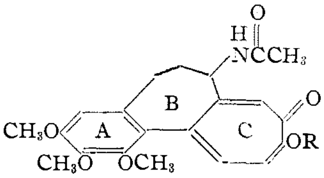
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

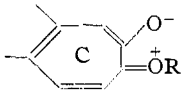
Studies in the Structure of Colchicine. An Infrared Study of Colchicine Derivatives and Related Compounds[1,2]

BY G. P. SCOTT AND D. S. TARBELL*

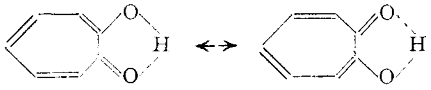
It was proposed by Dewar[3] that colchiceine (obtained from colchicine by dilute acid hydrolysis) and the mold metabolite, stipitatic acid, both contained the 2-hydroxycycloheptatrienone ring, the unknown parent compound being designated as "tropolone" (III). Colchicine and colchiceine were postulated to have structures I and II, respectively.



I Colchicine, R = CH_3
II Colchiceine, R = H



I-a

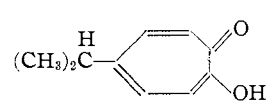


III, Tropolone

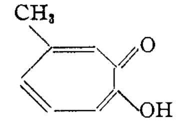
In colchicine resonance with the ionic form I-a was proposed to explain its unusually high solubility in water. In the tropolone ring itself, on the other hand, it was supposed that the active hydrogen was statically located between the two oxygen atoms in such a way that resonance was possible without zwitter-ion formation by shift of the double bonds and OH bonds as indicated. Subsequently, interatomic distance calculations showed that for this non-ionic type of resonance to occur the OH bond would have to be stretched.[4] A highly mobile tautomeric system of two forms, each having the ionic type of resonance, was suggested as an alternative.

Chemical evidence has recently been obtained in support of formulas I and II.[4a] Moreover, the tropolone ring has been conclusively shown to exist in α, β and γ-thujaplicin,[5] and the related benzotropolone system has been definitely established in purpurogallin.[6]

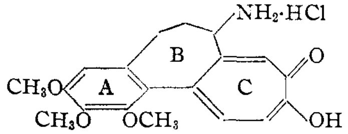
It was the purpose of the present investigation to compare the infrared spectra of colchicine and its derivatives with those of compounds known to have the tropolone structure, in order to secure further evidence as to the correctness of structures I and II. The tropolone derivatives studied were γ-thujaplicin[5,7] (IV) and β-methyltropolone[8,9] (V). In order to determine which features of the infrared spectra of colchicine derivatives were due to ring C, the spectra of trimethylcolchicinic acid hydrochloride[10] (VI), which lacks the N-acetyl group, and two reduction products of colchiceine[2] VII and VIII, were obtained. The region examined was from 1250 to 1800 cm.$^{-1}$ (8.0 to 5.5μ) since most of the bands known to arise from unsaturated carbon groups generally occur here. In addition, the spectra of colchiceine and γ-thujaplicin were measured up to 3800 cm.$^{-1}$ (2.6μ) to observe the C–H, N–H and O–H stretching frequencies. A series of simple seven-ring ketones was also studied in the carbonyl band region (1600 to 1750 cm.$^{-1}$) for



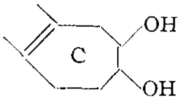
IV
γ-Thujaplicin



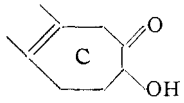
V
β-Methyltropolone



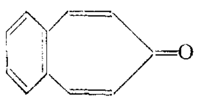
VI
Trimethylcolchicinic acid hydrochloride



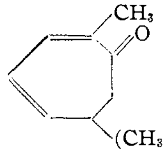
VII
Hexahydrocolchiceine



VIII
Tetrahydrocolchiceine



(IX)



(X)

---

* Harvard University Ph.D. 1937.

[1] Aided by a grant from the National Institute of Health.

