THERMAL DECOMPOSITION OF NARCEINE IMIDE METHOHYDROXIDE*

J.TROJÁNEK, Z.KOBLICOVÁ, Z.VESELÝ, V.SUCHAN and J.HOLUBEK

Research Institute for Pharmacy and Biochemistry, 194 04 Prague 9

Received April 16th, 1974

Dedicated to Professor F. Šantavý on the occasion of his 60th birthday.

Thermal decomposition of narceine imide methiodide (*II*) in the presence of 30% aqueous potassium hydroxide affords a mixture of (*Z*)- and (*E*)-narceone imides (*III*) and (*IV*) along with 10,11-methylenedioxy-3,4,12-trimethoxy-7,8-dihydro-5*H*-isoindolo[1,2-*b*] [3]benzazepin-5--one (*IX*) which was also obtained by cyclisation of (*Z*) or (*E*)-narceone imide (*III*) or (*IV*) in alkaline medium. In the thermal decomposition of narceine imide methohydroxide (*XVIII*), the resulting narceone imides *III* and *IV* are accompanied by a lesser amount of 7-methyl-9,10--methylenedioxy-3,4,11-trimethoxy-6,7-dihydro-5*H*-isoindolo[1,2-*b*]isoquinol-5-one (*XX*) which is also formed by cyclisation of the narceone imide *III* or *IV* in refluxing aqueous-methanolic hydrogen chloride. As a by-product of this cyclisation a substance is obtained of the probable structure *XXII*. The structures of particular compounds were inferred on the basis of chemical and spectral properties.

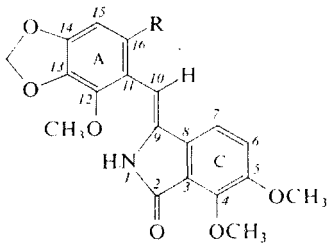
Some time ago, we have reported[1] on the isolation of narceine imide[2] (*I*) from mother liquors obtained in production of morphine by the ion exchange process. In connection with identification of this compound we were interested in the Hofmann degradation of its methohydroxide. In our hands, the whole process appeared more complex than observed by Freund and Michaels[2]. Our findings are the object of the present paper.

For the experiments, we have used the freshly crystallised narceine imide which is stable for a certain but not very long period of time and which represents the more stable (*Z*)-form[3] *I*. When boiled with methyl iodide, narceine imide afforded a high yield of the methiodide *II* which was then refluxed with 30% aqueous potassium hydroxide for 5 hours[2]. The reaction product was separated into portions insoluble (A) and soluble (B) in benzene. Crystallisation of portion A afforded two isomeric des-bases (brutto formula $C_{21}H_{19}NO_6$) which were assigned the structures of stereoisomeric (*Z*)- and (*E*)-narceone imides (*III*) and (*IV*) on the basis of chemical transformations (*vide infra*) and spectral analysis.

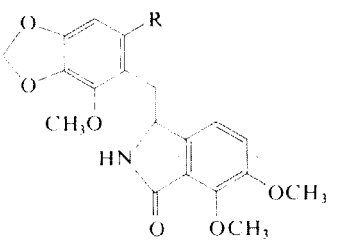
* Part XXXII in the series On Alkaloids; Part XXXI: This Journal *39*, 3168 (1974).

In accordance with the structures proposed, infrared spectra of des-bases *III* and *IV* exhibit characteristic absorption bands of the lactam system and of the NH group. Catalytic hydrogenation of compounds *III* and *IV* over a platinum catalyst in glacial acetic acid affords the same tetrahydronarceone imide *V* which is also formed by thermal decomposition of the methiodide *VI* (accessible from the dihydronarceine imide[1] *VII*) in the presence of 30% aqueous potassium hydroxide and the subsequent catalytic hydrogenation of the resulting dihydronarceone imide *VIII*. Structures of compounds *V*, *VI*, and *VIII* may be inferred from relations to the known[1] dihydronarceine imide *VII* as well as from spectral data. On the basis of these findings, the des-bases *III* and *IV* differ solely by the relative arrangement of substituents on the enamide double bond. The stereochemistry was inferred by means of NMR spectra, namely, by the chemical shift of vicinal protons on $C_{(6)}$ and $C_{(7)}$ carbon atoms occurring in both spectra as an AB quartet with the coupling constant of 9·0 Hz. The doublet signals of this system are situated at δ 7·52 and 7·16 p.p.m. in the spectrum of the predominating isomer (m.p. 210.5–212·0°C) while a shift to higher values of the magnetic field (6·92 and 6·62 p.p.m.) may be observed in the case of the minor isomer (m.p. 200–202°C). Such a shift may be explained only by shielding of the two vicinal protons (particularly of that on the $C_{(7)}$ carbon atom) by the aromatic ring A; as it follows from inspection of models, such a situation is possible in the case of the *E* isomer only. The higher-melting stereoisomer thus possesses the configuration *Z* (*III*) while the configuration *E* (*IV*) belongs to the lower-melting counterpart. The narceone imide specimen (m.p. 177·5–178·0°C) of Freund and Michaels[2] was most probably a mixture of the two stereoisomers. Concerning the geometric isomerism in the series of benzalphthalimidines see ref.[3].

Portion B (soluble in benzene) was subjected to column chromatography on alumina to afford a yellow substance with a green-yellow fluorescence under ultraviolet light and of the same brutto formula as compounds *III* and *IV*. Larger quantity of



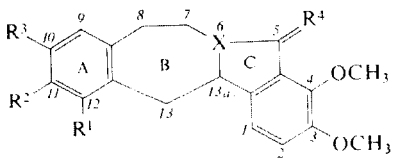
I, R = $(CH_2)_2N(CH_3)_2$
II, R = $(CH_2)_2N(CH_3)_3]^{(+)}\,I^{(-)}$
III, R = $CH{=}CH_2$
XVIII, R = $(CH_2)_2N(CH_3)_3]^{(+)}\,OH^{(-)}$



V, R = CH_2CH_3
VI, R = $(CH_2)_2N(CH_3)_3]^{(+)}\,I^{(-)}$
VII, R = $(CH_2)_2N(CH_3)_2$
VIII, R = $CH{=}CH_2$

this substance, named as des-base B_1, was isolated from a batch of the so called narcotine fraction obtained in the manufacture of morphine from poppy capsules. Most probably, the des-base B_1 is not a constant component of this fraction.

