Tetrahedron Letters No. 34, pp 2977 - 2980, 1977. Pergamon Press. Printed in Great Britain.

NEW CHEMISTRY OF COLCHICINE AND RELATED COMPOUNDS.
I. REACTION WITH ALIPHATIC ANHYDRIDES LEADING TO ACHIRAL COMPOUNDS.

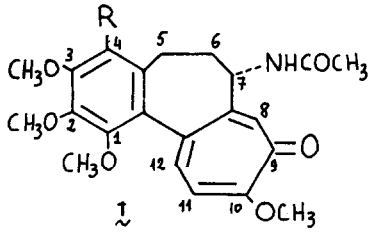
Artur Bladé-Font[1]

Research Department, Productos Frumtost, S.A.

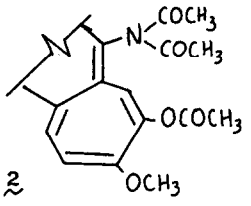
Suiza, 9, Barcelona (Spain).

(Received in UK 31 May 1977; accepted for publication 29 June 1977)

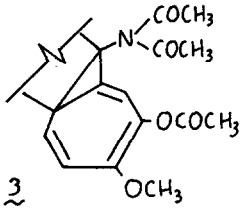
Some time ago while working on new derivatives of colchicine[2,3] we found that prolonged treatment of 4-formylcolchicine oxime (1, R = CHNOH) with boiling acetic anhydride resulted in partial racemisation of the main product, 4-cyanocolchicine (1, R = CN), and in formation of an unidentified secondary product, which was optically inactive and non-tropolonic in nature.



1



2



3

This observation prompted us to investigate the general reaction of aliphatic anhydrides with colchicine (1, R = H) and several of its analogs. We report now on this reaction which provides new aspects of colchicine chemistry and affords a more efficient method for racemisation of colchicine-related compounds as compared to the only procedure described till now[4] based on a lengthy sequence of reactions.

Treatment of colchicine with excess acetic anhydride at reflux temperature for 24 hours afforded[5,6] a yellow crystalline product (73% yield), mp. 170°; $[\alpha]_D$ 0° (c 2% $CHCl_3$). From the mother liquors (±)colchicine[4] (10% yield, mp. 280°) can be isolated by chromatography on alumina. The ir spectrum of the new product (Nujol, 1765, 1705 cm^{-1}) does not show the presence of secondary amide, nor that of the most characteristic bands of the tropolonic ring of colchicine[7,8].

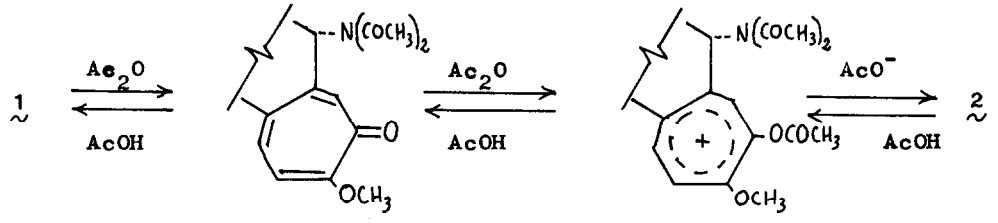
The ir absorptions shown can be attributed to the presence of both an enol acetate group and an N-diacyl function. The uv spectrum (EtOH), 281 nm (4.12), confirms the absence of the tropolonic chromophore[9]. The ^{1}H-nmr spectrum (60 MHz, $CDCl_3$) indicates the presence of three acetyl groups: δ 2.20 (3H,s), 2.29 (3H,s), 2.36 (3H,s); four methoxy groups: δ 3.68 (6H,s, 2 x CH_3O), 3.90 (6H,s, 2 x CH_3O), and four olefinic protons: δ 5.60 (1H,t, J = 2Hz), 5.80 (1H,d, J = 8Hz), 6.25

(1H,d, J = 8Hz) and 6.55 (1H,s). The singlet can be attributed to the benzenic proton, the doublets to protons at C-11 and C-12, and the ill-resolved triplet to proton at C-8. Irradiation of the methylenic region of the spectrum at δ2.60 changes the triplet at δ 5.60 into a singlet, thus showing a long-range coupling between H-C_8 and some methylene protons of ring C, probably those of C-6[10].