[2] Previous paper in this series, Arnstein, Tarbell, Scott and Huang, THIS JOURNAL, **71**, 2448 (1949).

[3] Dewar, *Nature*, **155**, 50, 141 (1945).

[4] Dewar, *ibid.*, **155**, 479 (1945).

[4a] Polarographic evidence in support of the tropolone structure has been reported by Santavy, *Collection Czechoslovak. Chem. Commun.*, **14**, 145 (1949).

[5] (a) Erdtman and Gripenberg, *Acta Chemica Scandinavia*, **2**, 625 (1948); (b) Gripenberg, *ibid.*, **2**, 639 (1948); (c) Anderson and Gripenberg, *ibid.*, **2**, 644 (1948).

[6] Haworth, Moore and Pauson, *J. Chem. Soc.*, 1045 (1948); *cf.* Barltrop and Nicholson, *ibid.*, 116 (1948).

[7] We are greatly indebted to Professor H. Erdtman, Royal Technical Institute, Stockholm, for the sample of γ-thujaplicin.

[8] The preparation of this compound by degradation of purpurgallin is described by Haworth (ref. 6). The tropolone structure appears definitely established.

[9] The designation of substituted tropolones as α, β or γ follows Erdtman and Gripenberg.[5a]

[10] Zeisel, *Monatsh.*, **9**, 1 (1888).

TABLE I

PREPARATION OF MATERIALS

Compound	Method of preparation	Method of purification	M. p., °C.
Colchicine	U. S. P.	Chromatography and recrystallization from ethyl ac.	154–156[a]
Colchiceine	Ref. 2	Recrystallization from ethyl acetate and ether	174–175[b]
Trimethylcolchicinic acid·HCl	[c]	Recrystallization from water	180–190 dec.[c]
Hexahydrocolchiceine	Ref. 2	Recrystallization from dry methanol and ether	202–204[d] (uncor.)
Tetrahydrocolchiceine	Ref. 2	Not recrystallized[n]	
γ-Thujaplicin	Ref. 7	Sublimation and recrystallization from petroleum ether	79–80[e]
β-Methyltropolone	Ref. 6	Same as above	75.5–77[f]
Cycloheptanone	[g]	Fractionation and bisulfite addition product	n^{20}D 1.4613[h]
2,3-Benzocycloheptanone	[i]	Fractionation	n^{15}D 1.5670[i]
2,6,6-Trimethylcycloheptadiene-2,4-one (eucarvone)	[j]	Fractionation and recrystallization of the semicarbazone	n^{19}D 1.5110[k]
4,5-Benzocycloheptadiene-2,7-one	[l]	Sublimation and recrystallization from petroleum ether	69–70[l]
2-Chlorocycloheptanone	[m]	Fractionation	n^{20}D 1.4870

[a] Ashley and Harris, *J. Chem. Soc.*, 677 (1944), report m. p. of 155° for chromatographed colchicine. [b] Reported m. p. (ref. 2), 175–175.5°. [c] Zeisel, *Monatsh.*, **9**, 1 (1888), no m. p. reported. [d] Reported m. p. (ref. 2), 205–206° (uncor.). [e] Reported m. p. (ref. 5a), 82°. [f] Reported m. p. (ref. 6), 76°. [g] Kohler, Tishler, Potter and Thompson, THIS JOURNAL, 61, 1057 (1939). [h] Wallach, *Ann.*, **353**, 331 (1907), reported n^{21}D 1.4604. [i] Plattner, *Helv. Chim. Acta*, **27**, 804 (1944); n^{13}D 1.5650 is reported. [j] Wallach, *Ann.*, **339**, 104 (1905). [k] Auwers and Eisenlohr, *J. prakt. Chem.*, **84**, 80 (1911), report n^{20}D 1.5104. [l] Thiele and Weitz, *Ann.*, **377**, 1 (1910); reported as yellow, m. p. 66–67°. Our sample was white after sublimation. [m] Steadman, THIS JOURNAL, 62, 1606 (1904); n^{20}D reported, 1.4870. [n] The amorphous compound was not subjected to heat, but the methanol was thoroughly removed by repeated addition of chloroform followed by vacuum evaporation.

information as to the effect of conjugation and substitution on the carbonyl frequency. These compounds included, in addition to cycloheptanone, its 2-chloro and 2,3-benzo derivative, the unsaturated ketones, 4,5-benzocycloheptadienone (IX) and the trimethylcycloheptadienone, eucarvone (X).