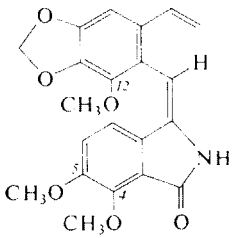
Ultraviolet spectrum of the des-base B_1 indicates the presence of an extensive conjugated system as also suggested by absorption bands of the conjugated N-substituted lactam grouping (1 690 cm^{-1}) and a conjugated double bond (1 642 cm^{-1}) in the corresponding infrared spectrum. It appears probable on the basis of these data and relations to the starting material that in the formation of the des-base B_1, the side chain of the quaternary ammonium iodide *II* got attached (after elimination of the basic function) to the nitrogen atom of the lactam grouping. Under this assumption, the final structure ought to be tetracyclic as established later on by means of both spectral and chemical evidence[4]. The NMR spectrum of the des-base B_1 exhibits signals of the methylenedioxy group, two methoxyl groups, and three aromatic protons situated almost in the same positions as in the spectrum[1] of narceine imide (*I*). On the other hand, some higher-field shifts may be observed of the singlet of the further methoxyl group (4·01 p.p.m.) and of the olefinic proton singlet (6·74 p.p.m.) as well as of the four-proton multiplet in the Ar—$\underline{CH_2}$—$\underline{CH_2}$—N system (3·10 to 2·80 p.p.m.). Finally, the NMR spectrum of the des-base B_1 lacks the signal of the lactam system proton and of the dimethylamino group protons in contrast to the spectrum of narceine imide (*I*). The presence of a C-methyl group in the molecule was thus unequivocally excluded by the NMR spectrum. In the choice between the 1-azabicyclo[5.3.0]decane or quinolizidine (in the case of an rearrangement) system, the former arrangement has been ascribed to the des-base B_1 (*IX*) by combination of chemical transformations and mass spectrometry.



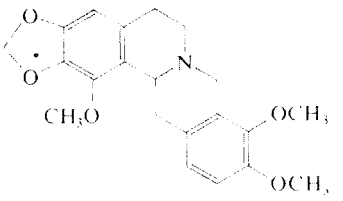
	R^1	R^2 R^3	R^4	X
IX,	OCH_3	OCH_2O	O	N (13, 13a double bond)
X,	OCH_3	OCH_2O	O	N
XI,	OCH_3	H OH	O	N
XII,	OCH_3	H $OCOCH_3$	O	N
XIII,	OCH_3	H $OCOC_6H_5$	O	N
XIV,	OCH_3	OCH_2O	H_2	N
XV,	OCH_3	OCH_2O	H_2	$N(CH_3)]^{(+)}\,I^{(-)}$
XVII,	H	OCH_2O	H_2	N

Catalytic hydrogenation of the des-base B_1 (*IX*) on the Adams catalyst in acetic acid is difficult. Moreover, the saturation of the $\Delta^{13,13a}$-double bond leading to the dihydro compound *X* is always accompanied by a hydrogenolytical cleavage of the methylenedioxy grouping. The hydrogenolytical product may be ascribed the structure *XI* since its NMR spectrum lacks the signal of the methylenedioxy group and exhibits in addition to the AB quartet of protons on $C_{(1)}$ and $C_{(2)}$ carbon atoms and the proton signal on $C_{(9)}$ (6.51 p.p.m.), a signal of a further aromatic proton at 6.58 p.p.m. which must be bound to the $C_{(11)}$ carbon atom as it follows from its characteristic *meta*-coupling with the proton on $C_{(9)}$. The product of hydrogenolysis was characterised as the acetyl derivative *XII* and the benzoyl derivative *XIII*. The structure of the normal dihydro product *X* is in accordance with the ultraviolet spectrum which lacks the features of conjugation and exhibits only a maximum at 288 nm corresponding to absorption of isolated substituted aromatic rings. In the NMR spectrum of compound *X*, there is absent as expected the signal of the olefinic proton on $C_{(13)}$ and is replaced (in the 2·00–3·90 p.p.m. region) by a six-proton multiplet of hydrogen atoms on $C_{(7)}$, $C_{(8)}$ and $C_{(13)}$, and the one-proton multiplet centered at 4·65 p.p.m. which is attributable to the proton on $C_{(13a)}$.

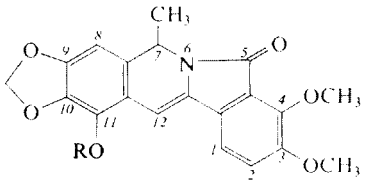
While the lithium aluminium hydride reduction of the des-base B_1 (*IX*) did not afford any defined product, a basic dihydrodeoxy derivative *XIV* was obtained from the dihydro compound *X* in tetrahydrofuran as solvent. Quaternisation of compound *XIV* with methyl iodide led to compound *XV*. The mercuric acetate oxidation of the base *XIV* in 50% aqueous acetic acid according to Walterová and Šantavý[5] recovers the des-base *IX* in an almost quantitative yield; consequently, the stepwise reduction of compound *IX* to the fully saturated derivative *XIV* is not accompanied by rearrangements. In accordance with the structure proposed, the ultraviolet spectrum of the saturated base *XIV* exhibits a single maximum at 280 nm and the infrared spectrum lacks the bands of the carbonyl, hydroxyl as well as NH group. However, there are present bands in the 2700–2800 cm^{-1} region indicating the *trans*-junction[6] of rings B/C. The NMR spectrum of the saturated base *XIV* (when compared with that of the dihydro substance *X*) exhibits additional doublets of two geminal protons in the Ar-CH_2-N system at 4·40 and 3·63 p.p.m. These spectral properties are very similar to those of 1-methoxycanadine[7] (*XVI*) but any identity of compounds *XIV* and *XVI* may be excluded by direct comparison as well as by mass spectra. The mass spectrum of compound *XIV* consists of some rather intensive peaks only and its pattern is similar to that of the Schöpf and Schweickert[8] "amine *VI*" (formula *XVII* in the present paper) except for the expected mass shifts of the corresponding peaks which reflect the different substitution of the aromatic ring A. The most important spectral features consist in the absence of the *m/e* 164 peak (excluding thus the tetrahydroprotoberberine[8,9] structure *XVI*) and in the presence of a peak (though poorly intensive) at *m/e* 176 which was also observed[8] in the mass spectrum of the demethoxy derivative *XVII*. Consequently, the reduction product possesses the structure *XIV* and the



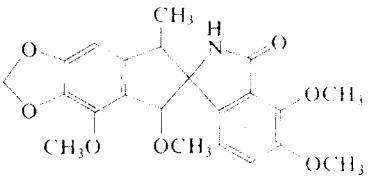
IV



XVI



XIX, R = C_2H_5
XX, R = CH_3
XXI, R = $CH_2C_6H_5$



XXII

des-base B_1 is logically 3,4,12-trimethoxy-10,11-methylenedioxy-7,8-dihydro-5*H*-isoindolo[1,2-*b*][3]benzazepin-5-one (*IX*). Correctness of our proposals[10] has been independently confirmed by the recent synthesis of compounds *X* and *XIV* performed by the team of Brossi[11].

