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UNUSUAL SPECTRAL BEHAVIOR OF MONASCAMINE, ISODIHYDROMONASCAMINE AND MONASCAMINONE

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Abstract—The IR and UV spectra of monascamine and isodihydromonascamine are complicated in that they are extremely sensitive to conditions of spectroscopic measurements and this has been attributed to keto-enol equilibria. The unusual effects of alkyl substituents on the UV spectra of an 8-hydroxyisoquinoline derivative, dihydromonascaminone, is discussed.

Monascamine and N-*methylmonascamine*

THE IR spectra of monascamine in various media (Table 1) all showed three main absorptions at about 1735, 1710 and 1625 cm^{-1} in the 1740–1610 cm^{-1} region. Since the three bands were also present in N-methylmonascamine (Ik, R = Me), which has a fixed ketonic structure, it is apparent that monascamine exists in form Ik (R = H) under the conditions of measurements. The presence of cross-conjugated vinylogous amide structures in the monascamine molecule would give rise to mixing of fundamental vibrations and a one-to-one correspondence between the peaks and mode of vibrations is not feasible. However, if the three bands in order of decreasing frequencies are assigned to the lactone, side-chain ketone and annular ketone, respectively, the complicated IR spectra of monascamine and derivatives can be qualitatively correlated with keto and enol tautomers in quite a satisfactory and simple manner. The conclusions drawn from IR results are also consistent with the UV results. The chloroform solution of monascamine was anomalous under both IR and UV conditions but the cause for this is not clear.

The IR spectrum of monascamine hydrochloride also exhibits three peaks; furthermore, the N^+–H stretching region is of the secondary ammonium salt type,[1] and the so-called immonium band around 2000 cm^{-1} characteristic for the pyridinium type salts[2] is missing. The hydrochloride of N-methylmonascamine also showed three carbonyl peaks and a tertiary ammonium type spectrum. Accordingly, both hydrochlorides exist simply as the nitrogen-protonated Ik form, that is as Ik (R = H or CH_3).

The chloroform solution of monascamine was peculiar in that the IR spectrum only showed two peaks at 1713 and 1623 cm^{-1} in the specified region (Fig. 1). When increasing amounts of chloroform was added to a tetrahydrofuran solution, the intensity of the highest frequency peak (1738 cm^{-1}, Table 1) gradually decreased until it finally disappeared. However, a sample of monascamine recovered from chloroform still showed the three peaks under conditions other than in chloroform, and this meant that no chemical transformation had occurred. Although the conjugate-chelated form Ie could account for the absorption in chloroform, this is not considered to be the

[1] K. Nakanishi, T. Goto and M. Ohashi, *Bull. Chem. Soc. Japan* **30**, 403 (1957).
[2] B. Witkop, *J. Amer. Chem. Soc.* **76**, 5597 (1954).

case since there is no reason that the less polar Ie form should predominate in chloroform while the more polar Ik form (R = H) predominates in the less polar carbon tetrachloride. Even if structure Ie were not the correct representation for the other modification of monascamine, the fact that the same type of spectra are obtained with the KBr disk and the carbon tetrachloride solution, whereas a different spectrum is obtained in chloroform, which has an intermediary polar environment, cannot be explained on the basis of the polarity of media. Whatever the reason may be, the conspicious difference in the carbonyl region between carbon tetrachloride and chloroform solution spectra (Fig. 1) is quite an unusual phenomenon.

