THE TOTAL SYNTHESIS OF QUININE[1]

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 $C_{15}H_{18}ON_2$: C, 74.36; H, 7.49; N, 11.57. Found: C, 73.79; H, 7.65; N, 11.86) into 7-hydroxy-8-methylisoquinoline (m. p. 232.0–233.5°; *Anal.* Calcd. for $C_{10}H_9ON$: C, 75.44; H, 5.70; N, 8.80. Found: C, 74.96; H, 5.51; N, 8.94). Hydrogenation over platinum oxide to 7-hydroxy-8-methyl-1,2,3,4-tetrahydroisoquinoline (m. p. 246–250°; *Anal.* Calcd. for $C_{10}H_{13}ON$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.41; H, 8.26; N, 8.63), and acetylation gave N-acetyl-2,7-hydroxy-8-methyl-1,2,3,4-tetrahydroisoquinoline (m. p. 191–198°; *Anal.* Calcd. for $C_{12}H_{15}O_2N$: C, 70.22; H, 7.35. Found: C, 70.54; H, 7.20). Further hydrogenation over Raney nickel led to a mixture of stereoisomeric N-acetyl-7-hydroxy-8-methyldecahydroisoquinolines (*Anal.* Calcd. for $C_{12}H_{21}O_2N$: C, 68.20; H, 10.02; N, 6.63. Found: C, 68.06; H, 9.75. 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 $C_{12}H_{19}O_2N \cdot H_2O$: 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-oximinodihydrohomomeroquinene ethyl ester (two polymorphic forms—*labile*, m. p. 96–98°; *stable*, m. p. 108.5–109.0°; *Anal.* Calcd. for $C_{14}H_{24}O_4N_2$: 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-aminodihydrohomomeroquinene dihydrate, m. p. 186.5–188°; *Anal.* Calcd. for $C_{10}H_{20}O_2N_2 \cdot 2H_2O$: 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 $C_{17}H_{33}O_3N_2I$: 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 $C_{11}H_{18}O_3N_2$: C, 58.40; H, 8.02; N, 12.39; CH_3-C, nil. Found: C, 58.13; H, 7.45; N, 12.39; CH_3-C, 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 quininate, following the general methods elaborated by Rabe [*Ber.*, **51**, 1360 (1918); *ibid.*, **52**, 1842 (1919)], working with related natural materials [*cf.* Prelog, *Helv. Chim. Acta*, **26**, 1965 (1943)], gave *dl*-quinotoxine. The racemic alkaloid was resolved through its salts with dibenzoyl-*d*-tartaric acid. The pure synthetic *d*-quinotoxine dibenzoyl-*d*-tartrate had m. p. 185.5–186°, 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, $[\alpha]_D$ +43°. Conversion of *d*-quinotoxine to quinine was first effected over twenty-five years ago by Rabe [*Ber.*, **51**, 466 (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.

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THIOPHANE DERIVATIVES

Sir:

The appearance of reports by Karrer, Schmid and Kehrer [*Helv. Chim. Acta*, **27**, 116, 124, 127, 142 (1944), Received April 3, 1944] on thiophane derivatives prompts us to record our experiments in that field.

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-carbomethoxy-3-ketothiophane (m. p. 37–38°, b. p. 128.5–129.5° [20 mm.]. *Anal.* Calcd. for $C_6H_8O_3S$: 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 $C_7H_{11}O_3N_3S$: 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 $C_{13}H_{12}O_3S$: C, 62.9; H, 4.8. Found: C, 62.7; H, 5.2) and a *monofurfurylidene derivative* (m. p. 157–158°. *Anal.* Calcd. for $C_{11}H_{10}O_4S$: C, 55.5; H, 4.2. Found: C, 55.6; H, 4.6) were obtained. When the initial condensation was carried out at room temperature in ether with sodium