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NEW CHEMISTRY OF COLCHICINE AND RELATED COMPOUNDS. II. A NON-TROPOLONIC PRECURSOR OF COLCHICINE AND ITS ENOL ACETATES.

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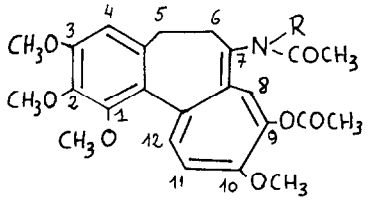
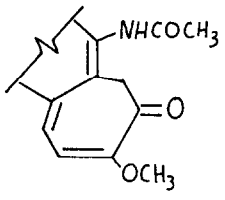
We recently described[2] the reaction of colchicine with aliphatic anhydrides leading to achiral enol esters 1a and 1b. Several tetracyclic compounds derived from 1a were also characterized. We now report on further products[3] which may be obtained from intermediate 1b.



1a ; R = $COCH_3$

1b ; R = H



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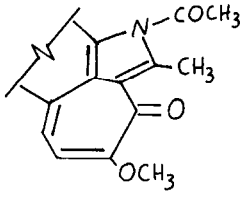


3

Brief treatment[4] of enol acetate 1b with bases in methanol solution affords ketone 2 (60% yield), yellow crystals, mp. 242°(AcOEt); uv (EtOH) 372 nm (3.98); ir (Nujol) 3300 (NH), 1690 (amide I), 1675 (C=C-C=O), 1560 cm^{-1} (amide II); ^{1}H-nmr (60 MHz, $CDCl_3$) δ 2.25 (3H,s, $C\underline{H}_3CON$), 2.95 (4H,br.s, $-C\underline{H}_2-C\underline{H}_2-$), 3.50 (2H,br.s, $-C\underline{H}_2CO$), 3.80 (3H,s, $C\underline{H}_3O$), 3.85 (3H,s, $C\underline{H}_3O$), 4.00 (6H,s, 2 x $C\underline{H}_3O$), 6.15 (2H,s, $=C\underline{H}-C\underline{H}=$), 6.60 (1H,s, $\underline{H}-C_4$), 7.35 (1H,br.s, $N\underline{H}$).

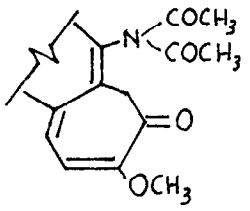
Ketone 2 is an interesting non-tropolonic precursor of (±)colchicine. Isomerisation of 2 into racemic colchicine is easily accomplished in a few hours by the action of aqueous bases at room temperature or by short treatment (1 hour at steam-bath temerature) with hot acetic acid.

When enol acetate 1b is left to react with aqueous bases for several hours at room temperature the final product is, as expected, (±)colchicine, but in contrast[5] to 1a, conversion of 1b to (±)colchicine by the action of acetic acid is complete after one hour at steam-bath temperature.

Reaction of ketone 2 with acetic anhydride at reflux temperature gives a mixture of O,N-diacetate 1a and the N-acylpyrrole 3 previously described[1]. Pre-

sumably 3 arises from N-diacetylaminoketone 4, which is also the probable intermediate in the alkaline hydrolysis[2] of O,N-diacetate 1a.

On the other hand, treatment of 1b with refluxing acetic anhydride for one hour gives O,N-diacetate 1a in 82% yield.



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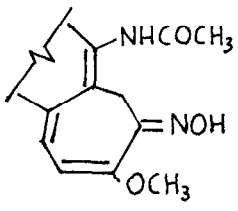

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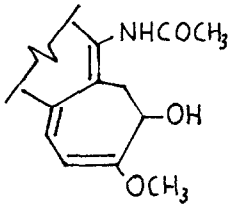
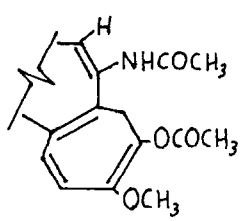


6

From ketone 2 or enol acetate 1b, reaction with hydroxylamine in ethanol affords oxime 5 (90% yield), yellow prisms, mp. 230°(AcOEt); uv (EtOH) 365 nm (4.06); ir ($CHCl_3$) 3550, 3200 (=NOH), 3350 (NH), 1685 cm^{-1} (amide I).

Treatment of 2 or 1b with sodium borohydride in aqueous methanol leads to the same alcohol 6 (60-70% yield), colourless prisms, mp. 197°(AcOEt); uv (EtOH) 316 nm (3.99); ir (Nujol) 3460 (OH), 3330 (NH), 1690 (amide I); ^{1}H-nmr (60 MHz, $CDCl_3$) δ 2.02 (3H,s, $C\underline{H}_3CON$), 3.68 (3H,s, $C\underline{H}_3O$), 3.80 (3H,s, $C\underline{H}_3O$), 3.90 (6H,s, 2 x $C\underline{H}_3O$), 4.62 (1H,br.t, -C$\underline{H}$OH), 5.30 (1H,d, J = 9Hz, $\underline{H}$-C_{11}), 5.83 (1H,d, J = 9Hz, $\underline{H}$-C_{12}), 8.42 (1H,s, N$\underline{H}$).