Experimental

Measurement of Infrared Spectra.—Percentage transmission curves were plotted from the sample and solvent tracings obtained with a Perkin–Elmer single beam recording infrared spectrometer (model 12-071), using a rock salt prism. The figures in parentheses indicate the slit-widths (in mm.) used for the indicated frequency range (in cm.$^{-1}$): 1200–1400 (0.116); 1400–1530 (0.100); 1530–1700 (0.088); 2270–2930 (0.049); 2930–4380 (0.045).

Preparations of Materials.—The methods of preparing the compounds used are indicated in Table I.

Discussion of Results

Inspection of Table II and the curves in Fig. 1 indicates some correlations of structure with absorption bands. The band at 1675 cm.$^{-1}$ (5.97μ) in colchiceine is present in all its derivatives except trimethylcolchicinic acid hydrochloride and can therefore be assigned to the amide carbonyl group. This frequency agrees well with those found by Richards and Thompson[11] for the carbonyl stretching frequency of monoalkyl amides in chloroform solution. The band present in all derivatives at 1488–1492 cm.$^{-1}$ (6.72–670 μ) must be the lower of the two well known aromatic ring frequencies[12] arising from ring A. The upper band is evident in the reduced compounds at 1598 cm.$^{-1}$ (6.26μ) and in colchicine at 1590 cm.$^{-1}$ (6.28μ), but is apparently obscured in colchiceine and trimethylcolchicinic acid hydrochloride by a stronger band at 1613 cm.$^{-1}$ (6.19μ). Bands between 1350 and 1480 cm.$^{-1}$ are probably due to various hydrogen bending frequencies[12]. Most significant, however, are those bands which appear in colchiceine and trimethylcolchicinic acid hydrochloride, but are absent in the reduced compounds, since the

TABLE II

INFRARED BANDS IN THE 1250–1800 CM.$^{-1}$ REGION[b]

	Colchiceine				γ-Thujaplicin IV		β-Methyltropolone V	
Colchicine	Free	Acid[a] HCl	Hexahydro	Tetrahydro	In[c] CHCl$_3$	In[d] CCl$_4$	In[c] CHCl$_3$	In[d] CCl$_4$
..	..	..	..	1710	..	..	..	..
1674	1675	..	1659	1670	..	..	..	..
1618	1613	1614	..	..	1618	1624	1612	1620
1594	..	..	1598	1598	..	..	..	..
1558	1548	1542	..	..	1552	1567	1547	1556
1490	1490	1492	1488	1492	..	..	..	..
1464	1458	1464	1459	1459	1466	1472	1474	1470
1435	..	..	..	..	1440	1441	1447	1446
1400	1405	1405	1403	1404	1396	1398	1394	1398
1370	..	1380	..	..	1367	1367	1360	1360
1350	1354	1352	..	..	..	..	..	..
1325	1326	1328	1324	1325	..	..	..	..
1290	..	1296	..	..	1287	1290	1290	1286
..	1280	1280	..	..	1267	1258	1268	1257
1256	..	..	..	..	..	..	..	..

[a] Trimethylcolchicinic acid·HCl. [b] Solvent chloroform, unless otherwise stated; cell thickness 0.076 mm., unless stated; concentrations 2.6–5.4%. [c] Cell thickness, 0.152 mm. [d] Cell thickness, 0.127.