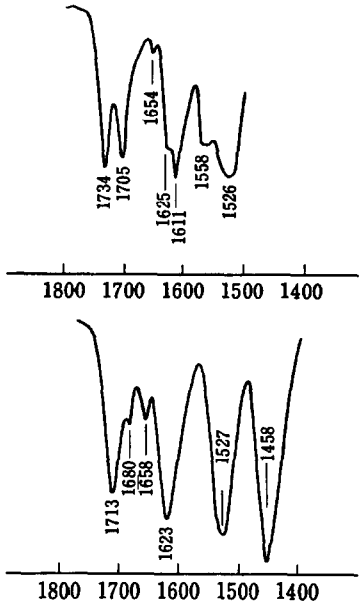


FIG. 1. IR spectra of monascamine
(a) in CCl_4
(b) in $CHCl_3$

The UV spectra of monascamine (Table 2; see also Fig. 2) were confusing because they depended on concentration, water content (i.e., the spectra in absolute and 98% methanol differed), and in certain cases on the time after preparation of the solution (chloroform). Characteristic absorption peaks for the keto and enol forms were sorted out (Chart 1), and interpretation based on these peaks are given in the last column of Table 2.

The peaks of N-methylmonascamine (Fig. 2, curve 4) at 427 and 502 mμ are clearly due to the keto form (Ik, R = Me). It follows that the similar UV spectrum of monascamine in concentrated methanol ($6{\cdot}35 \times 10^{-5}$ mole/l.; Fig. 2, curve 1) also arises from Ik (R = H). However, a most unexpected phenomenon was encountered with concentration variation. In the $3{\cdot}11 \times 10^{-5}$ mole/l. solution the keto peak had disappeared (Fig. 2, curve 2), which showed that the enol form Ie is the only species involved. Under further dilution to $1{\cdot}24 \times 10^{-5}$ mole/l. the curve reverted to the keto type and finally at $4{\cdot}95 \times 10^{-6}$ mole/l. the curve was of the enol type. The changes

were accompanied by the appearance of one set of isosbestic points at 234, 278, and 380 mμ (log e 4·08, 4·18, and 3·92). Although the changes themselves were reproducible, the concentrations under which the change in type occurred were not exactly reproducible and probably another factor is involved. This aspect is being studied further but at the moment it can only be stated that under dilute and concentrated conditions monomeric enol and polymeric keto forms are involved, and that under intermediary conditions a complicated equilibrium between different molecularities is operating. A 2·56 $\times$ 10^{-5} mole/l. solution of monascamine in 0·1 N HCl–90% EtOH

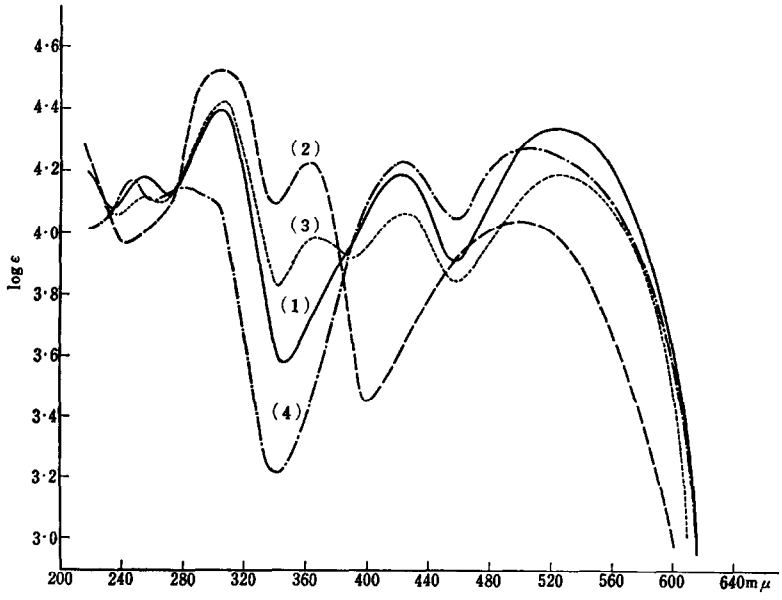


FIG. 2. Ultraviolet absorption spectra of monascamine

(1) in abs MeOH, 6·35 $\times$ 10^{-5} mole/l.
(2) in abs MeOH, 3·11 $\times$ 10^{-5} mole/l.
(3) in 95% EtOH, 2·60 $\times$ 10^{-5} mole/l.
(4) N-Me-deriv. in 95% EtOH
2·56 $\times$ 10^{-5} mole/l.

