crystallization from dichloromethane. The colorless hygroscopic volatile crystals, m.p. 32–40°, sublime above 29° (Kofler). (*Anal.* Calcd. for $C_2H_2F_3NO_2$: C, 18.61; H, 1.56; N, 10.86; neut. eq., 129.0. Found: C, 18.16; H, 2.21, N, 9.88; neut. eq. 130.2.)

A more detailed account of these reactions is being prepared.

This work was performed under the auspices of the U. S. Atomic Energy Commission.

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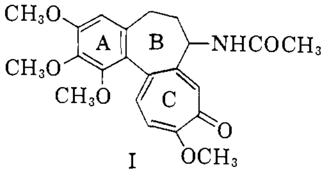
RECEIVED OCTOBER 29, 1959

THE TOTAL SYNTHESIS OF COLCHICINE

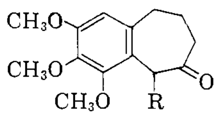
Sir:

Summarized below are steps which constitute the total synthesis of the alkaloid colchicine (I).[1]



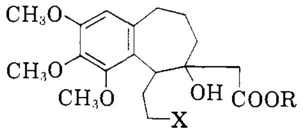
I

The trimethoxy-β-benzo-suberone II,[2,3,4] served as the starting point for an economical construction of a tricyclic system with a tropolonoid C-ring.

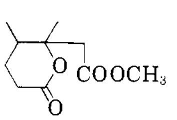


II, R = H
III, R = CH_2CH_2CN

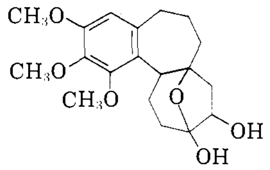
Ketone II can be cyanoethylated at room temperature in the presence of potassium *t*-butoxide. The resulting cyanoketone (III) (m.p. 110.5–111°) was converted under normal Reformatsky conditions to the diastereoisomeric β-hydroxyesters IVa (m.p. 119.0–119.5°) and IVb (m.p. 145–146°); saponification of IVb provided the corresponding hydroxydiacid (IVc) (m.p. 206–208°, dec.). In order to permit acyloin ring closure and to avoid Dieckmann reaction promoted by the free *t*-hydroxyl group, the lactone ester V (m.p. 150–150.5°), obtained by successive treatment of IVc with N,N-dicyclohexylcarbodiimide and diazomethane, was utilized. Cyclization of V with sodium in liquid ammonia[5] led to formation of among other products the tetracyclic hemiketal VI (m.p. 149–154°; λ max 282 mμ (ε = 1200); intense absorption at *ca.* 3.0 μ, weak peak 5.82 μ; one mole consumption of periodate). Without purification of intermediates, VI was oxidized by means of cupric acetate in methanol to the corresponding ketone VII (peaks at 2.95 and 5.68 μ), which, on being heated with *p*-toluenesulfonic acid in refluxing benzene, was dehydrated to the enedione VIII (λ max 365 mμ). Brief treatment of the latter with one mole of N-bromosuccinimide in refluxing chloroform afforded desacetoamidocolchiceine (IXa) (m.p. 165–170°), identical in all respects with IXa obtained by degradation of natural colchicine.



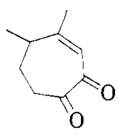
IV (a,b) X = CN R = CH_3
(c) X = COOH R = H