---

(11) Richards and Thompson, *J. Chem. Soc.*, 1248 (1947).

(12) (a) Barnes, Gore, Stafford and Williams, *Anal. Chem.*, **20**, 402 (1948); (b) Thompson, *J. Chem. Soc.*, 328 (1948); (c) Barnes, Gore, Lidell and Williams, "Infrared Absorption Spectroscopy," Reinhold Publishing Corp., New York, N. Y., 1944.

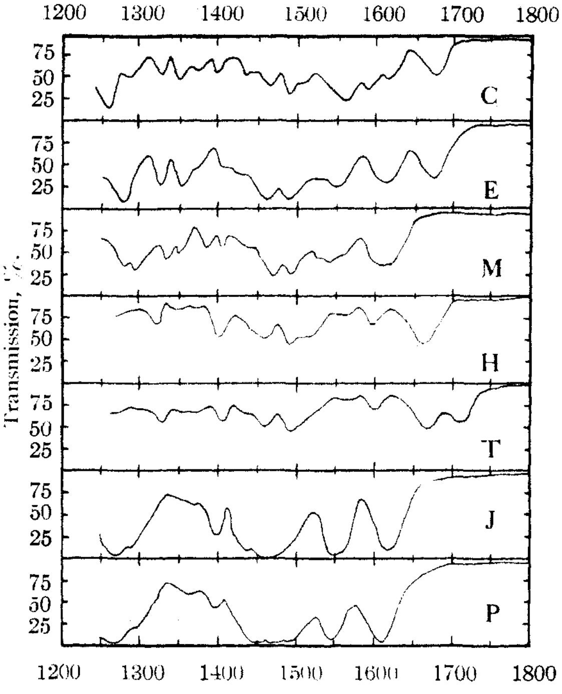


Fig. 1.—Infrared absorption spectra of colchicine derivatives and related compounds in chloroform solution: C, colchicine; E, colchiceine; M, trimethylcolchicinic acid hydrochloride; H, hexahydrocolchiceine; T, tetrahydrocolchiceine; J, γ-thujaplicin; P, β-methyltropolone.

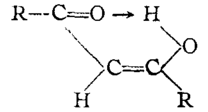
latter differ from the former primarily by the absence of the unsaturated resonant system of ring C. Thus, the bands at 1613–1614 cm.$^{-1}$ (6.19μ), 1548–1543 cm.$^{-1}$ (6.46–6.48μ), 1280 cm.$^{-1}$ (7.81μ) (a doublet in the amine salt), and possibly also the band at 1354 cm.$^{-1}$ are related to this system. As might be expected, these same bands appear in colchicine at somewhat different frequencies and relative intensities.[13]

Turning then to the spectra of γ-thujaplicin and β-methyltropolone (Figure IF and G and Table II), two striking facts appear: first, that the two compounds resemble each other very closely throughout nearly the entire range (1250–1800 cm.$^{-1}$), which is of some interest in itself, because the structure of the latter has thus far rested on somewhat indirect evidence; second, that these tropolone compounds possess strong bands at 1618–1612 cm.$^{-1}$ (6.17–6.19μ), 1552–1547 cm.$^{-1}$ (6.44–6.46μ), and strong doublets at 1267, 1287–1268, 1290 cm.$^{-1}$ (7.89, 7.76μ), which correlate well with the bands mentioned above as related to ring C in colchiceine. (There are also weak bands at 1367–1360 cm.$^{-1}$) These similarities may be accepted as substantial evidence in further support of the presence of the tropolone ring in colchiceine.