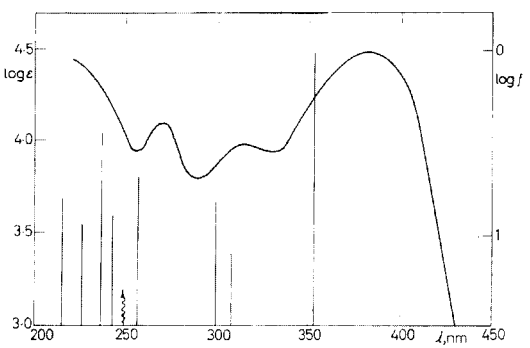


FIG. 1

Electron Spectrum of Compound *IX*

Results of the semiempiric calculation are indicated by vertical lines; the right scale represents calculated intensities (f = theoretical strength of the oscillator) and the left scale shows experimental values: the vertical wavy line with an arrow represents forbidden transition.

The attempted interpretation of the electronic spectrum of the des-base B_1 also favours the structure *IX*. The bond lengths and oscillator strengths were calculated by the modified[12] Pariser–Parr–Pople LCI-SCF method. Sixteen monoexcited configurations were taken into account in the LCI calculation. As indicated by comparison of calculated values with experimental data of the absorption curve, the longest-wavelength band is due to a simple transfer. The preliminary assignment is shown on Fig. 1.

Aiming at a suitable route for the preparation of the des-base *IX*, we have also paid our attention to the thermal decomposition of narceine imide methohydroxide (*XVIII*) which was obtained from the methiodide *II* by the action of moist silver oxide. As indicated by meticulous thin-layer chromatography, the degradation product was not homogeneous similarly to that obtained by the thermal decomposition of the methiodide *II*. The subsequent column chromatography on alumina and systematic recrystallisations afforded three substances, two of which (about 55% of the reaction mixture) were identified as (*Z*)-narceone imide (*III*) and (*E*)-narceone imide (*IV*). The third component, called the des-base B_2, was not identical but isomeric with the above des-base B_1 (*IX*).

Similar chromatographic mobility, insolubility in common organic solvents as well as a great similarity of ultraviolet and mass spectra indicated that structures of des-bases B_1 and B_2 are closely related. The attempted hydrogenation of the des-base B_2 over a platinum catalyst in glacial acetic acid failed. It also was not possible to measure the NMR spectrum because of the insolubility of the substance. The structural proof is based on the reaction of the des-base B_2 with sodium ethoxide in refluxing benzene. In this reaction, one of the methoxy groups is quantitatively replaced by the ethoxy group. The NMR spectrum of the ethoxy derivative (deuteriochloroform) exhibits in addition to proton signals of the ethoxy group further proton signals of the Ar—CH$<^{CH_3}_{N}$ system while the signals of the remaining functional groups are situated similarly to those of the des-base *IX*. In contrast to des-base *IX*, however, ring B is contracted and the ethoxy derivative possesses the structure *XIX*. Location of the ethoxy group at position 11 has not been proved but appears as the most probable. The original des-base B_2 may be thus ascribed the structure of 3,4,11-trimethoxy-7-methyl-9,10-methylenedioxy-6,7-dihydro-5*H*-isoindolo[1,2-*b*]isoquinol-5-one (*XX*). In accordance with this proposal is the detection of the C-methyl group by the modified Kuhn–Roth oxidation[13] (in the case of compound *IX*, the test was negative).

The correlation between compounds discussed in the present paper may also be illustrated by cyclisation reactions of narceonimides *III* and *IV*. The des-base *XX* is formed in about 60% yield when (*Z*)-narceone imide (*III*) or its geometric isomer *IV* are heated with 10% hydrochloric acid in methanol. From mother liquors, there was isolated a substance (brutto formula $C_{22}H_{23}NO_7$); its ultraviolet spectrum exhibited absorption maxima of a substituted aromatic ring and in the infrared

spectrum, there were present bands of the lactam system. All the 23 protons were identified by analysis of the NMR spectrum. The spirocyclic structure *XXII* appears thus as the most probable for the by-product $C_{22}H_{23}NO_7$.

When refluxed in 30% aqueous potassium hydroxide (*i.e.*, under conditions of the Freund degradation[2]), (*Z*) as well as (*E*)-narceone imides (*III*) and (*IV*) afford the des-base *IX* in low yields. In the cyclisation reaction, there is presumably involved a Michael type addition of the NH group to the styrene-like double bond; the low yield (about 8 to 15%) might be *inter alia* due to the formation of a seven-membered ring.

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Boetius block) and are uncorrected. Ultraviolet spectra were measured on a Universal spectrophotometer of Carl Zeiss, Jena, in methanolic solutions. Infrared spectra were recorded on a UR-10 apparatus (Carl Zeiss, Jena) either in 6% chloroform solution or in nujol. The NMR spectra were taken on a ZKR 60 (Carl Zeiss, Jena) apparatus in 6% deuteriochloroform solution with the use of tetramethylsilane as internal standard unless stated otherwise. Mass spectra were measured on a 70 eV LKB-9000 apparatus (LKB Producter, Stockholm, Sweden); all peaks of intensity higher than 5% are listed. The homogeneity of substances was verified *a*) by chromatography on paper Whatman No 1 in the solvent systems[14–16] S_5, S_6, and S_7; *b*) by thin-layer chromatography on loose alumina in benzene containing from 2 to 8% of ethanol (detection under ultraviolet light, with sulfuric acid or with the Dragendorff reagent); *c*) by thin-layer chromatography on silica gel with binder in the following solvent systems: ethanol (6 ml) and 6 drops of aqueous ammonia were made up with chloroform to 50 ml (experiments with narceine imide), or, ethanol (6 ml) and 2 drops of aqueous ammonia were made up with benzene to the volume of 100 ml (in experiments with des-bases). Detection with nitric acid, colours: brown (des-bases *III* and *IV*); first blackish blue to greenish blue, than vermillion-red (des-base B_1); deep red (des-base B_2).

Narceine Imide Methiodide (*II*)

Narceine imide[1] (I; 100 g; m.p. 151–152°C; crystallised from acetone) was dissolved in refluxing methanol (800 ml) and the hot solution was treated with methyl iodide (92 g). Yield, 130 g (97·5%). M.p. 261–263·5°C (decomp.; water); reported[2], m.p. 244–245°C (ethanol–water). UV spectrum, λ_{max} nm (log ε): 263 (4·20), 341 (4·22). IR spectrum (nujol): 3320 (NH), 1708 (lactam), 1619 (aromatic vibrations), 1495 cm^{-1} (subst. arom. rings).