V

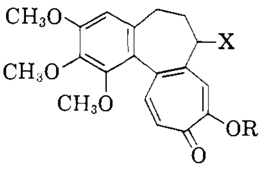


VI



VIII

Completion of the synthesis was accomplished by means of relay reactions. Trimethylcolchicinic acid[6] was converted to N,N-dimethylcolchicinic acid hydroiodide[7] (m.p. 252–254° dec.) by methyl iodide in dioxane at 75°; after liberation of the free tertiary amine further treatment under the same conditions gave the quaternary iodide IXb (m.p. 228–234°). Catalytic hydrogenolysis, carried out in dilute aqueous alkali in the presence of palladium-on-carbon, provided desacetoamidocolchiceine (m.p. 168–170°; λ max 244 mμ (ε = 35,600), 351 mμ (ε = 18,400). The O-methyl ether of m.p. 149–150° (IXc), isolated by fractional crystallization from the isomeric mixture formed by treatment of IXa with diazomethane, was converted in small yield to *dl*-IXd with N-bromosuccinimide.[8,9] Reaction of IXd with sodium azide in methanol solution at 100° gave the alkyl azide IXe (m.p. 166–169°, peak at 4.72 μ). Catalytic reduction over palladium-on-carbon then afforded *dl*-trimethylcolchicinic acid methyl ether, which without isolation was hydrolyzed with aqueous hydrochloric acid; *dl*-trimethylcolchicinic acid (m.p. 241–245° dec.),[10] identical in the infrared



a, R = H, X = H
b, R = H, X = $(NCH_3)_3^+$, I^-
c, R = CH_3, X = H
d, R = CH_3, X = Br
e, R = CH_3, X = N_3

IX

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[1] The total synthesis of colchicine also has been accomplished recently by J. Schreiber, W. Leimgruber, M. Pesaro, P. Schudel and A. Eschenmoser, *Angew. Chem.*, **71**, 637 (1959).

[2] H. Rapoport and J. Campion, THIS JOURNAL, **73**, 2239 (1951).

[3] A. Eschenmoser, H. H. Rennhard, *Helv. Chim. Acta*, **36**, 290 (1953).

[4] G. N. Walker, THIS JOURNAL, **77**, 6699 (1955).

[5] J. C. Sheehan and W. F. Erman, *ibid.*, **79**, 6050 (1957), and preceding references.

[6] R. F. Raffauf, A. L. Farren and G. E. Ullyot, *ibid.*, **75**, 5292 (1953).

[7] V. V. Kiselev and G. P. Men'shikov, *Doklady Akad. Nauk U.S.S.R.*, **88**, 825 (1953).

[8] For a closely-related precedent, see Ng. Ph. Buu-Hoï and J. Lecocq, *Compt. rend.*, **222**, 1441 (1946).

[9] The bromo compound IXd also serves as an intermediate in the synthesis of Eschenmoser, *et al.* (ref. 2), who carried out the NBS reaction on IXc prepared from colchicine according to an unpublished procedure developed by Prof. R. B. Woodward, Harvard University. We wish to acknowledge receipt of this information from Dr. Eschenmoser while our experiments on the bromination were in progress.

[10] H. Corrodi and E. Hardegger, *Helv. Chim. Acta*, **40**, 194 (1957).

(chloroform solution) with (−)trimethylcolchicinic acid, was produced. In view of the reported racemization and resolution of (−)trimethylcolchicinic acid,[10] and the reconversion of the latter to colchicine,[1] the above operations represent the total synthesis of the natural product.[11]

Acknowledgment.—We are indebted to the Wisconsin Alumni Research Foundation and the National Institutes of Health for financial support.

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RECEIVED NOVEMBER 5, 1959

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[11] Complete analytical and spectral data on all isolated intermediates will be presented in a full publication.

BOOK REVIEWS

Punched Cards: Their Applications to Science and Industry. Second Edition. Edited by ROBERT S. CASEY, W. A. Sheaffer Pen Co., Fort Madison, Iowa, JAMES W. PERRY, Center for Documentation and Communication Research, Western Reserve University, Cleveland, Ohio, MADELINE M. BERRY, National Science Foundation, Washington, D. C., and ALLEN KENT, Center for Documentation and Communication Research, Western Reserve University, Cleveland, Ohio. Reinhold Publishing Corporation, 430 Park Avenue, New York 22, N. Y. 1958. x + 697 pp. 16.5 × 23.5 cm. Price, $15.00.

If you are a salaried employee of a large organization, a stockholder, a payer of bills and taxes, a subscriber to magazines, and a borrower from public libraries, you may have begun to suspect that the economic structure of the United States is sheltered in a house of punched cards. As a scientist, you may also have utilized computing machinery, much of which requires input data in the form of punched cards. Except for a chapter on library routines and occasional remarks elsewhere, however, this book has nothing to say about these comparatively well-known applications. And it does have something to say about tools that can and perhaps should be used *instead* of punched cards. In fact, the book could be entitled "Binary-Code and Other Storage and Retrieval Systems for Scientific Information."