A further interesting band is noted at 1710 cm.$^{-1}$ (5.78μ) in the spectrum of tetrahydrocolchiceine. This product is prepared from colchiceine by the absorption of exactly two moles of hydrogen using a palladium–charcoal catalyst.[2] Although it has not been made to crystallize and is probably a mixture, its ketonic nature has been demonstrated by the preparation of a 2,4-dinitrophenylhydrazone.[2] The band at 1710 cm.$^{-1}$ can therefore be assigned to the carbonyl stretching frequency of the α-hydroxy ketone structure which must be present in this product. While this value is significantly higher than the value of 1699 cm.$^{-1}$ (5.88μ) (Table III) found for cycloheptanone,[14] the value of 1715 cm.$^{-1}$ (5.82μ) for the 2-chloro derivative shows that an electron-attracting group in the α-position could easily account for this difference.[14a]

The definite assignment of bands to specific linkages of the tropolone ring presents certain difficulties. The absence of any band in the usual carbonyl range (1670–1720 cm.$^{-1}$) may be explained in two ways. It is well known[15] that conjugation of a carbonyl group with unsaturated groups or with aromatic rings lowers the carbonyl frequency; this is emphasized in Table III, particularly by benzocycloheptadienone (IX)[16] with a band at 1641 cm.$^{-1}$ The complete conjugation of the tropolone ring may lower the normal carbonyl frequency to the range 1612–1620 cm.$^{-1}$ observed in this series.

An alternative explanation is based on the observation[17] that enolic compounds like acetylacetone XI show a very strong band at frequencies (1639–1538 cm.$^{-1}$) below the usual carbonyl range.



XI

This absorption is evidently associated with the presence of the conjugated chelate ring, because it disappears if chelation is prevented by acetylation. In the colchicine series, the band in the 1620 cm.$^{-1}$ region does not appear to be much more intense than the other bands, and it is still present in colchicine itself, which, being a methyl ether, cannot chelate.

---

[13] There is a possibility (suggested by the reviewer) that the 1548 cm.$^{-1}$ band in colchiceine and trimethylcolchicinic acid hydrochloride may be due to the N-acetyl and the –NH$_3^+$ groups respectively, rather than to ring C. However, there are no strong bands near this frequency in the reduced compounds.

[14] For comparable Raman bands in cycloheptanones see D. Biquard, *Bull. soc. chim.*, [5] **7**, 894 (1940), and Godchot and Cauquil, *Compt. rend.*, **208**, 1065 (1939).

[14a] Recent work by Gutsche (This Journal, **71**, 3513 (1949)) shows that the chlorocycloheptanone prepared by ring enlargement of 2-chlorocyclohexanone is a mixture, consisting mainly of the 3-chloro compound, with a smaller proportion of the 2-chlorocycloheptanone.

[15] Hartwell, Richards and Thompson, *J. Chem. Soc.*, 1436 (1948).

[16] It is interesting to note that Thiele and Weitz, *Ann.*, **377**, 1 (1910), were unable to prepare carbonyl derivatives from this compound.

[17] Rasmussen, Tunnicliff and Brattain, This Journal, **71**, 1068 (1949).

TABLE III

ADSORPTION OF SOME SEVEN-RING KETONES IN THE CARBONYL REGION (1750–1600 CM.$^{-1}$)[a]

Compound	Band minima, cm.$^{-1}$
Cycloheptanone	1699
2-Chlorocycloheptanone	1715
2,6,6-Trimethylcycloheptadiene-2,4-one (X)	1661 1603
2,3-Benzocycloheptanone	1683 1602
4,5-Benzocycloheptadiene-2,7-one (IX)[b]	1641 1603

[a] Measurements made on the pure liquid except as indicated. [b] Measured in carbon tetrachloride.

TABLE IV

γ-THUJAPLICIN AND COLCHICEINE IN THE 2800–3800 CM.$^{-1}$ REGION (BAND MINIMA (CM.$^{-1}$))

γ-Thujaplicin in carbon tetrachloride[a]	Colchiceine	
	in chloroform[b]	in benzene[c]
2958	3010	2990
3196	3265	3265

[a] Concentration, 3.9 and 1.2%. [b] Concentration, 6.5%. [c] Saturated (1%).