Thermal Decomposition (*cf.*[2]) of Narceine Imide Methiodide (*II*)

A suspension of the methiodide *II* (117·3 g) in 30% aqueous potassium hydroxide (1000 ml) was refluxed for 7 h. Trimethylamine was introduced into hydrochloric acid and identified as the hydrochloride, m.p. 271–275°C (decomp.) undepressed on admixture with an authentic specimen; the yield was quantitative. The remaining reaction mixture was then cooled down and filtered with suction. The solid phase was washed with water, dried (74·7 g), and extracted with boiling benzene (850 ml). The insoluble portion (*A*) was crystallised from methanol to afford 64·05 g (81·5%) of (*Z*)-narceone imide (*III*) as plates, m.p. 210·5–212·0°C; reported[2], m.p. 177·5–178·0°C (acetic acid). For $C_{21}H_{19}NO_6$ (381·4) calculated: 66·20% C, 4·98% H, 3·68% N; found: 66·11% C,

5·29% H, 3·78% N. UV spectrum, λ_{max} nm (log ε): 220 (4·59), 272 (4·30), 348 (4·13). IR spectrum (chloroform): 3430 (NH), 1690, 1710 (lactam), 1600 (aromatic vibrations), 1495 (O-alkyl on the arom. ring), 1270, 1100, 1088, 1050 cm^{-1} (—O—C). NMR spectrum (δ p.p.m.): 7·68 (1 H, broad s) (NH); 7·52 (d), 7·16 (d), J = 9·0 Hz (2 o-H arom., ABq); 6·72 (dd) ($\underline{H}_A$), 5·20 (dd) ($\underline{H}_B$), 5·58 (dd) ($\underline{H}_C$), J_{AB} = 11·0 Hz, J_{AC} = 18·0 Hz, J_{BC} = 2·0 Hz (Ar—C$\underline{H}_A$=C$\underline{H}_B\underline{H}_C$; 6·82 (1 H, s) (Ar—C$\underline{H}$=C); 6·30 (1 H, s) ($\underline{H}$ arom.); 5·97 (2 H, s) (OC$\underline{H}_2$O); 4·06 (3 H, s) ($C_{(5)}$—OC$\underline{H}_3$); 3·92 (3 H, s); ($C_{(12)}$—OC$\underline{H}_3$); 3·90 (3 H, s) ($C_{(4)}$—OC$\underline{H}_3$).

From mother liquors, there was isolated 7·8 g (9·9%) of (*E*)-narceone imide (*IV*), needles, m.p. 200—202°C (benzene). For $C_{21}H_{19}NO_6$ (381·4) calculated: 66·20% C, 4·98% H, 3·68% N; found: 65·92% C, 5·10% H, 4·02% N. UV spectrum, λ_{max} nm (log ε): 215 (4·59), 272 (4·20), 349 (4·04). IR spectrum (chloroform): 3430, 3200 (free and associated NH), 1700 (lactam), 1600 (arom. vibrations), 1498 cm^{-1} (subst. arom. rings). NMR spectrum (δ p.p.m.): 9·54 (1 H, broad s) (N$\underline{H}$); 6·92 (d), 6·62 (d), J = 9·0 Hz (2 o-H arom., ABq); 6·80 (dd) ($\underline{H}_A$), 4·99 (dd) ($\underline{H}_B$), 5·50 (dd) ($\underline{H}_C$) J_{AB} = 11·0 Hz, J_{AC} = 18·0 Hz, J_{BC} = 2·0 Hz (ArC$\underline{H}_A$=C$\underline{H}_B\underline{H}_C$); 6·90 (1 H, s), (Ar—C$\underline{H}$=C); 6·20 (1 H, s) ($\underline{H}$ arom.); 5·98 (2 H, s) (OC$\underline{H}_2$O); 4·05 (3 H, s) ($C_{(5)}$—OC$\underline{H}_3$); 3·85 (3 H, s) ($C_{(12)}$—OC$\underline{H}_3$); 3·80 (3 H, s) ($C_{(4)}$—OC$\underline{H}_3$).

Portion B (*i.e.*, the benzene extract remaining after separation of compounds *III* and *IV*) was evaporated and the residue (2·1 g) chromatographed on a column of alumina (60 g; Brockmann activity II—III); fractions, 50 ml. The benzene fractions 1—9 afforded 1·17 g (1·5%) of the des-base B_1 (*IX*), yellow needles, m.p. 191—192°C (benzene–light petroleum). For $C_{21}H_{19}NO_6$ (381·4) calculated: 66·20% C, 4·98% H, 3·68% N, 24·42% OCH_3; found: 66·04% C, 5·06% H, 3·37% N, 24·23% OCH_3. UV spectrum, λ_{max} nm (log ε): 215 (4·29), 269 (4·11), 314 (3·99), 380 (4·49); λ_{min} nm (log ε): 255 (3·95), 289 (3·81), 330 (3·95). IR spectrum (nujol): 1690 (conjugated substituted lactam), 1642 (conjugated double bond), 1605 (arom. vibrations), 1498 (subst. arom. rings), 1280, 1090, 1078 (—O—C), 810, 778 cm^{-1} (arom. H). NMR spectrum (δ p.p.m.): 7·43 (d), 7·02 (d), J = 9·0 Hz (2 o-H arom., ABq); 6·74 (1 H, s) (Ar—C$\underline{H}$=C); 6·34 (1 H, s) ($\underline{H}$ arom.); 5·86 (2 H, s) (OC$\underline{H}_2$O); 4·05, 4·01, 3·86 (a 3 H, s) (3 OC$\underline{H}_3$); 2·80—3·10 (4 H, m) (Ar—C$\underline{H}_2$—C$\underline{H}_2$—N). Mass spectrum, *m/e*, (%): 381 (M^+, 100), 367(8), 366 (36), 352 (8), 351 (6), 338 (5), 336 (8), 190·5 (M^{++}, 8), 183 (5).

Fractions 20—25 (3 : 1 benzene–chloroform) afforded 0·26 g (0·33%) of compound *III*. Fractions 26 and 27 (3 : 1 benzene–chloroform) and 28—34 (1 : 1 benzene–chloroform) yielded 0·28 g (0·36%) of compound *IV*.