On the other hand, it could be called "First Approaches to The Dream" of many scientists and science-fiction writers, in which the dreamer picks up his phone, dials ENCYCLOPEDIA, asks the machine "What are the common uses of lutecium sulfate?" and gets an immediate answer. Neither of these suggested titles is a good one, and the best compromise is to let well enough alone. The book deals with "Punched Cards: Their Applications [other than accounting and computing] to Science and Industry."

It starts off with an elementary exposition of the use of simple punched cards. The second section adds descriptions of scores of ways in which punched cards, or tape, or film, have been and are being used for storage, retrieval, and sometimes correlation of scientific information. Chemistry is well represented. Indeed, it almost dominates. This may be because chemists are quick on the draw, or because chemical information retrieval by other methods is cumbersome, or because chemists are unusual in believing that information *can* be retrieved. Or it may be fortuitous. The knotty problem of linear notations for chemical formulas is included in the third section of the book, which expands on the first section's treatment of "Fundamental Considerations in Coding and Systems Design." The importance of such considerations cannot be overstressed. Although the book does not say so, the reviewer ventures to guess that punched-card systems which continue to be useful are outnumbered by those that were inadequately designed and have sunk into desuetude.

A speculative fourth section is followed by an extension of the bibliography of 276 references in the first edition. References in the new edition are numbered from 277 to 677. As for other changes from the first edition (published seven years earlier) 25 of the 30 chapters are extensively revised or entirely new.

The book was written by 32 authors, many of whom present not only their own views but those of other workers (including mine). The presentation is therefore, inevitably, somewhat incoherent. This flaw is more than compensated by the fair and comprehensive over-all effect. The wealth of detail considered ranges from methods of punching cards for manual sorting to the use of magnetic cores for rapid memory. James W. Perry (page 392) points out that "Punched cards and electronic machines enable us to surmount the limitations of three-dimensional space. These newer tools are essentially multiple dimensional in character by virtue of their ability to search out and to select information on the basis of new combinations of characteristics, that is to say, combinations not formulated or established at the time the information is analyzed. Thanks to their multi-dimensional character of operation, the newer tools, as exemplified by punched cards, enable us to center our attention on *selecting* and *retrieving* information for use. We are thereby released from the limitations of systems which function by deciding *where* we are going to put documents within a fixed array of one type or another."

A warning note is added by E. J. Crane and Charles L. Bernier (page 513). "There are many more or less specific purposes in the field of scientific information for which machines can provide effective help. Our purpose in emphasizing limitations is to suggest the wisdom of substituting an element of precautionary realism for some of the enthusiasm which is leading to higher claims for literature mechanization than present attainment has provided."

This is where matters stand now. What, I wonder, will the third edition be like?

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The Chemistry of Heterocyclic Compounds. Volume XII. Six-Membered Heterocyclic Nitrogen Compounds with Three Condensed Rings. By C. F. H. ALLEN, Eastman Kodak Co., Rochester, N. Y., Arnold Weissberger, Consulting Editor. Interscience Publishers, Inc., 250 Fifth Avenue, New York 1, N. Y. 1958. xxii + 624 pp. 16 × 23.5 cm. Price, $26.00. Subscription price, $24.00.

This volume is the twelfth of a series of monographs whose object is to provide a detailed survey of heterocyclic chemistry. Volume 12 presents the chemistry of nitrogen heterocycles which possess three fused six-membered rings, *i.e.*, azaanthracenes, azaphenanthrenes and *peri*-azabenzonaphthalenes. Acridines, phenazines and alloxazines have been excluded since they are to be treated separately. The literature covered is complete only to 1952, though some of the cited references are as recent as 1957.

The authors are obviously aware of the disconcerting task faced by the reader who must decipher the complex numbering and nomenclature associated with many heterocyclic systems. Accordingly, the carefully selected subject matter has been very liberally supplemented with structural formulas and equations. The tables which follow the discussion of each ring system have been arranged according to functional groups, and are easy to consult. The "a" system of nomenclature is employed for the general headings,