It would appear, therefore, that the lowered frequency of the carbonyl band in the tropolone compounds is due to conjugation rather than to the presence of a chelate ring like XI. It is true that the curves of colchiceine and γ-thujaplicin in the higher frequency region (Fig. 2A and B, and Table IV) show no bands above 3500 cm.$^{-1}$ (below 2.86μ) as would be expected of a completely unbonded O–H. However, the β-diketones mentioned above, gave bands only at much lower wave numbers (2703 cm.$^{-1}$) than the bands found in colchiceine and γ-thujaplicin at 3196 and 3265 cm.$^{-1}$, respectively.

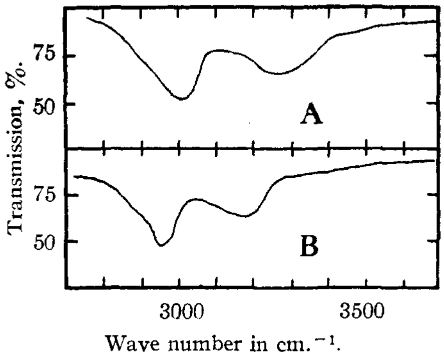


Fig. 2.—A, Colchiceine in chloroform and B, γ-thujaplicin in carbon tetrachloride in the 3μ region.

The bands at 1547–1552 cm.$^{-1}$ (6.89μ) in the tropolone compounds may be analogous to bands at about 1570 cm.$^{-1}$ (6.37μ) found by Gunthard and Plattner[18] in azulenes. The bands in the region 1250 to 1300 cm.$^{-1}$ (7.69 to 8.0μ) may arise from the enol C–O bond, the frequency being raised still higher than is the case in phenols (1200 to 1250 cm.$^{-1}$)[12a] by conjugation.

Summary

Infrared absorption spectra of colchicine and five of its derivatives have been investigated together with those of γ-thujaplicin and β-methyltropolone. Some characteristic bands have been found, and it is considered that the results are in agreement with the Dewar formula for ring C of colchicine. The carbonyl bands for several seven-ring ketones have also been measured.

(18) Gunthard and Plattner, *Helv. Chim. Acta*, **32**, 284 (1949).

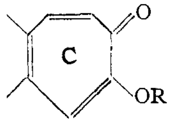
ROCHESTER, NEW YORK RECEIVED APRIL 27, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

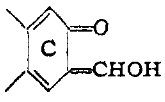
Studies on the Structure of Colchicine. Reduction Products from Ring C[1]

BY ALEXANDER D. KEMP AND D. STANLEY TARBELL*

Evidence has been presented in preceding papers[2] which supports the Dewar "tropolone" structure (I)[3] for ring C of colchicine, as against the Windaus formula (III).[4] It was shown by periodate oxidation studies that hexahydrocolchiceine is a 1,2-glycol[2a]; furthermore, infrared studies on colchicine derivatives showed marked similarities to the spectra of compounds known to contain the tropolone ring.[2a,5] However, direct degradative studies on ring C to establish the position of the oxygen functions relative to ring B, and to provide additional evidence of the presence of the seven-membered ring, were obviously desirable.



I, R = CH_3
II, R = H



III

Some catalytic reduction products from ring C described by Bursian[6] appeared to be suitable starting materials for such degradative studies.

---

* Harvard University Ph.D. 1937.

(1) Aided by a grant from the National Institute of Health.

(2) (a) Arnstein, Tarbell, Scott and Huang, THIS JOURNAL, **71**, 244 (1949); (b) Scott and Tarbell, *ibid.*, **72**, 240 (1950).

(3) Dewar, *Nature*, **155**, 141, 479 (1945).

(4) Windaus, *Ann.*, **439**, 59 (1924).

(5) (a) Erdtman and co-workers, *Acta Chem. Scandinavia*, **2**, 625, 639, 644 (1948); (b) Haworth, Moore and Pauson, *J. Chem. Soc.*, 1045 (1948).

(6) Bursian, *Ber.*, **71**, 245 (1938).