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THE SYNTHESIS OF SHIHUNINE AND RELATED COMPOUNDS FROM *ORTHO*-CARBOXYPHENYL CYCLOPROPYL KETONE

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Abstract—Reaction of dicyclopropyl cadmium and phthalic acid monochloride monomethyl ester gives *o*-carboxyphenyl cyclopropyl ketone (**2**). Reaction of the methyl ester of **2** with methylamine gives 2 - methyl - 3 - hydroxy-3-cyclopropyl-1-isoindolinone (**4b**), which is converted by hydrogen halides in chloroform to the rearranged homoallylic halides **5a-c**. Thionyl chloride in chloroform converts **2** to 3-(3-chloropropylidene) phthalide (**7**) which upon reaction with methylamine gives isoshihunine (**8**). Heating of keto acid **2** with aniline leads to N-phenyl-N-norshihunine (**9**), while upon heating of **2** with methylamine spiro [(1 - methylpyrrolidine) - 2 - 3' - (2' - methyl - 1' - isoindolinone)] (**10**) is obtained. **10** is converted to shihunine (**1**) by 48% HBr solution. The mechanisms of the reactions are discussed.

INTRODUCTION

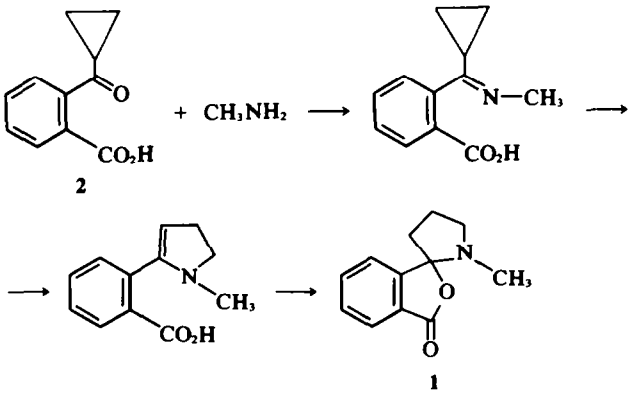
About ten years ago Inubushi *et al.* isolated from *Dendrobium lohonense* a phthalide-pyrrolidine alkaloid which they named shihunine, as it was a component of Shi-Hu, a popular chinese drug sold on the Hong Kong market. Shihunine was shown by Inubushi *et al.* to possess structure **1**.[2,3]

In recent years we studied the conversion of cyclopropyl ketones to pyrrolidines[4,5] and in the course of these studies we achieved a one-step synthesis of nicotine from cyclopropyl 3-pyridyl ketone.[6] Regarding shihunine (**1**) we considered it likely that this alkaloid could be formed in one step by heating *o*-carboxyphenyl cyclopropyl ketone (**2**) with methylamine, according to Scheme I.

In this paper we wish to describe our studies concerning the synthesis and properties of *o*-carboxyphenyl cyclopropyl ketone (**2**) and its derivatives, which resulted in the synthesis of shihunine (**1**) and some related compounds.

RESULTS AND DISCUSSION

Initially we attempted to prepare keto acid **2** from phthalic anhydride and cyclopropyl magnesium bromide or dicyclopropyl cadmium.[7-12] After these attempts failed keto acid **2** was finally obtained from the monochloride monomethyl ester of phthalic acid[13] and dicyclopropyl cadmium. Keto acid **2** was found to be an oil, unstable at temperatures above 100°, and could only be purified *via* its methyl ester (**3**). Examination of the various spectral



2 1

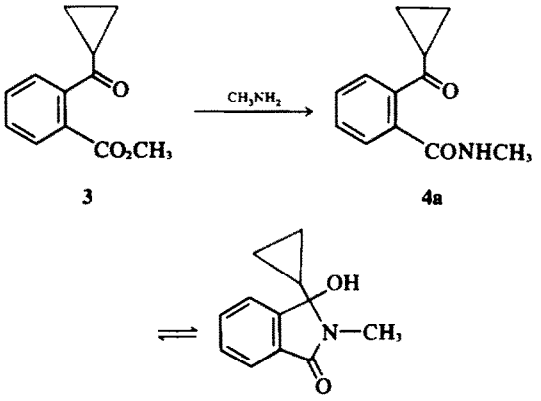
SCHEME 1

†This could be in part due to the ability of the cyclopropane to release electrons,[15] resulting in a decrease in the electrophilicity of the carbonyl carbon as compared so that in *o*-butyryl benzoic acid.[16]

properties of **2** and their comparison with those of *o*-butyryl benzoic acid (Experimental) clearly indicate that the former exists as the "chain-tautomer", in contrast to the latter that exists as the "ring tautomer".†[14]

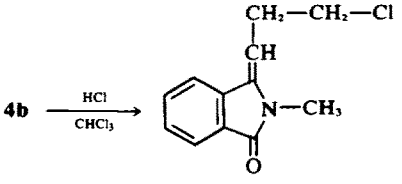
Esterification of both keto acids by diazomethane gave the corresponding "normal" esters.[17] Due to the thermal instability of keto acid **2** we did not attempt to react it with methylamine at elevated temperatures in the initial stages of this work.