Separation of the Narcotine Fraction

A suspension was prepared from 1000 g of the narcotine fraction (yellow crystalline substance obtained in Slovakofarma Works from the acetone extract after the purification of crude morphine; m.p. 128—167°C; R_F values on paper Whatman No 4: 0·96 and 0·48 in the solvent system S_6; 0·98 and 0·72 in S_7) in benzene (6000 ml) and filtered off. The insoluble solid portion was stirred at 35°C in benzene (1000 ml), collected with suction again and washed with two 200 ml portions of benzene to afford 430 g (43%) of narceine imide (*I*), m.p. 151—152°C, identical with an authentic specimen[1]. The combined benzene portions (7400 ml) were kept in 15% ethanolic potassium hydroxide (1000 ml) for 45 min and the whole washed with one 1200 ml portion and three 1000 ml portions of 4% aqueous sodium hydroxide, and finally with water (1000 ml). The aqueous alkaline layers were combined and extracted with two 600 ml portions of benzene; all the benzene layers were combined and processed as given below. The aqueous alkaline phase was adjusted to pH 2—3 with hydrochloric acid, the whole kept with active charcoal for one hour, and filtered. The filtrate was precipitated by a slow addition of 30% aqueous sodium hydroxide

to afford 403 g (40·3%) of narcotine, m.p. 174–175°C, identical with an authentic specimen[1]. The combined benzene solutions were washed with two 700 ml portions of 6% aqueous acetic acid (with stirring), then with 5% aqueous sodium hydroxide (700 ml), and finally with water (700 ml). The aqueous layer was made alkaline with 15% aqueous sodium hydroxide (stirring) to deposit 114 g of narceine imide (*I*), m.p. 151–152°C, undepressed on admixture with the above specimen; overall yield, 544 g (54·4%). The benzene solutions were concentrated under diminished pressure to 1/8 of the original volume to deposit yellow needles which were collected with suction, washed with a mixture (70 ml) of benzene and light petroleum (2 : 1), and dried (47 g). From mother liquors, there was obtained an additional crop (6 g). Overall yield, 53 g (5·3%) of the des-base B_1 (*IX*), m.p. 191–192°C (benzene–light petroleum) identical with the substance obtained by the thermal degradation of the methiodide *II*.

Thermal Decomposition of Narceine Imide Methohydroxide (*XVIII*)

To a hot solution of the methiodide *II* (11·4 g; 20 millimol) in water (800 ml) there was added a moderate excess of freshly prepared silver oxide. The suspension was shaken for 4 h under exclusion of day light, filtered through a column of diatomaceous earth, and the column washed with water to the loss of alkaline reaction. The filtrates were combined, evaporated under diminished pressure, and the residue taken down at ordinary pressure in the stream of nitrogen on an oil bath. Water (250 ml) was then added and the whole process repeated. The final residue was dissolved in chloroform, the solution dried, and evaporated to afford 5·91 g of a brown-yellow residue. A portion (715 mg) was chromatographed on a column of alumina (55 g; Brockmann activity II); fractions, 50 ml. Fractions 1–5 (benzene) and 6–25 (99 : 1 benzene–chloroform) yielded 228 mg (31·9%) of the des-base B_2 (*XX*), m.p. 242–244°C (1-propanol). For $C_{21}H_{19}NO_6$ (381·4) calculated: 66·20% C, 4·98% H, 3·68% N; found: 65·82% C, 5·20% H, 3·93% N. UV spectrum, λ_{max} nm (log ε): 240 sh (4·25), 273 (4·21), 320 (3·88), 397 (4·42); λ_{min} nm (log ε): 257 (4·03), 296 (3·80), 347 (3·83). IR spectrum (nujol): 1689 (subst. lactam), 1601, 1649 (arom. vibrations), 1492 cm^{-1} (substituted aromatic rings). Mass spectrum, *m/e* (%): 381 (M^+, 35), 368 (5), 367 (34), 366 (100), 352 (5), 351 (22), 350 (8), 322 (6), 190·5 (M^{++}, 7), 183 (5).

Fractions 35–40 (95 : 5 benzene–chloroform) and 41–64 (75 : 25 benzene–chloroform) afforded 412 mg (57·6%) of a mixture containing the des-bases *III* and *IV*. The mixture was systematically crystallised from methanol to afford the des-base *III*, m.p. 210–212°C, and the des-base *IV*, m.p. 198·5–202°C, undepressed on admixture with the corresponding products from the decomposition of the methiodide *II*.

Dihydronarceine Imide Methiodide (*VI*)

From dihydronarceine imide[1] (*VII*; 428 mg) in methanol (3 ml) and methyl iodide (1 ml) there was obtained 503 mg (88%) of the methiodide *VI*, m.p. 190–193°C (ethanol). For $C_{24}H_{31}IN_2O_6$ (570·4) calculated: 50·53% C, 5·48% H, 4·91% N, 22·25% I; found: 50·80% C, 5·79% H, 4·99% N, 21·32% I.

Dihydronarceone Imide (*VIII*)

A solution of the methiodide *VI* (503 mg) in 30% aqueous potassium hydroxide 20 ml was refluxed for 7 h, cooled down, diluted with water, neutralised with hydrochloric acid, and extracted with chloroform to afford 245 mg (73%) of compound *VIII*, m.p. 178–179°C (acetone). For $C_{21}H_{21}NO_6$ (383·4) calculated: 65·78% C, 5·52% H, 3·65% N; found: 65·64% C, 5·53% H, 3·78% N. UV spectrum, λ_{max} nm (log ε): 238 sh (4·35), 270 (3·95), 301 (3·80); λ_{min} nm (log ε):

256 (3·93). IR spectrum (chloroform): 3430 (NH), 1690 (lactam), 1601 (aromatic vibrations), 1492 cm^{-1} (substituted aromatic rings).

Tetrahydronarceone Imide (*V*)

A. Hydrogenation of compound *III* (3·81 g) in glacial acetic acid (40 ml) over the Adams catalyst (1 g) yielded 2·22 g (74·5%) of the imide *V*, m.p. 167—168°C (acetone). For $C_{21}H_{23}NO_6$ (385·4) calculated: 65·44% C, 6·02% H, 3·63% N; found: 64·82% C, 6·05% H, 3·88% N. UV spectrum, λ_{max} nm (log ε): 235 sh (4·30), 292 (3·64), 302 (3·65); λ_{min} nm (log ε): 268 (3·38). IR spectrum (chloroform): 3430 (NH), 1689 (lactam), 1615 (aromatic vibrations), 1492 cm^{-1} (substituted aromatic rings).

B. Hydrogenation of compound *IV* (381 mg) in glacial acetic acid (3·15 ml) over the Adams catalyst (0·1 g) yielded 228 mg (59·5%) of the tetrahydro derivative *V*, m.p. 168—170°C, identical with the specimen prepared by procedure *A*.