No absorption at the δ 4.50 region due to a proton on a carbon adjacent to a nitrogen, such as that of H-C_7 in colchicine, appears on the spectrum. The nmr data thus clearly points to structure 2.

Alternative structure 3, which also agrees with the nmr spectrum is not considered since it corresponds to a highly strained bicyclo[5.1.0]octatriene system of which no representative has been isolated so far[11].

Compound 2, an enolic acetate of N-acetylcolchicine, probably originates through the following reversible reactions:

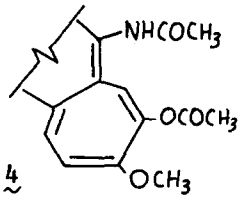


This scheme is in agreement with the fact that the experimental rates of loss of optical activity and dissapearance of the tropolonic chromophore are the same[12], and that treatment of 2 with boiling acetic acid for 5 hours gives (±)colchicine in excellent yield.

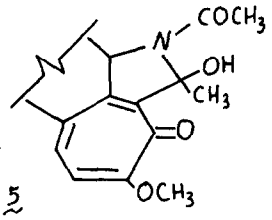
From a practical point of view (±)colchicine may be obtained in good yield directly from (-)colchicine without isolating 2[13].

Chromatography of 2 on acid-washed alumina (Grade II) or stirring of a methylene chloride solution of 2 with acid-washed alumina for 3-4 hours, leads to selective N-monodeacylation. The resulting product (75% yield), enolic acetate 4, is a yellow crystalline product: mp. 246°(AcOEt); uv (EtOH) 278 nm(4.18); ir (Nujol) 3150 (NH), 1760 (enolic ester), 1640 (amide II), 1525 cm^{-1}(amide II); ^{1}H-nmr (60 MHz, $CDCl_3$) δ 2.05 (3H,s, $C\underline{H}_3$-CON), 2.20 (3H,s, $C\underline{H}_3CO_2$), 3.70 (3H,s, $C\underline{H}_3O$), 3.73 (3H,s, $C\underline{H}_3O$), 3.85 (6H,s, 2x$C\underline{H}_3O$), 5.70 (1H,s, H-C_8), 5.76 (1H,d, J = 8Hz, H-C_{11}), 6.15 (1H,d, J = 8Hz, H-C_{12}), 6.55 (1H,s, H-C_4), 6.90 (1H,br,s, NH).

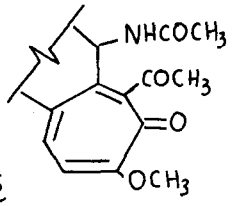
When O,N-diacetate 2 is reacted at room temperature with aqueous bases in methylene chloride - metanol solution, the main product is (±)colchicine (61% yield), but there is also obtained a new tropolonic product (20% yield), N-acetylcarbinolamine, 5, mp. 190°(AcOEt); uv (EtOH) 244 (4.48), 348 nm (4.23); ir ($CHCl_3$) 3440 (chelated OH), 1625 cm^{-1}(tertiary amide); ^{1}H-nmr (60MH$_z$, $CDCl_3$) δ 2.06 (3H,s, $C\underline{H}_3CON$), 2.40 (3H,s, $C\underline{H}_3$-C-OH), 3.65 (3H,s, $C\underline{H}_3O$), 3.92 (3H,s, $C\underline{H}_3O$) 3.95 (3H,s, $C\underline{H}_3O$), 4.08 (3H,s, $C\underline{H}_3O$), 5.05 (1H,t, H-C_7), 5.92 (1H,s, HO), 6.58 (1H,s, H-C_4), 7.00 (1H,d, J = 10Hz, H-C_{11}), 7.43 (1H,d, J = 10Hz, H-C_{12}).



