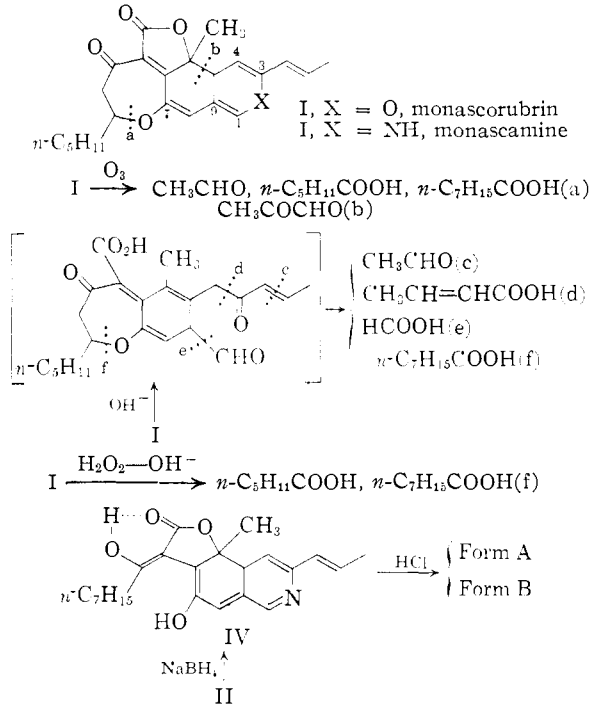
tonic group are conjugated with the annular heteroatom X since the shift of the infrared bands to lower wave numbers in the conversion of I to II is not due to a C=O· · ·H–N hydrogen bonding as evidenced by the band positions of N-methylmonascamine, m.p. 105°. The assumption also is supported by the hypsochromic shifts in infrared peaks of II–HCl, m.p. 198–202°, and accordingly the n-C_7H_{15}-CO-C- side-chain in III can only be attached to C-6.

SCHEME I

(parenthesized letters show position of cleavage)



Production of acetaldehyde from I and butyric acid from dihydromonascorubrin, m.p. 119–121°, upon ozonolysis requires attachment of a propenyl group at C-3 and a double bond at C_3-C_4. The C_1-C_9 double bond accounts for the production of formic acid with alkali.[3] Secomonascamine (IV), m.p. 218–220°, $C_{23}H_{29}O_4N$ (C, 72.1; H, 7.71; N, 3.74), positive enol tests, showed only a single carbonyl absorption, and this suggested the two carbonyl functions to be located in positions capable of conjugate chelation. Secomonascamine hydrochloride, m.p. 125°, was obtained in two modifications, the unstable A and stable B. Form A presumably results from simple N-protonation of structure IV (hypsochromic shift of infrared peak, 1703→1715 cm.$^{-1}$; also presence of immonium band besides ammonium band), whereas Form B corresponds to the N-protonated form of II cleaved at dotted line (a) (infrared peaks compare well with those of monascamine hydrochloride). Structures I and II are consistent with current biogenetic considerations.[4]

(3) *E.g.*, D. H. Johnson, A. Robertson and W. B. Whalley, *J. Chem. Soc.*, 2971 (1950); J. C. Roberts and C. W. H. Warren, *ibid.*, 2992 (1955); N. B. Graham, H. Page, A. Robertson, R. B. Travers, K. Turner and W. B. Whalley, *ibid.*, 4924 (1957).

(4) A. J. Birch, P. Fitton, E. Pride, A. J. Ryan, H. Smith and W. B. Whalley, *ibid.*, 4576 (1958).

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RECEIVED SEPTEMBER 9, 1959

TWO NEW SYNTHESES OF NITRILES FROM ALDEHYDES, USING O,N-BIS-(TRIFLUOROACETYL)-HYDROXYLAMINE OR TRIFLUOROACETOHYDROXAMIC ACID

Sir:

There are a number of methods of preparing nitriles from the corresponding aldehydes,[1] most of which require vigorous reaction conditions or involve several steps. We have found that O,N-bis-(trifluoroacetyl)-hydroxylamine (I) reacts with aldehydes in a one-step reaction to give the corresponding nitriles. Yields are mostly between 70–90% (Table I). Reaction conditions are mild: a solution of I, the aldehyde, and pyridine (molar ratio 1:1:2) in benzene is heated to reflux for 1–2 hours; the reaction also proceeds smoothly at room temperature, but more slowly.