was completely ketonic (Table 2). Upon acidification of the solution with hydrochloric acid, the 535 mμ peak became weaker while the 425 mμ peak was slightly intensified with appearance of an isosbestic point at 480 mμ (log e 4·0); in a 1·2 N HCl solution* the 535 mμ peak had disappeared (Table 2). The behavior of the N-methyl derivative was exactly parallel (Table 2). In view of the existence of the solid hydrochlorides in keto form IIk (IR data), apparently it is this species that predominates in the acidic ethanol solution (hence N-protonation rather than O-protonation, which would give IIe). See Table 2 for effect of H_2O on UV of monascamine in MeOH.

* We are indebted to the referee for suggesting usage of a more concentrated HCl solution.

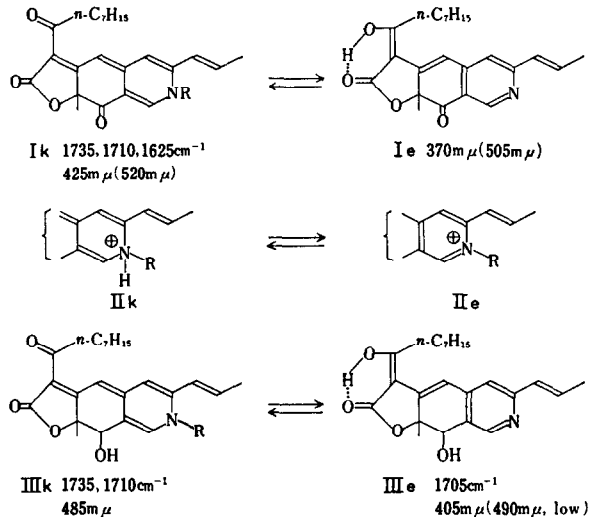


Chart I. Characteristic IR and UV peaks for tautomers of monascamine and derivatives

(UV peaks in parentheses are the non-characteristic peaks above 340 mμ)

TABLE 1. CARBONYL ABSORPTION OF MONASCAMINE*

Compound	Medium				Form
Monascamine	KBr	1736	1705	1625	Ik
	CCl_4	1734	1705	1611	Ik
	THF	1738	1711	1628	Ik
	abs. MeOH	1720	1708	1613	Ik
	$CHCl_3$	1713		1623	?
Monascamine hydrochloride	KBr	1745	1718	1611	IIk
N-Methylmonascamine	KBr	1731	1716	1623	Ik
	CCl_4	1734	1712	1640	Ik
	$CHCl_3$	1728	1712	1634	Ik
N-Methylmonascamine hydrochloride	KBr	1750	1727	1623	IIk
Isodihydro-monascamine	Nujol	1740	1700		IIIk
	KBr	1703			IIIe
Isodihydromonascamine hydrochloride	Nujol	1715			IIe
	KBr	1745	1725		IIk
N-Methyl-isodihydro-monascamine	$CHCl_3$	1725	1708		IIIk
N-Methyl-isodihydro-monascamine hydrochloride	KBr	1740	1720		IIIk

* All compounds listed in the Table showed weak~medium bands at ca. 1650 cm^{-1} due to the side-chain double bond.