C. Hydrogenation of the dihydro substance *VIII* (178 mg) in glacial acetic acid (20 ml) over the Adams catalyst (50 mg) yielded compound *V*, m.p. 167·5—169·5°C, identical with specimens obtained by procedures *A* and *B*.

Hydrogenation of the Des-Base B_1 (*IX*)

A solution of compound *IX* (5 g) in glacial acetic acid (750 ml) was hydrogenated over the Adams catalyst (1 g) at room temperature. When the hydrogen uptake ceased, another portion (1 g) of the catalyst was added and the hydrogenation was continued. Additions of the fresh catalyst were repeated twice. Finally, the catalyst was filtered off, the filtrate evaporated under diminished pressure, and the residue was crystallised once from methanol and twice from benzene and a little light petroleum to yield 3 g (60%) of 3,4,12-trimethoxy-10,11-methylenedioxy-7,8,13,13a-tetrahydro-5*H*-isoindolo[1,2-*b*] [3]benzazepin-5-one (*X*), m.p. 207—208°C. For $C_{21}H_{21}NO_6$ (383·4) calculated: 65·78% C, 5·52% H, 3·65% N; found: 65·68% C, 5·75% H, 4·09% N. UV spectrum, λ_{max} nm (log ε): 288 (3·72); λ_{min} nm (log ε): 275 (3·68). IR spectrum (chloroform): 1675 (conjugated substituted lactam), 1618 (aromatic vibrations), 1494, 1480 (substituted aromatic rings), 1090, 1070, 1048 cm^{-1} (—O—C). NMR spectrum (δ p.p.m.): 7·17 (d), 7·02 (d), J = 9·0 Hz (2 *o*-H arom., ABq); 6·38 (s) (1 H, s) (H-arom.); 4·65 (1 H, m) (Ar—CH_2—CH<Ar, N>), 5·85 (2 H, s) (OCH_2O); 4·04, 3·93, 3·85 (à 3 H, s) (3 OCH_3); 3·90 (2 H, overlap) (Ar—CH_2—CH); 3·10—2·00 (4 H, m) (Ar—CH_2—CH_2—N). Mass spectrum, *m/e* (%): 383 (M^+, 100), 382 (17·5), 368 (40), 365 (36), 354 (9), 352 (8·5), 205 (20), 192 (52), 191·5 (M^{++}, 30), 191 (100), 190 (23), 179 (13), 178 (14), 161 (22), 34 (10), 133 (20), 91 (12·5), 77 (10).

The above methanolic mother liquors were evaporated under diminished pressure, the residue dissolved in benzene (130 ml), the solution washed with two 40 ml portions of 5% aqueous sodium hydroxide and two 20 ml portions of water, dried, and evaporated to yield 0·6 g of the dihydro substance *X*, m.p. 200—206°C (overall yield, 72%). The aqueous layers were acidified to Congo Red paper with 10% aqueous hydrochloric acid to deposit 146·6 mg (3·2%) of 10-hydroxy-3,4,12-trimethoxy-7,8,13,13a-tetrahydro-5*H*-isoindolo[1,2-*b*][3]benzazepin-5-one (*XI*), m.p. 121·5—123·5°C (acetone–light petroleum). For $C_{20}H_{21}NO_5.CH_3OH$ (387·4) calculated: 65·10% C, 6·58% H, 3·62% N; found: 64·97% C, 6·33% H, 3·76% N. UV spectrum: no absorption between 220—350 nm. IR spectrum (chloroform): 3590, 3300 (free and associated OH), 1670 (substituted lactam), 1610 (aromatic vibrations), 1494 cm^{-1} (substituted aromatic rings). NMR spectrum in CF_3CO_2H (δ p.p.m.): 7·56 (d), 7·35 (d), J = 9·0 Hz (2 *o*-H arom., ABq); 6·58 (1 H, s *meta*-

coupled) (H arom.); 6·51 (1 H, s *meta*-coupled) (H arom.); 4·73 (2 H, broad d) (Ar—CH_2—$C\underline{H}_2$——N^+); 4·30 (1 H, m) (Ar—CH_2—$C\underline{H}$ ); 3·70—3·20 (4 H, m) (Ar—$C\underline{H}_2$—CH_2, Ar—$C\underline{H}_2$——CH). Mass spectrum, *m/e* (%): 355 (M^+, 100), 354 (25), 340 (29), 338 (12·5), 337 (44), 326 (16), 324 (10), 322 (11), 193 (14), 192 (18), 190 (11·5), 178 (17·5), 177·5 (M^{++}, 22·5), 164 (14), 163 (41·5), 162 (14·5).

10-Acetoxy-3,4,12-trimethoxy-7,8,13,13a-tetrahydro-5*H*-isoindolo[1,2-*b*] [3]benzazepin-5-one (*XII*)

A mixture of the phenol derivative *XI* (57 mg) and acetic anhydride (1·5 ml) was refluxed for 2 h, decomposed with water (5 ml), extracted with three 10 ml portions of benzene, the combined extracts washed with two 5 ml portions of aqueous sodium hydroxide and water, dried over anhydrous sodium sulfate, and evaporated. The residue (63 mg) was dissolved in benzene and the solution filtered through a column of alumina (0·5 g). Yield, 42 mg (70·5%) of the acetoxy derivative *XII*, m.p. 161·5—162·5°C (acetone–light petroleum). For $C_{22}H_{23}NO_6$ (397·4) calculated: 66·49% C, 5·83% H, 3·52% N; found: 66·88% C, 6·35% H, 3·43% N. UV spectrum: no absorption between 220 and 350 nm. IR spectrum (chloroform): 1750, 1270 (acetate), 1685 (substituted lactam), 1594 (aromatic vibrations), 1491 cm^{-1} (substituted aromatic rings).

