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.

(1) This work was undertaken as a research project of Polaroid Corporation by the senior author, instructor in chemistry at Harvard University and chemical consultant to Polaroid Corporation.

RESEARCH LABORATORY, POLAROID CORPORATION
CONVERSE MEMORIAL LABORATORY
HARVARD UNIVERSITY R. B. WOODWARD
CAMBRIDGE 38, MASS. W. E. DOERING

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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

methoxide, the major product was 2-carbomethoxy-3-ketothiophane (oil, b. p. 116–116.5° [9 mm.]). From this keto-ester, a *semicarbazone* (m. p. 187–187.5° [mixed with the semicarbazone of the other isomer, m. p. 170–176°]. *Anal.* Calcd. for $C_7H_{11}O_3N_3S$: C, 38.7; H, 5.1. Found: C, 38.8; H, 4.7), a *monobenzylidene derivative* (m. p. 129–130°. *Anal.* Calcd. for $C_{18}H_{12}O_3S$: C, 62.9; H, 4.8. Found: C, 62.7; H, 4.9) and a *monofurfurylidene derivative* (m. p. 139.5–140.0°. *Anal.* Calcd. for $C_{11}H_{10}O_4S$: C, 55.5; H, 4.2. Found: C, 55.7; H, 4.3) were prepared.

Either of the isomeric β-keto-esters gave on hydrolysis 3-ketothiophane (oil, b. p. 58.2–58.4° [7 mm.]. *Anal.* Calcd. for C_4H_6OS: S, 31.4. Found: S, 30.3). A *dibenzylidene derivative* (m. p. 187.5°. *Anal.* Calcd. for $C_{18}H_{14}OS$: C, 77.8; H, 5.1; S, 11.5. Found: C, 77.9; H, 5.3; S, 11.7) and a *difurfurylidene derivative* (m. p. 191–192°. *Anal.* Calcd. for $C_{14}H_{10}O_3S$: C, 65.1; H, 4.2. Found: C, 65.1; H, 3.9) were prepared.

The 2-carbomethoxy-3-ketothiophane is remarkable in that on treatment with weak oxidizing agents (iodine, ferric chloride) it is rapidly and quantitatively converted to a double compound, $C_{12}H_{14}O_6S_2$ (m. p. 188.5–189.5°. *Anal.* Calcd. for C, 45.3; H, 4.4; S, 20.1. Found: C, 45.3; H, 4.6; S, 20.3), *dibenzylidene derivative* (m. p. 236°. *Anal.* Calcd. for $C_{26}H_{22}O_6S_2$: C, 63.0; H, 4.5. Found: C, 63.0; H, 4.6). From the double compound, by desulfurization, a *substance*, $C_{12}H_{18}O_6$ (m. p. 125–126°. *Anal.* Calcd. for C, 55.8; H, 7.0. Found: C, 56.7; H, 7.3), and from the latter by treatment with dilute mineral acids, an *acid*, $C_{10}H_{12}O_5$ (m. p. 152–153°. *Anal.* Calcd. for C, 56.7; H, 5.7. Found: C, 56.8; H, 6.0) were obtained, which we believe to be, respectively, dimethyl α,α′-dipropionyl succinate, and 2,5-diethylfuran-3,4-dicarboxylic acid.

We should like to take this opportunity to point out that the 2-furfurylidene-3-ketothiophane-4-carboxylic acid methyl ester described above possesses the complete continuous carbon–sulfur skeleton of biotin.

CONVERSE MEMORIAL LABORATORY
HARVARD UNIVERSITY R. B. WOODWARD
CAMBRIDGE 38, MASS. R. H. EASTMAN

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NEW BOOKS

The Chemistry of Organic Medicinal Products. By GLEN L. JENKINS, Dean and Professor of Pharmaceutical Chemistry, School of Pharmacy, Purdue University, and WALTER G. HARTUNG, Professor of Pharmaceutical Chemistry, School of Pharmacy, The University of Maryland. Second Edition. John Wiley & Sons, Inc., New York, N. Y.; Chapman and Hall, Ltd., London. iv + 675 pp. 14.5 × 12 cm. $6.50.

The second edition of this excellent compilation of organic medicinal compounds according to the accepted scheme of chemical classification is, in many respects, a much improved revision of the first planographed edition of 1941. Care has been taken to eliminate the trivial typographical errors, misspellings, misuse of words and phrases, and careless punctuation which marred the initial text. Rearrangement of the material into more compact paragraphs and better classified sections, and the gathering of the literature references into terminal chapter bibliographies have made the matter more easily and pleasantly readable. New material has been introduced and in many sections the explanatory text has been expanded, particularly in the chapter on Stereoisomerism where an excellent discussion of *cis–trans* isomerism about the ethylene bond is presented; a matter of some present importance in view of the recent revival of interest in the vitamin properties of the unsaturated fatty acids. A novel and interesting chapter entitled "Some Physical Chemical Properties of Medicinal Products" has been added. It is realized that a critical review and discussion of all theories and hypotheses is beyond the scope of this book but one would have liked to have seen some mention of the importance of physical chemical factors in the evaluation of the sulfonamides. This present text is intended for students in the more advanced courses in pharmaceutical, chemical, biological and medical science but will undoubtedly prove of great value and interest, not only to practitioners in these fields, but to the growing army of workers in the medicinal chemical industry.

C. R. ADDINALL

The Extra Pharmacopoeia. By MARTINDALE. 22nd Edition in Two Volumes. Published by Direction of the Council of the Pharmaceutical Society of Great Britain. The Pharmaceutical Press, 17 Bloomsbury Square, W.C. 1, London, England, 1943. xxxiii + 1217 pp. 11.5 × 18 cm. Price, 27/6; postage 6d. extra.

The first edition of "The Extra Pharmacopoeia" appeared in 1883 as a manual of 313 pages. The latest edition, the 22nd, published by direction of the Council of the Pharmaceutical Society of Great Britain, consists of two volumes: volume I, published in 1941, contains 1289 pages; volume II, the subject of this review, is a book of 1217 pages. It hardly seems possible to account for the 60-year existence and the continual growth in size of this particular "pharmacopoeia" except by the explanation that there has been a steady demand for a work of this nature, and that these volumes have satisfied the demand.

"The Extra Pharmacopoeia" is a repository of a vast amount of important, interesting and up-to-date information, and has been written particularly for the pharmacist, the physician, and the chemist who deals with foods and medicinal products. A rough estimate of the number of very diverse subjects, listed in the common index for the two volumes, is 13,000. Although too much space would be required to mention all of the chapter headings for volume II, 42 in number, the following examples will convey some idea of the nature of the topics which are discussed: Proprietary Medicines, Nomenclature of Organic Compounds, Chemotherapy, Polarographic Analysis, Nutrition and Food Values, Notes on Water Analysis, X-Ray Diagnosis and Actinotherapy.