TABLE 2. ULTRAVIOLET MAXIMA (in mμ and log ε)

Compound	Solvent	Conc ($\times 10^{-5}$ mole/1.)	Maxima	Form (enol %)*
Monascamine	abs MeOH	6·35	*258(4·18)*, 304(4·40), **420(4·18)**, 520(4·27)	Ik
	abs MeOH	3·11	*260(4·02)*, 303(4·52), **364(4·23)**, 500(4·05)	Ie
	50% MeOH	3·11	*260(4·05)*, 305(4·47), **363(4·05)**, **417(3·96)**, 515(4·16)	Ik, Ie (60)**
	20% MeOH	3·11	*260(4·08)*, 305(4·45), ***364(3·94)***, **408(4·09)**, 513(4·20)	Ik, Ie (45)**
	95% EtOH	2·60	253(4·13), 304(4·44), **371(4·00)**, **426(4·09)**, 528(4·22)	Ik, Ie (35)**
	0·1N HCl–90%EtOH	2·56	253(4·23), 305(4·33), **423(4·29)**, 535(4·27)	Ik
	1·2N HCl–90%EtOH	2·56	244(4·40), 320(4·11), 427(4·13)	IIk
N-Methyl-monascamine	95% EtOH	2·56	248(4·18), 278(4·15), *294(4·13)*, **427(4·23)**, 502(4·28)	Ik
	0·1N HCl–90%EtOH	2·56	248(4·11), 280(4·13), *295(4·11)*, **423(4·26)**, 503(4·14)	Ik
	1·2N HCl–90%EtOH	3·81	280(4·09), 420(4·24)	IIk
Isodihydro-monascamine	95% EtOH	2·61	238(4·25), 295(4·21), **400(3·91)**, **488(4·55)**	IIIk, IIIe (60)
	95% EtOH	0·26	287(4·44), **400(4·34)**, **492(3·70)**	IIIe
	0·1N HCl–90% EtOH	4·31	245(4·31), 293(4·13), 406(4·39), 483(3·87)	IIk, IIIk
	1·2N HCl–90% EtOH	2·86	244(4·50), 290(4·23), 402(4·45)	IIk
N-Methylisodihydro-monascamine	95% EtOH	2·56	261(4·16), *285(4·08)*, **483(4·56)**	IIIk
	0·1N HCl–90% EtOH	2·56	250(4·14), *285(4·01)*, 407(4·16), 475(3·82)	IIk, IIIk
	1·2N HCl–90% EtOH	2·42	240(4·29), 300(4·10), 402(4·20)	IIk

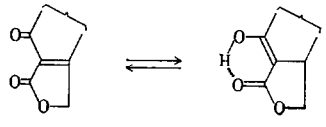
Bold figures refer to characteristic peaks for free keto and enol forms; italicized figures are shoulders.

* Position of the equilibrium was estimated by taking, for example curves (1) and (2) of Fig. 2, as reference curves for the keto and enol forms respectively.

** Enol content decreases with increasing amounts of water. This is in agreement with polarity considerations of structures Ik and Ie.

Isodihydromonascamine and N-*methylisodihydromonascamine*

The reaction of sodium borohydride on monascamine and N-methylmonascamine both resulted in the reduction of one carbonyl group to give the isodihydro compounds. Although there is a choice between three carbonyl groups that could have been affected, the NMR evidence was only compatible with the reduction of the annular ketone.[3] N-methylisodihydromonascamine, having no tautomerizable hydrogen atom, can be represented by the fixed structure IIIk (R = Me), and showed two carbonyl peaks at 1725 and 1708 cm^{-1} arising from the lactone and side-chain ketone, respectively (Table 1). The KBr disk spectrum of isodihydromonascamine, on the other hand, surprisingly revealed only one peak at 1703 cm^{-1}, which suggested that it existed as form IIIe and not as form IIIk (R = H) under the conditions. Because this was incompatible with the results of UV measurements that showed the keto form to be the more favored under concentrated conditions (hence, in the KBr disks), the solvent was evaporated from an ethanol solution and the IR spectrum of the residue was carefully measured in nujol. As expected, two peaks corresponding to the keto form were observed at 1740 and 1700 cm^{-1}; when this IIIk (R = H) modification of isodihydromonascamine was either ground in nujol for 10 minutes or made into KBr disks it was converted into the more stable enol modification (IIIe, 1703 cm^{-1}) mentioned above. A similar conversion, but in the opposite direction, was encountered with the hydrochloride. Namely, if a nujol mull of the hydrochloride is prepared without much grinding, a single peak at 1715 cm^{-1} is accompanied by ammonium and immonium bands (form IIe, R = H), but if the mull is ground for about 10 minutes or a KBr disk is prepared, the immonium band disappears and two carbonyl peaks are revealed at 1745 and 1725 cm^{-1} (form IIk, R = H). Thus interestingly, in the free base the enol form (IIIe) is the more stable, while in the hydrochloride the keto form (IIk, R = H) is the more stable. Although these transformation cannot strictly be regarded as occurring in the solid phase because of the participation of the paraffin oil or potassium bromide solution, a similar solid phase interconversion of keto and enol forms has recently been reported for hydroxyphenazines.[4]