TABLE I

SYNTHESES OF NITRILES FROM ALDEHYDES AND BIS-(TRIFLUOROACETYL)-HYDROXYLAMINE

Aldehyde	Nitrile	Yield, %
Heptanal	Heptanenitrile	71.5
Veratraldehyde	Veratronitrile	86.6
Salicylaldehyde	Salicylonitrile	53.6
Anisaldehyde	Anisonitrile	73.7
Cinnamaldehyde	Cinnamonitrile	87.6
3-Indolecarboxaldehyde	3-Indolecarbonitrile	82.0
m-Nitrobenzaldehyde	*m*-Nitrobenzonitrile	78.9

O,N-Bis-(trifluoroacetyl)-hydroxylamine is prepared readily by refluxing 3.2 moles of trifluoroacetic anhydride with 1 mole of hydroxylamine hydrochloride for 1.5 hours. After removal of trifluoroacetic acid and trifluoroacetyl chloride under vacuum, the residue is recrystallized from dichloromethane. The product is an 80% yield of hygroscopic and easily volatile needles of O,N-bis-(trifluoroacetyl)-hydroxylamine; 50° (transition), m.p. 62° (with sublimation, in a sealed capillary, Kofler hot stage). (*Anal.* Calcd. for $C_4HF_6NO_3$: C, 21.35; H, 0.45; N, 6.22; neut. eq., 112.5. Found: C, 21.73; H, 0.78; N, 6.45; neut. eq., 112.8.)

It also has been found that trifluoroacetohydroxamic acid ($CF_3CONHOH$) reacts with aldehydes to give nitriles, although more slowly and in a lower yield under similar conditions. Trifluoroacetohydroxamic acid was prepared in 74% yield by the reaction of 2.1 moles of trifluoroacetic anhydride with hydroxylamine hydrochloride, and then re-

(1) *Cf.* reviews by V. Migrdichian, "The Chemistry of Organic Cyanogen Compounds," Reinhold Publ. Corp., New York, N. Y., 1947, p. 2; D. T. Mowry, *Chem. Rev.*, **42**, 189 (1948); P. Kurtz in "Methoden der Organischen Chemie (Houben-Weyl)," Georg Thieme Verlag, Stuttgart, 1952, Vol. VIII, pt. 3, p. 265.

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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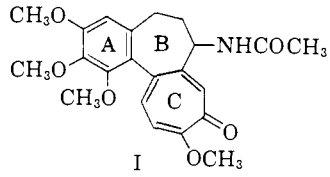
RECEIVED OCTOBER 29, 1959

THE TOTAL SYNTHESIS OF COLCHICINE

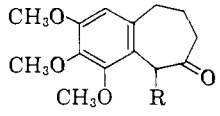
Sir:

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



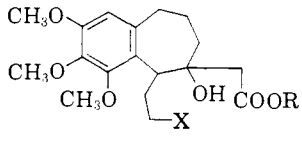
I

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.

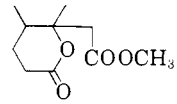


II, R = H
III, R = CH_2CH_2CN

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

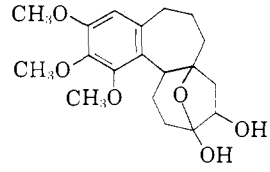


IV (a,b) X = CN R = CH_3
(c) X = COOH R = H

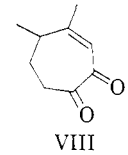


V

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



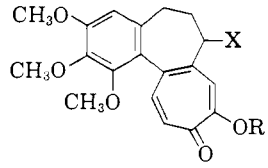
VI



VIII

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.

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



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

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

(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).