10-Benzoyloxy-3,4,12-trimethoxy-7,8,13,13a-tetrahydro-5*H*-isoindolo[1,2-*b*] [3]benzazepin-5-one (*XIII*)

The benzoylation was performed according to ref.[17] Benzoyl cyanide (50 mg) was added to a suspension of the phenol derivative *XI* (50 mg) in anhydrous triethylamine (5 ml) and the whole shaken for 8 h. After 5 days at room temperature, the mixture was treated with additional benzoyl cyanide (50 mg), diluted with benzene (10 ml), and allowed to stand for 14 days (until the starting compound disappeared). Water (0·1 ml) was then added, the mixture evaporated to dryness, the residue dissolved in benzene, and the solution filtered through a column of alumina (0·5 g; Brockmann activity II—III). Yield, 49 mg (81%) of the benzoyl derivative *XIII*, m.p. 174—177°C (acetone–light petroleum). For $C_{27}H_{25}NO_6$ (459·5) calculated: 70·57% C, 5·48% H, 3·05% N; found: 70·27% C, 5·73% H, 3·09% N. UV spectrum: no absorption between 220 and 350 nm. IR spectrum (chloroform): 1730 (ester), 1678 (substituted lactam), 1595 (aromatic vibrations), 1492 cm^{-1} (substituted aromatic rings). NMR spectrum (δ p.p.m.): 8·26 (2 H, m), 7·62 (3 H, m) ($C_6\underline{H}_5$—CO); 7·30 (d), 7·08 (d), J = 9·0 Hz (2 H, ABq) (2 *o*-H arom.); 6·70 (2 H, s) (2 arom. H); 4·70 (1 H, m) (Ar—CH_2—$C\underline{H}$ ); 4·20 (2 H, m) (Ar—$C\underline{H}_2$—CH); 4·05, 3·96, 3·86 (à 3 H, s) (3 $OC\underline{H}_3$); 3·10—2·0 (4 H, m) (Ar—$C\underline{H}_2$—$C\underline{H}_2$—N).

3,4,12-Trimethoxy-10,11-methylenedioxy-7,8,13,13a-tetrahydro-5*H*-isoindolo[1,2-*b*] [3]benzazepine (*XIV*)

To a solution of the dihydro substance *X* (200 mg) in tetrahydrofuran (30 ml) there was added a suspension of lithium aluminium hydride (0·2 g) in tetrahydrofuran (3 ml) with stirring. The whole mixture was refluxed for 3 h, decomposed with water under cooling with tap water and stirring, diluted with ether (100 ml), treated with 40% aqueous sodium hydroxide (25 ml), and extracted with ether. The ethereal extracts were washed with water, dried over anhydrous potassium carbonate, and evaporated to yield 93 mg (48·7%) of compound *XIV*, m.p. 176·5—178°C (methanol). R_F values: 0·93 and 0·96 (in solvent systems S_6 and S_7, resp.). For $C_{21}H_{23}NO_5$

(369·4) calculated: 68·28% C, 6·28% H, 3·79% N; found: 68·02% C, 6·52% H, 3·76% N. UV spectrum, λ_{max} nm (log ε): 236 sh (4·06), 280 (3·61); λ_{min} nm (log ε): 258 (3·25). IR spectrum (chloroform): 1619 cm^{-1} (aromatic vibrations). NMR spectrum (δ p.p.m.): 7·02 (d), 6·80 (d), J = 9·0 Hz (2 H, ABq) (2 *o*-H arom.); 6·43 (1 H, s) (H arom.); 5·86 (2 H, s) (OCH_2O); 4·40 (1 H, d) (eq. Ar—CH_2—N); 3·63 (1 H, d) (ax. Ar—CH_2—N), J = 13·0 Hz; 3·80 (1 H, m) (Ar—CH_2—CH(Ar)(N)); 3·50—2·20 (6 H, m) (Ar—CH_2—CH_2—N, Ar—CH_2—CH); 4·00, 3·89, 3·87 (à 3 H, s) (3 OCH_3). Mass spectrum, *m/e* (%): 369 (M^+, 100), 354 (29), 194 (11), 193 (46·5), 192 (32·5), 191 (10), 176 (11).

Methiodide (XV). A solution of the base *XIV* (55·5 mg) in methanol (10 ml) and methyl iodide (1 ml) was refluxed for 2 h and the solvent was evaporated. Yield, 52·3 mg (68%) of the methiodide *XV*, m.p. 231—233°C (decomp.) (acetone–light petroleum). For $C_{22}H_{26}INO_5$ (511·4) calculated: 51·76% C, 5·12% H, 2·74% N, 24·82% I; found: 51·70% C, 5·35% H, 2·93% N, 24·14% I. UV spectrum, λ_{max} nm (log ε): 220 (4·62), 281 (3·59); λ_{min} 258 nm (log ε 3·14). IR spectrum (nujol): 1620, 1590 cm^{-1} (substituted aromatic rings). Mass spectrum: except for *m/e* 142, $(CH_3I)^+$, and 127, $(I)^+$, identical with that of the base *XIV*.

Picrate. From the methiodide *XV* and sodium picrate. M.p. 148—151°C (acetone–light petroleum). For $C_{28}H_{28}N_4O_{12}$ (612·5) calculated: 54·90% C, 4·61% H, 9·15% N; found: 54·72% C, 4·98% H, 9·41% N.

Des-Base B_1 (*IX*)

A) A solution of compound *XIV* (100 mg) and mercuric acetate (676 mg) in 50% aqueous acetic acid (25 ml) was refluxed for 6 h and then extracted with five 20 ml portions of benzene. The extracts were combined, washed with water, two 20 ml portions of 5% aqueous sodium hydroxide, and water again, dried over anhydrous sodium sulfate, and evaporated. The residue (126 mg) was passed in benzene through a column of alumina (1 g; Brockmann activity II—III) and the effluent processed as usual to afford 79·2 mg (77%) of the des-base *IX*, m.p. 189—190·5°C, identical with the above specimen.

B) A solution of compound *III* (381 mg) in 30% aqueous potassium hydroxide (20 ml) was refluxed for 7 h, cooled down, made neutral with dilute hydrochloric acid, and extracted with chloroform. The extract was dried, evaporated, the residue taken into benzene, the solution filtered through a column of alumina (30 g; Brockmann activity II), and the effluent evaporated to afford 30 mg (8%) of the des-base *IX*, m.p. 188—191°C (benzene), identical with the specimen from paragraph *A*. The same procedure was performed with the compound *IV*. From 50 mg of *IV*, 7 mg (14%) of *IX* was obtained.

11(?)-Ethoxy-3,4-dimethoxy-7-methyl-9,10-methylenedioxy-6,7-dihydro-5*H*-isoindolo[1,2-*b*]-isoquinol-5-one (*XIX*)

To a suspension of the des-base *XX* (60 mg) in benzene (15 ml) there was added 1 ml of ethanolic sodium ethoxide (from 0·2 g of sodium and 10 ml of ethanol), the whole refluxed for 40 min, cooled down, washed with two 5 ml protions of water, dried over anhydrous sodium sulfate, and evaporated to afford 53 mg (92·5%) of the ethoxy derivative *XIX*, m.p. 178—181°C. For $C_{22}H_{21}NO_6$ (395·4) calculated: 67·46% C, 5·35% H, 3·54% N; found: 67·11% C, 5·65% H, 3·30% N. UV spectrum, λ_{max} nm (log ε): 274 (4·18), 320 (3·86), 396 (4·38). IR spectrum chloroform): 1682 (subst. lactam), 1601 cm^{-1} (aromatic vibrations); the OH or NH absorption is absent. NMR spectrum (δ p.p.m.): 7·43 (d), 7·08 (d), J = 9·0 Hz (2 H, ABq) (2 *o*-H arom.);

6·64 (1 H, s) (H olef.); 6·41 (1 H, s) (H arom.); 5·90 (2 H, s) (OCH_2O); 5·44 (1 H q), $J = 6·0$ Hz (Ar—$CH<^{N}_{CH_3}$); 4·32 (2H, q), $J = 7·0$ Hz (O—CH_2—CH_3); 4·03, 3·86 (à 3 H, s) (2 OCH_3); 1·44 (3 H, t), $J = 7·0$ Hz (CH_3—CH_2); 1·40 (3 H, d), $J = 6·0$ Hz (CH_3—CH).