When reaction of ketone 2 and acetic anhydride is conducted at room temperature for 5 hours in the presence of p-toluenesulfonic acid as catalyst there is obtained enol acetate 7 (60% yield), greyish crystals, mp. 202° (AcOEt); uv (EtOH) 207 (4.64), 304 nm (3.93); ir (Nujol) 3220 (NH), 1760 (enol ester) 1650 (amide I), 1525 cm^{-1} (amide II); ^{1}H-nmr (60 MHz, $CDCl_3$) δ 1.98 (3H,s, $C\underline{H}_3CON$), 2.25 (3H,s. $C\underline{H}_3COO$-), 2.80 (2H,s, $C\underline{H}_2$-C-O-$COCH_3$), 2.85 (2H,m, -$C\underline{H}_2$-CH=C-) 3.60 (3H,s, $C\underline{H}_3O$), 3.65 (3H,s, $C\underline{H}_3O$), 3.86 (6H,s, 2 x $C\underline{H}_3O$), 6.35 (1H,t, J = 6Hz, $\underline{H}$-C_6), 6.47 (1H,d, J = 12Hz, $\underline{H}$-C_{11}), 6.55 (1H,s, $\underline{H}$-C_4), 7.03 (1H,d, J = 12Hz, $\underline{H}$-C_{12}). 7.40 (1H,s. N$\underline{H}$). Irradiation of the multiplet at δ 2.85 converts the triplet at δ 6.35 into a singlet.



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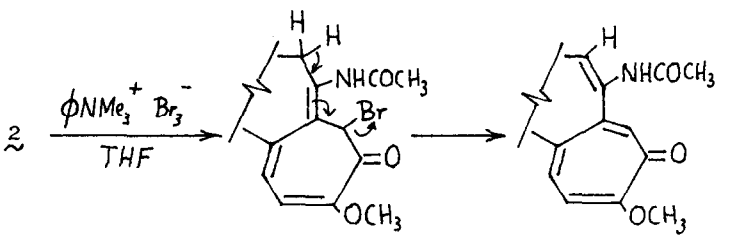
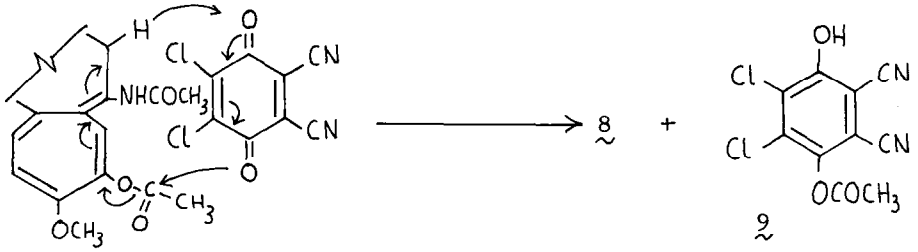


8

Attempted bromination at C-8 of ketone 2 with one equivalent of trimethylphenylammonium perbromide[6] in tetrahydrofuran leads, probably through a facile

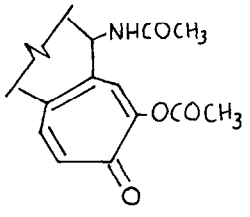
dehydrohalogenation step, involving loss of a proton at C-6, to 6-dehydrocolchicine 8 (90% yield), orange-yellow crystals[7], mp. 254°(AcOEt); uv (EtOH) 247 (4.39), 312 (4.26), 370 nm (4.05); ir (Nujol) 3220, 3180 (NH), 1690 (amide I), 1530 cm^{-1} (amide II); ^{1}H-nmr (60 MHz, $CDCl_3$) δ 1.98 (3H,s, $C\underline{H}_3CON$), 2.94 (2H,d, J = 7.5Hz, $-C\underline{H}_2-CH=$), 3.61 (3H,s, $C\underline{H}_3O$), 3.91 (6H,s, 2 x $C\underline{H}_3O$), 4.07 (3H,s, $C\underline{H}_3O$), 6.56 (1H,t, J = 7,5Hz, $-CH_2-C\underline{H}=C-$), 6.56 (1H,s, $\underline{H}$-C4), 6.94 (1H,d, J = 11z , $\underline{H}$-C_{11}), 7.61 (1H,d, J = 11Hz, $\underline{H}$-C_{12}), 7.86 (1H,s, $\underline{H}$-C_8), 9.71 (1H,s, $N\underline{H}$). Irradiation of the doublet at δ 2.94 converts the triplet at δ 6.56 into a singlet superimposed on the signal of the benzenic proton. Conversely, irradiation at δ 6.56 converts the doublet at δ 2.94 into a singlet.