The UV data were interpreted similarly by taking the 483 mμ band of the free N-methyl compound to be diagnostic for the keto form (IIIk, R = Me). Tautomerism depending on concentration took place in the ethanol solution of isodihydromonascamine as shown in Fig. 3; keto form IIIk (R = H) was predominant in concentrated solutions, and *vice versa.*

Since the band at 492 mμ (Fig. 3, curve 1) remained constant in solutions of lower concentration, although with an intensity (log *e* 3·70) much lower than the ca. 485 mμ keto form band (log *e* ca. 4·60), this band as well as the 400 mμ band are both regarded to originate from the enol form (IIIe). The behavior of isodihydromonascamine and

[3] Preceding paper.
[4] A. G. Cairns-Smith, *J. Chem. Soc.* 182 (1961).

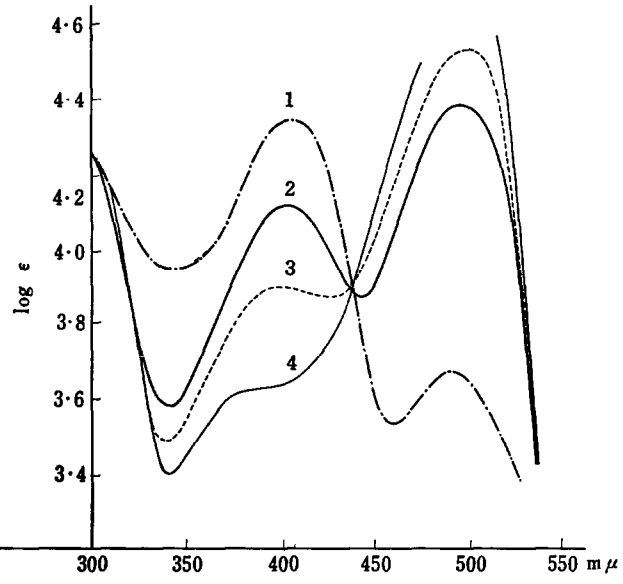
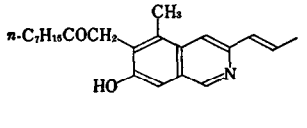


FIG. 3. UV spectra of isodihydromonascamine (95% EtOH)
(1) 0·26 × 10^{-5} mole/l.
(2) 1·3 × 10^{-5} mole/l.
(3) 2·6 × 10^{-5} mole/l.
(4) 5·2 × 10^{-5} mole/l.

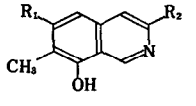
its N-methyl derivative in acidic ethanol were quite similar to those of the above-mentioned monascamine. Namely, intensities of the keto peaks at 485 mμ were reduced while those of the 405 mμ peak, were slightly intensified with appearance of isosbestic points at 435 mμ (log *e* 4·15) and 437 mμ (log *e* 4·00), respectively. Thus these hydrochlorides also exist in the N-protonated form IIk. Although the acidic dissociation constants of the hydrochlorides were not measured, the change in spectra upon acidification of solutions clearly showed (Table 2) that monascamine and its N-methyl derivative were weaker bases than the isodihydro compounds; this tendency is in qualitative agreement with expectations based on comparisons of structures Ik and IIIk.