4



5



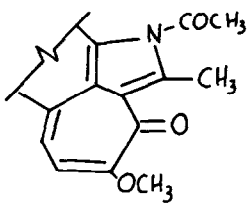
6

N-acylcarbinolamine 5 is the cyclic form of 8-acetylcolchicine 6. Preference for that form is not surprising in view of the proximity of the acetylamino and the methylketone groups, and the ease of formation of five-membered cyclols[14].

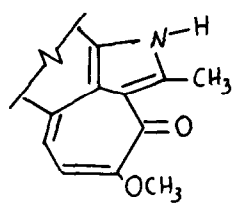
Formation of 5 on hydrolysis of 2 can be explained by intramolecular attack of the free enol from 2 on one of the acyl groups of the imide function, followed by isomerisation to the tropolone structure.

Brief treatment of 5 with mineral acids or hot acetic anhydride leads to N-acetylpyrrole 7 (82% yield), yellow crystals, mp. 172°(MeOH); uv (EtOH) 263 (4.42), 429 nm (3.65); ir (Nujol) 1735 (N-acylpyrrole), 1610 cm^{-1} (C=C-C=O); ^{1}H-nmr (60 MHz, $CDCl_3$) δ 2.62 (3H,s, C<u>H</u>3-C=C), 2.73 (3H,s, $C\underline{H}_3CON$), 3.45 (3H,s, $C\underline{H}_3O$), 3.83 (3H,s, $C\underline{H}_3O$), 3.89 (3H,s, $C\underline{H}_3O$), 3.90 (3H,s, $C\underline{H}_3O$), 6.16 (1H,d, J = 9Hz, <u>H</u>-C_{11}), 6.44 (1H,d, J = 9Hz, <u>H</u>-C_{12}), 6.56 (1H,s, <u>H</u>-C_4).

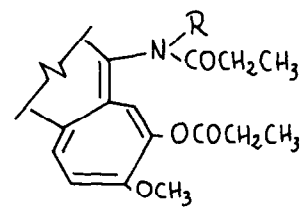
In agreement with the known lability of N-acylpyrrole groups, reaction of 7 with aqueous bases readily gives pyrrole 8, ("anhydrocolchicine"), orange crystals, mp. 326° (AcOEt); uv (EtOH) 257 (4.24), 312 (4.20), 437 nm (3.55); ir (Nujol) 3400 (NH), 1600 cm^{-1} (C=C-C=O); ^{1}H-nmr (60 MHz, $CDCl_3$) δ 2.66 (3H,s, $C\underline{H}_3$-C=C), 3.42 (3H,s, $C\underline{H}_3O$), 3.82 (3H,s, $C\underline{H}_3O$), 3.88 (3H,s, $C\underline{H}_3O$), 3.90 (3H,s, $C\underline{H}_3O$), 6.30 (1H,d, J = 9Hz, <u>H</u>-C_{11}), 6.43 (1H,d, J = 9Hz, <u>H</u>-C_{12}), 6.55 (1H,s, <u>H</u>-C_4), 9.10 (1H,br, s, N<u>H</u>).



7



8



9a ;R = $COCH_2CH_3$
9b ;R = H

When colchicine was treated with propionic anhydride under reflux for 5 hours, it was possible to isolate O,N-dipropionate 9a (30% yield), yellow crystals, mp. 132° (MeOH); uv (EtOH) 284 nm (4.12) and N-desacetyl-N-propionyl-(±)-colchicine (24% yield), mp. 208° (AcOEt), $[\alpha]_D$ 0° (c 2% EtOH); uv (EtOH) 246 (4.46), 351 nm (4.23); ir (Nujol) 3260 (NH), 1675 (amide I), 1540 cm^{-1} (amide II);