Dehydrocolchicine 8 is also obtained, although in lower yields, through reaction of enol acetates 1b and 7 with dichlorodicyanoquinone in methylene chloride. Curiously, in addition to 8, the reaction affords a mixture of dichlorodicyanohydroquinone and its diacetate instead of the expected monoacetylderivative 9. This result would not be in favour of a concerted process[8] of the type shown:



However, the fact that O,N-diacetate 1a does not react with dichlorodicyanoquinone suggests that the reaction is subject to steric hindrance as demanded by the cyclic process[9].

Treatment of enol acetate 1b with aqueous mineral acids in acetone or tetrahydrofuran leads to a mixture[10] of (±)colchiceine acetate[11], 10 (30% yield) and ketone 11 (18% yield), yellow crystals, mp. 230°(AcOEt); uv (EtOH) 365 nm (3.98); ir ($CHCl_3$) 3440 (NH), 1750 (enol ester), 1685 (amide I), 1660 cm^{-1} (C=C-C=O); ^{1}H-nmr (60 MHz, $CDCl_3$) δ 2.12 (3H,s, $C\underline{H}_3CON$), 2.26 (3H,s, $C\underline{H}_3COO$), 2.84 (4,br.s, $-C\underline{H}_2-C\underline{H}_2-$), 3.37 (2H,s, $-C\underline{H}_2-CO-$), 3.79 (3H,s, $C\underline{H}_3O$), 3.88 (6H,s, 2 x $C\underline{H}_3O$) 6.13 (1H,d, J = 8Hz, $\underline{H}$-C_{11}), 6.56 (1H,s, $\underline{H}$-C_4), 6.66 (1H,d, J = 8Hz, H-C_{12}), 7.10 (1H,s, $N\underline{H}$).



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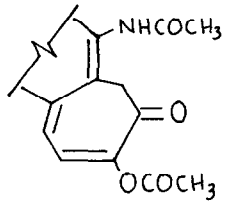

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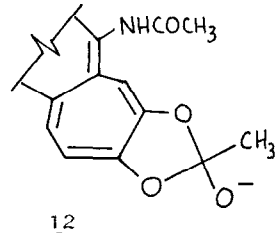

12

A commun cyclic intermediate[12] such as 12 could explain the formation of

both 10 and 11.

Catalytic hydrogenation of enol acetate 1b in different conditions afforded an inseparable mixture of products.

Attempted Diels-Alder reaction of enol acetates 1a and 1b with maleic anhydride, dimethyl acetylenedicarboxylate or quinone gave negative results, whereas reaction with tetracyanoethylene led to decomposition products.

Three well-known analogues of colchicine: isocolchicine, thiocolchicine, and colchiceine have also been found to react with aliphatic anhydrides giving achiral enol esters similar to 1a and 1b. Full details concerning these products and the structural factors which affect the reaction of colchicine-related compounds with aliphatic anhydrides will be published later.

References and Notes.

1. This work was begun at the Centre de Recherches Roussel-UCLAF, Romainville, France.
2. A. Bladé-Font, Tetrahedron Letters,
3. Satisfactory elemental analyses 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).
4. Enol acetate 1b (1.105 g) in methylene chloride-methanol solution was treated with 2.50 ml of 1N NaOH. After stirring for 4 minutes at room temperature the solution was neutralized with CH_3CO_2H. Usual work-up and column chromatography on alumina affords ketone 2 and some (±)colchicine.
5. Acetolysis of O,N-diacetate 1a to (±)colchicine requires heating in acetic acid for 5-6 hours at reflux temperature (Ref. 2).
6. A. Marquet and J. Jacques, Bull.Soc. Chim. France, 90 (1962).
7. V. Delaroff and P. Rathle, Bull.Soc. Chim. France, 1621 (1965).
8. This kind of cyclic process in the oxidation of enol esters with quinones has already been suggested in the literature. L. Mandell, J.Am.Chem.Soc., 78, 3199 (1956).
9. Examination of molecular models shows that the N-diacetyl group at C-7 of enol acetate 1a can undoubtedly hinder the simultaneous approach of the quinone molecule to both reacting centres of 1a.
10. Enol acetate 1b (0.300 g) in 50 ml acetone was treated with 3.0 ml 2N HCl and stirred for 5 hours at room temperature. After neutralising the solution with aqueous $NaHCO_3$ the products were extracted in methylene chloride. Direct crystallization of the mixture of products in ethyl acetate afforded (±)colchiceine acetate, mp. 232°. From the mother liquors ketone 11 was isolated through chromatography on acid-washed alumina.
11. The product was identical in all respects to an authentic sample prepared from (±)colchiceine and acetic anhydride in pyridine.
12. Analogous cyclic intermediates have been proposed in acyl group transfer involving a neighbouring ketone function. S. Masamune, A.V. Kemp-Jones, J. Green, D.L. Rabenstein, M. Yasunami, K. Takase and T. Nozoe, Chem. Comm., 283, (1973); J. Hercovici, M. Bessodes and K. Antonakis, J.Org.Chem., 41 3827 (1976).