Monascaminone

An attempt was made to establish the position of the hydroxyl group in monascaminone by comparing the UV spectra of monascaminone derivatives with model hydroxyisoquinolines.



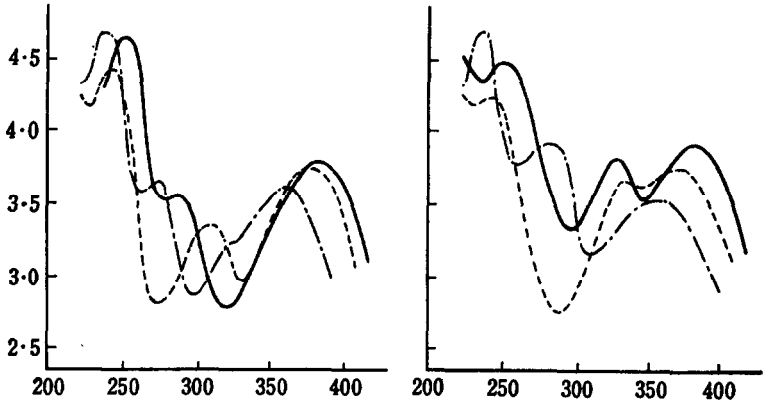
IV



V $R_1 = n\text{-}C_7H_{15}COCH_2-$; $R_2 = -CH=CH-CH_3$
VI $R_1 = n\text{-}C_7H_{15}COCH_2-$; $R_2 = -CH_2CH_2CH_3$
VII $R_1 = n\text{-}C_7H_{15}CHOHCH_2-$; $R_2 = -CH_2CH_2CH_3$

These results seemed to point out quite definitely to a 7-hydroxyisoquinoline nucleus, which meant that monascaminone should be IV, and this in turn led to a

structure for monascorubrin[5] that later was found to be incompatible with NMR results.[3] The correct structure for monascaminone is V. It has been shown[6] that, independent of ionic species involved, the spectra of various monohydroxyisoquinolines[6–8] monohydroxyquinolines,[7,8] their methyl ethers and methiodides, measured in neutral, acid and basic methanol could be divided into two classes. The azanaphthalenes with the oxygen function either at the α- or γ-position with respect to the ring nitrogen constitute a different type since they exist predominantly in the amide form in solvents of low dielectric constant.[7–10] The conditions of measurements were chosen so that an equilibrium between species with different net charge need not



(a) 0·1*N* HCl–MeOH (b) 0·1*N* NaOH–MeOH

FIG. 4. UV spectra of dihydromonascaminone and models
——— Dihydromonascaminone
— - - — 7-Hydroxyisoquinoline
- - - - 8-Hydroxyisoquinoline

be taken into consideration; and the three major absorptions were named π_1, π_2 and π_3 in order of decreasing wave lengths. The two classes are the α- and β-naphthol types. In the α-naphthol type spectra the lowest trough is between the π_3 and π_2 bands; 5- or 8-hydroxyisoquinolines, 5- or 8-hydroxyquinolines and derivatives belong to this class (Fig. 4). In the β-naphthol type spectra the lowest trough is between the π_2 and π_1 bands; 7-hydroxyisoquinoline, 3-, 6-, or 7-hydroxyquinolines and derivatives belong to this class (Fig. 4). Exceptions to this generalization were: cations of the β-naphthol type quinolines (i.e., 3-, 6-, 7-hydroxy) in which the lowest trough is between the π_3 and π_2 bands;[7] 6-hydroxyisoquinoline and derivatives, which belonged to neither type presumably owing to contributions from canonical structures of an extended *p*-quinonoid form.