Aminolysis of keto ester **3** with methylamine gave the corresponding keto amide **4**. The spectral properties of this product and their comparison with analogies in the literature[18] indicate that it exists as the "ring tautomer", 3 - cyclopropyl - 3 - hydroxy - 2 - methylisoindolinone (**4b**).



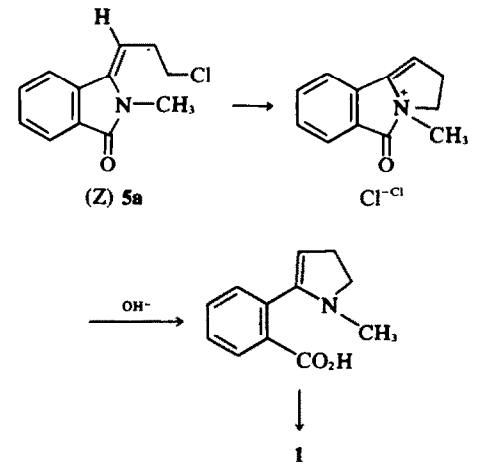
Lactam **4b** is an isomer of shihunine. Consequently we explored the possibility of its conversion to the desired alkaloid by thermal isomerization.

The rationale behind this experiment is outlined in Scheme 2. Lactam **4b** was recovered unchanged after heating it at its m.p. (184–6°) for 15 min. When this experiment was repeated at 200°, it resulted in complete decomposition. Carrying on with this approach we have reacted lactam **4b** with anhydrous hydrogen chloride in chloroform. Under these conditions **4b** underwent instantaneously homoallylic rearrangement to 2 - methyl - 3 - (3 - chloropropylidene) isoindolinone (**5a**). The analogous bromo and iodo derivatives (**5b** and **5c**) were also prepared by modified methods.

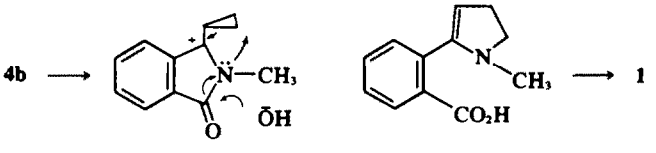


Halides **5a-c** were considered potentially useful synthetic intermediates, since we envisaged several alternative reaction pathways by which they could be converted to shihunine.

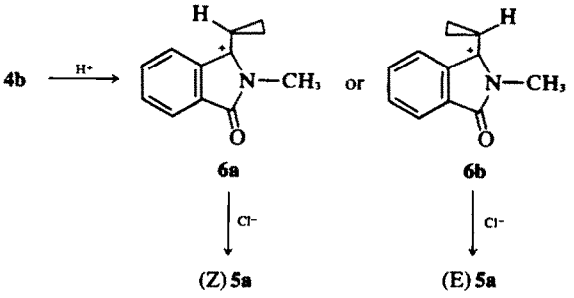
An intramolecular displacement of the halogen (Scheme 3) might be expected to proceed spontaneously, provided the stereochemistry around the double bond is Z. NMR spectra and the sharp m.ps obtained for halides **5a-c** indicate that the homoallylic rearrangement leading to these derivatives proceeded fully stereoselectively. It is well established that the stereochemistry of the products in homoallylic rearrangements is determined by the relative stabilities of the intermediate carbonium ions.[19] Since maximum stabilization of a cyclopropyl carbinyl carbonium ion is attained when the cyclopropane bisects the plane of the carbonium ion,[20] there are two possible intermediates for the homoallylic rearrangement of **4b**: **6a** and **6b**. Examination of molecular models