11(?)-Benzyloxy-3,4-dimethoxy-7-methyl-9,10-methylenedioxy-6,7-dihydro-5*H*-isoindolo-[1,2-*b*]isoquinol-5-one (*XXI*)

To a suspension of the des-base *XX* (53 mg) in benzene (20 ml) there was added 1 ml of a solution previously prepared from sodium (0·1 g) and benzyl alcohol (5 ml), and the mixture processed analogously to the preceding paragraph. Yield, 45 mg (77%) of the benzyloxy derivative *XXI*, m.p. 178—179°C. For $C_{27}H_{23}NO_6$ (457·5) calculated: 70·88% C, 5·07% H, 3·06% N; found: 70·55% C, 4·89% H, 3·22% N. IR spectrum (chloroform): 1680 (subst. lactam), 1600 (aromatic vibrations), 1490 cm^{-1} (substituted aromatic rings). NMR spectrum (δ p.p.m.): 7·80—7·25 (5 H, m) (C_6H_5); 7·30 (d), 7·05 (d), $J = 9·0$ Hz (2 H, ABq) (2 *o*-H arom.); 6·62 (1 H, s) (H olef.); 6·40 (1 H s) (H arom.); 5·90 (2 H, s) (OCH_2O); 5·45 (1 H, q), $J = 6·0$ Hz (Ar—$CH<^{N}_{CH_3}$); 5·30 (2 H, s) (C_6H_5—CH_2—O); 4·03, 3·82 (à 3 H, s) (2 OCH_3); 1·42 (3 H, d), $J = 6·0$ Hz (CH_3—CH).

Des-Base B_2 (*XX*)

A) A solution of the des-base *III* (20 g) in methanol (1 500 ml) and conc. hydrochloric acid (50 ml) was refluxed for one hour to deposit a solid and then concentrated to a small volume. The solid was collected with suction; yield, 10·9 g (55%) of the des-base *XX*, m.p. 235—238°C. The spectra of this product were identical with those of the specimen obtained by decomposition of the hydroxide *XVIII*. The filtrate deposited gradually 0·4 g (2%) of the spiro derivative *XXII*, m.p. 257—258·5°C (methanol). For $C_{22}H_{23}NO_7$ (413·4) calculated: 63·91% C, 5·61% H, 3·39% N; found: 64·28% C, 6·03% H, 3·31% N. UV spectrum, λ_{max} nm (log ε): 2·15 (4·84), 294 (3·75). IR spectrum (chloroform): 3480 (NH), 1700 (lactam), 1618 (aromatic vibrations), 1494 cm^{-1} (substituted aromatic rings). NMR spectrum (δ p.p.m.): 6·85 (d), 6·04 (d), $J = 9·0$ Hz (2 H arom., ABq); 6·66 (broad s) (NH); 6·45 (1 H, s) (arom. H); 6·00 (2 H, m) (OCH_2O); 4·34 (1 H, s) (Ar—CH—OCH_3); 4·05, 4·00, 3·79 (à 3 H, s) (3 arom. OCH_3); 3·65 (1 H, q, $J = 7·0$ Hz) (Ar—CH$<^{CH_3}_{C}$); 3·37 (3 H s) (C—OCH_3); 0·80 (3 H, d) (CH$<^{CH_3}_{C}$).

B) A solution of the des-base *IV* (0·1 g) in methanol (5 ml) and conc. hydrochloric acid (1 ml) was processed analogously to paragraph *A*. Yield, 47 mg (47%) of the des-base *XX*, identical with an authentic specimen.

The authors wish to thank Dr R. Zahradník, J. Heyrovský Institute of Physical Chemistry and Electrochemistry, Czechoslovak Academy of Sciences, Prague, for quantum calculation, interpretation, and permission to publish the results. Thanks are also due to Mrs I. Rudolská and Mrs J. Krumphanzlová for spectral measurements and Mr J. Kominek for microanalyses.

REFERENCES

1. Hodková J., Veselý Z., Koblicová Z., Holubek J., Trojánek J.: Lloydia *35*, 61 (1972).
2. Freund M., Michaels H.: Ann. *286*, 248 (1895).

3. Koblicová Z., Holubek J., Trojánek J.: Unpublished results.
4. Veselý Z., Holubek J., Kopecká H., Trojánek J.: This Journal, in press.
5. Walterová D., Šantavý F.: This Journal *33*, 1623 (1968).
6. Crabb T. A., Newton R. F., Jackson D.: Chem. Rev. *71*, 109 (1971).
7. Ohta M., Tani C., Morozumi S., Kodaira S.: Chem. Pharm. Bull. (Tokyo) *12*, 1080 (1964).
8. Schöpf C., Schweickert M.: Chem. Ber. *98*, 2566 (1965).
9. Budzikiewicz H., Djerassi C., Williams D. H.: *Structure Elucidation of Natural Products by Mass Spectrometry*, Vol. I, *Alkaloids*. Holden-Day, San Francisko 1964.
10. Veselý Z., Holubek J., Trojánek J.: Chem. Ind. (London) *1973*, 478.
11. Teitel S., Klötzer W., Borgese J., Brossi A.: Can. J. Chem. *50*, 2022 (1972).
12. Pancíř J., Matoušek I., Zahradník R.: This Journal *38*, 3039 (1973).
13. Garbers C. F., Schmid H., Karrer P.: Helv. Chim. Acta *37*, 1336 (1957).
14. Štrouf O., Trojánek J.: This Journal *29*, 447 (1964).
15. Moza B. K., Trojánek J.: Chem. Ind. (London) *1965*, 1260.
16. Kaul J. L., Trojánek J.: Lloydia *29*, 26 (1966).
17. Holý A., Souček M.: Tetrahedron Letters *1971*, 185.

Translated by J. Pliml.