The spectra of dihydromonascaminone (VI), its methyl ether and the methiodide of dihydromonascaminol (VII) were measured under the conditions given in Table 3. Comparisons with spectra of models clearly showed that the possibility of the natural

[5] K. Nakanishi, M. Ohashi, S. Kumasaki and S. Yamamura, *J. Amer. Chem. Soc.* **81,** 6339 (1959).
[6] K. Nakanishi, M. Ohashi, S. Kumasaki and H. Koike, *Bull. Chem. Soc. Japan* **34,** 533 (1961).
[7] G. W. Ewing and E. A. Steck, *J. Amer. Chem. Soc.* **68,** 2181 (1946).
[8] S. Mason, *J. Chem. Soc.* 5010 (1957).
[9] G. F. Tucker and J. L. Irvin, *J. Amer. Chem. Soc.* **73,** 1923 (1951).
[10] A. Albert and J. N. Phillips, *J. Chem. Soc.* **1294** (1956).

TABLE 3. ULTRAVIOLET SPECTRA OF MONASCAMINONE DERIVATIVES

Compound	Solvent	Ionic species	λ_{max}(in mμ) π_3	π_2	π_1	log ε π_3	π_2	π_1	Type*
1. Dihydromonascaminone	N	neutral	239	288 / 343		4·68	3·53 / 3·69		β
2.	A	cation	255	288 / 385		4·56	3·46 / 3·69		β
3.	B	anion	254 / 326		383	4·42 / 3·72		3·79	α
4. Dihydromonascaminone methyl ether	B	neutral	234	269 / 332		4·58	3·54 / 3·52		β
5.	A	cation	247	284 / 360		4·63	3·51 / 3·76		β
6. Dihydromonascaminol methiodide	B	neutral 217	274	345 / 475	4·75	4·59	3·76 / 3·86		β
7.	A	cation 215	257	291 / 388	4·52	4·75	3·43 / 3·75		β

N : MeOH
A : 0·1N HCl–MeOH
B : 0·1N NaOH–MeOH
* : α- and β-naphthol type spectra
/ : Position of lowest trough

product derivatives having a 6-hydroxyisoquinoline structure could be dismissed, and the same was true for the 5-hydroxyisoquinoline structure. Thus the 7-hydroxy structure (β-naphthol type) and 8-hydroxy structure (α-naphthol type) remained to be considered, and as shown in Table 3, all spectra (e.g., Fig. 4a) excepting that of the dihydromonascaminone anion (Fig. 4b) apparently belonged to the β-naphthol type. Furthermore, it is obvious from Table 4, which lists the wave length shift of respective peaks from corresponding peaks of models, that when compared with the 7-hydroxyisoquinolines the peaks are located at longer wave length in every case, whereas when compared with the 8-hydroxy isomers a shift to shorter wave length is observed in the π_2 band (Fig. 4). All these evidences seemed to suggest a 7-hydroxyisoquinoline skeleton for monascaminone, which turned out not to be the case. Interestingly, the only curve in Table 3 that belonged to the alternative type, namely that of the anion of dihydromonascaminone (no. 3), was actually giving the correct suggestion. However, a closer inspection into the model curves indeed revealed that the most clearcut

TABLE 4. WAVELENGTH SHIFTS OF PEAKS (IN Mμ)

Compound	Ionic species	Δ 7–OH π_1	π_2	π_3	Δ 8–OH π_1	π_2	π_3
1. Dihydromonascaminone	neutral	15	10	10	6	−16	9
2.	cation	14	10	17	10	−22	9
3.	anion	16	37	16	7	−2	13
4. Dihydromonascaminone methyl ether	neutral	11	14	0			
5.	cation	6	9	6			
6. Dihydromonascaminol methiodide	neutral	9	37	51	11	−2	15
7.	cation	14	11	21	7	−24	10

differentiation between the α- and β-monohydroxyazanaphthalenes could be obtained from the spectra of anions rather than cations or neutral species.