^{1}H-nmr ($CDCl_3$) δ 1.10 (3H,t, J = 7Hz, $\underline{CH}_3$-CH_2-CO), 2.00 (6-7H,m, -$\underline{CH}_2$-), 3.65 (3H,s, $\underline{CH}_3O$), 3.87 (3H,s, $\underline{CH}_3O$), 3.91 (3H,s, $\underline{CH}_3O$), 3.98 (3H,s, $\underline{CH}_3O$), 4.50 (1H,br.s, $\underline{H}$-C_7), 6.51 (1H,s, $\underline{H}$-C_4), 6.82 (1H,d, J = 11Hz, $\underline{H}$-C_{11}), 7.10 (1H,d, J = 5Hz, $\underline{NH}$), 7.30 (1H,d,J 11Hz, $\underline{H}$-C_{12}), 7.45 (1H,s, $\underline{H}$-C_8).

Selective N-deacylation of 9a on acid alumina (Grade II) leads to 9b, yellow crystals, mp. 180° (MeOH), uv (EtOH) 280 nm (4.18). The main absorptions in the ir (NH and CO bands) and the nmr (vinyl hydrogens) spectra of 9a and 9b are almost identical to those of 3 and 4 respectively.

Reaction of 9a or 9b with hot propionic acid gives N-desacetyl-N-propionyl-(±)colchicine in 60-70% yield.

References and Notes.

1. This work was begun at the Centre de Recherches Roussel-UCLAF, Romainville, France.
2. G. Muller, A. Bladé-Font and R. Bardone schi, Ann. 662, 105 (1963).
3. A. Bladé-Font, Tetrahedron Letters, 3607, (1969).
4. H.H. Corrodi and E. Hardegger, Helv. Chim. Acta, 40, 193 (1957). The procedure is essentially based on racemisation of N-benziliden-(-)desacetylcolchiceine with alkali.
5. Excess of acetic anhydride was removed under vacumm at steam-bath temperature and the residue directly crystallized from ethyl acetate.
6. Satisfactory microanalytical results in agreement with the given structures were obtained for all new compounds. Melting points were determined on a Kofler hotbench. Reactions were followed by TLC on SiO_2 (elution solvent: AcOEt / 5% EtOH).
7. G.P. Scott and D.S. Tarbell, J. Amer. Chem. Soc., 72, 240 (1950).
8. J. Fabian, V. Delaroff, P. Poirier and M. Legrand, Bull. Soc. Chim. France, 1455 (1955).
9. Colchicine shows characteristic absorption at 244 and 351 nm attributed to conjugation of the tropolone and the trimethoxybenzene chromophores (Ref. 8)
10. Although the coupling constant, J = 2Hz, seems rather large for such 5-bond coupling, it is not unusual for bis-allylic systems. Nufent F. Chamberlain, "The practice of NMR Spectroscopy", Plenum Press, New York-London, 1974, p. 305.
11. Bicyclo [5.1.0] octadienes are known. M. Bauman and G. Köbrich, Tetrahedron Letters, 1217 (1974). Although bicyclo [5.1.0] octatrienes undoubtedly would be very strained and probably very unstable compounds, they have been presumed sufficiently stable to be isolated. G. Köbrich, private communication.
12. For a 5% solution of colchicine in acetic anhydride at reflux temperature, the pseudo-first order reaction constant, as determined spectrophotometrically or following the decrease in optical rotation, was 0,094 hr^{-1}.
13. After treating colchicine in excess acetic anhydride under reflux for 24 hrs. and cooling to room temperature, enough water is added to hydrolyze 80-85% of the anhydride, and refluxing is resumed for a period of 5-6 hours. Distillation of the acetic acid under vacuum and direct crystallization of the residue from ethyl acetate affords (±)colchicine in better than 70% yield.
14. B. Witkop and L.A. Cohen, Ang. Chem. 73, 253 (1961); K.E. Schulte and J. Reisch, Arch. Pharm., 292, 125 (1959).