the latter, the pure cis-N-acetyl-7-keto-8-methyldecahydroisoquinoline (cis refers to the mode of locking of the rings) was isolated as the crystalline monohydrate (m. p. 80.5-82.5°; Anal. Calcd. for C_16H_20O_N.H_2O: C, 63.40; H, 9.32; N, 6.16. Found: C, 63.34; H, 8.85; N, 6.40) and converted by ethyl nitrite and sodium ethoxide to N-acetyl-10-oximinidihydrohomomeroquinene ethyl ester (two polymorphic forms—labile, m. p. 96-98°; stable, m. p. 108.5-109.0°; Anal. Calcd. for C_16H_20O_N: C, 59.14; H, 8.51; N, 9.85. Found: C, 59.39; H, 8.24; N, 10.02). Reduction of the oximino-ester to the corresponding amine (characterized as the free 10-amino-10-decahydrohomomeroquinene dihydrate, m. p. 186.5-188°; Anal. Calcd. for C_16H_20O_N.H_2O: C, 51.20; H, 10.24; N, 11.86. Found: C, 50.83; H, 9.90; N, 12.04) complete methylation by methyl iodide and potassium carbonate, followed by alkali treatment of the resulting quaternary salt (Anal. Calcd. for C_16H_20O_N.H_2O.Na: C, 46.45; H, 7.55; N, 6.35. Found: C, 46.67; H, 7.14; N, 6.18) gave dl-homomeroquinene, isolated as the N-uramido derivative (m. p. 165.2-165.8° [dec.]; Anal. Calcd. for C_16H_20O_N.H_2O.Na: C, 58.40; H, 8.02; N, 12.39; CH_3C, nil. Found: C, 58.13; H, 7.45; N, 12.39; CH_3C, nil). The free dl-homomeroquinene (m. p. 219-220° [dec.]) obtained on cleavage of the uramido group was converted by esterification and benzoylation to N-benzoylhomomeroquinene ethyl ester. Condensation of the latter with ethyl quinate, following the general methods elaborated by Rabe [Ber., 51, 1800 (1918); ibid., 52, 1842 (1919)], working with related natural materials [cf. Pro’ntenik and Prelog, Helv. Chim. Acta, 26, 1965 (1943)], gave de-quinotoxine. The racemic alkaloid was resolved through its salts with dibenzoyl-d-tartaric acid. The pure synthetic d-quinotoxine dibenzoyl-d-tartarate had m. p. 185.5-188°, and showed no depression in melting point on admixture with a sample of authentic material prepared from natural quinotoxine. The synthetic d-quinotoxine regenerated from the salt was a very pale yellow viscous oil, [α]_D +43°. Conversion of d-quinotoxine to quinine was first effected over twenty-five years ago by Rabe [Ber., 51, 460 (1918)], working with natural materials, during the course of his elegant work which resulted in the determination of the correct structures of the cinchona alkaloids.

Thiophane Derivatives

Sir:


The dimethyl ester of β-mercaptopropionic acid S-acetic acid, obtained by addition of methyl thioglycolate to methyl acrylate in the presence of piperidine, was cyclized in two ways. With sodium methoxide in toluene at 110°, the main product was 4-carbethoxy-3-ketothiophane (m. p. 37-38°, b. p. 128.5-129.5° [20 mm.]; Anal. Calcd. for C_16H_16O_3S: C, 45.1; H, 5.0; S, 20.0. Found: C, 44.3; H, 5.2; S, 19.8). This substance gave a permanent red-violet coloration with ferric chloride, and from it a semicarbazone (m. p. 189.5-190.0°. Anal. Calcd. for C_16H_15O_3N _2 S: C, 38.7; H, 5.1; N, 19.3. Found: C, 39.2; H, 4.7; N, 19.1), a monobenzylidene derivative (m. p. 158-159°. Anal. Calcd. for C_16H_16O_3N _2: C, 62.9; H, 4.8. Found: C, 62.7; H, 5.2 and a monofurfurylidene derivative (m. p. 157-158°. Anal. Calcd. for C_16H_16O_3N _2: C, 55.5; H, 4.2. Found: C, 55.6; H, 4.8) were obtained. When the initial condensation was carried out at room temperature in ether with sodium

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