It was attempted to ascertain the origin of π_2 bands by changing solvent polarity, but the behavior was anomalous in that the band split into two components; at the moment it is premature to give explanations.[11]

EXPERIMENTAL

Isodihydromonascamine hydrochloride. Conc hydrochloric acid was added to a solution of isodihydromonascamine in ethanol and the solvent was removed *in vacuo*. The residue was crystallized from a mixture of hydrochloric and aqueous ethanol to give yellow needles, m.p. 125° (Found: C, 63·7; H, 7·44; N, 3·01, $C_{23}H_{29}O_4N \cdot HCl \cdot H_2O$ requires: C, 63·1; H, 7·37; N, 3·20%). IR(KBr): 1745 and 1724; (nujol): 1715 and 1900 cm^{-1}. Isodihydromonascamine was recovered by treatment of the hydrochloride with sodium hydrogen carbonate.

Dihydromonascaminone methyl ether. A solution of monascamine methyl ether (0·35 g) in acetic acid (40 ml) was hydrogenated with platinum oxide (0·03 g) when 1 mole hydrogen had been consumed the solvent was removed and the residue purified by chromatography with benzene–ether (1:1) on alumina. Removal of the solvent gave dihydromonascaminone methyl ether as a syrup, which was crystallized from methanol containing a few drops of conc hydrochloric acid to give colorless needles, m.p. 124–126° (Found: C, 69·1; H, 9·18 ; N, 3·74; $C_{23}H_{33}O_2N \cdot HCl$ requires C, 70·4; H, 8·72; N, 3·57%). IR(KBr): 2900–2500, 2200, 2050, 1709, 1649, 1614 and 1583 cm^{-1}.

Monascaminone methiodide. A mixture of monascaminone (0·2 g) and methyl iodide (1·5 ml) was refluxed in acetone–benzene (20 ml, 1:1) for 3·5 hr. From the cooled solution the methiodide was obtained (0·22 g) m.p. 192–193° (ethanol) (Found: C, 54·9; H, 6·42. $C_{23}H_{32}O_2NI \cdot H_2O$ requires: C, 55·2; H, 6·45%). IR(nujol): 1713, 1632, 1606, 1569 and 1513 cm^{-1}.

Dihydromonascaminone methiodide. Dihydromonascaminone methiodide was prepared similarly as described for monascaminone methiodide, needles, m.p. 180–181° (Found: C, 54·9; H, 6·74. $C_{23}H_{34}O_2NI \cdot H_2O$ requires: C, 55·0; H, 6·83%). This material was converted into unstable red crystals by means of saturated aqueous sodium hydrogen carbonate, m.p. 123–125° (ether–pet ether) (Found: C, 70·6; H, 9·55; $C_{23}H_{33}O_2N \cdot 2H_2O$ requires: C, 70·6; H, 9·53%).

Dihydromonascaminol methiodide. Dihydromonascaminol methiodide was prepared similarly, m.p. 163–165° (ethanol) (Found: C, 56·6; H, 7·49. $C_{23}H_{36}O_2NI$ requires; C, 56·9; H, 7·50%). IR(KBr): 1645, 1610, 1567 and 1521 cm^{-1}.

The cinnoline derivative of monascaminone. Monascaminone was treated with benzene diazonium chloride according to the method described for rubropunctatin,[12] red needles, m.p. 194° (Found: C, 75·8; H, 7·09; N, 9·68; $C_{28}H_{31}ON_3 \cdot H_2O$ requires: C, 75·8; H, 7·50; N, 9·47%). IR(KBr): 3300, 1633, 1590 and 1483 cm^{-1}.

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[11] Recent unpublished calculations based on the perturbation theory by Dr. Y. Nishimoto, Osaka City University, have shown that substituents on position 6 of the 8-hydroxyisoquinoline nucleus are indeed expected to cause a blue shift in the band.

[12] E. J. Haws, J. S. E. Holker, A. Kelly, A. D. G. Powell and A. Robertson, *J. Chem. Soc.* 3598 (1959).