SCHEME 3



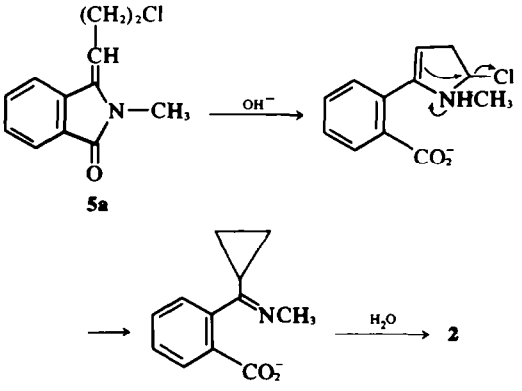
SCHEME 2



reveals that **6b** is preferred, due to greater interactions of the cyclopropane with the N-CH_3 group in **6a** than between the cyclopropane and the *ortho* H in **6b**. Consequently we believe that products **5a–c** are of the E configuration. Attempts to isomerize the double bond in these compounds by various methods were unsuccessful.[21]

Another conceivable route that might lead from halides **5** to shihunine is by nucleophilic substitution of the halogen by methylamine. The 3 - (3 - methylaminopropylidene) - isoindolone derivative that would result from this reaction would be converted by acid hydrolysis to *o*-(γ-methylaminobutyryl)-benzoic acid that should cyclize to shihunine spontaneously. However attempts to substitute the halogen in **5a-c** by methylamine using various conditions failed.[22]

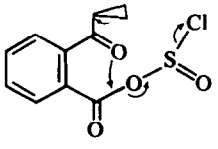
Finally, due to the apparent low reactivity of the halogens in nucleophilic displacement in compounds **5a–c**, we have attempted to hydrolyse the lactam ring, assuming that the resulting *o*-(γ-chlorobutyryl) benzoic acid could serve as an alternative synthetic intermediate for shihunine. However, action of sodium hydroxide or sodium carbonate upon **5a–c** gave a quantitative yield of *o*-carboxyphenyl-cyclopropyl ketone (**2**). This result can be rationalized by Scheme 4



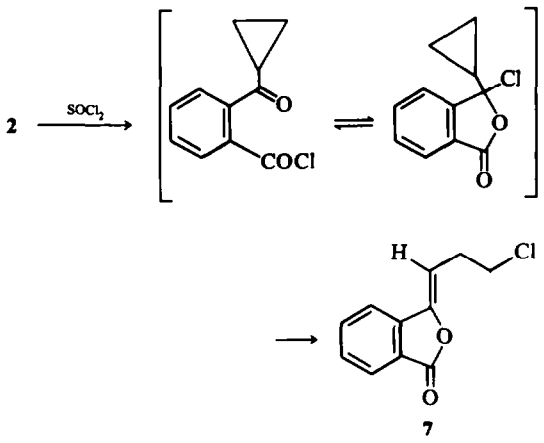
SCHEME 4

Further studying the chemical properties of keto acid **2**, we found that it reacts with thionyl chloride in chlorform solution at room temperature to give 3(-3-chloropropylidene)-phthalide (**7**) in good yield. Chlorolactone **7** may be viewed as the homoallylic rearrangement product of the "pseudo chloride" of keto acid **2**.* Its sharp

*The pseudo chloride of **2** may also be formed by a [3.2.1] bicyclic path.[23] An alternative possible way for the direct formation of **7** from the "normal" chloride of **2** is depicted by formula **A**



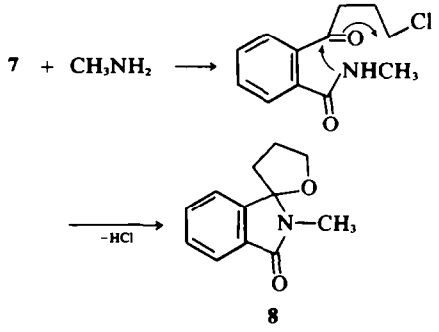
A



7

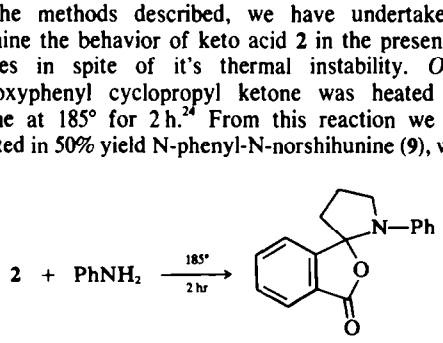
m.p. and NMR spectrum indicate the presence of one stereoisomer. Based on the same considerations that were presented in the discussion regarding the stereochemistry of the haloloactams **5a–c** we assume that the chlorolactone possesses the Z stereochemistry indicated in formula **7**. Chlorolactone **7** was also considered a potential synthetic intermediate to shihunine. Upon reacting it with ethanolic methylamine solution it gave however a lactamic product which was identified as spiro[tetrahydrofuran - 2 - 3' - (- 2' - methyl - 1' - isoindolinone)] (**8**). We named compound **8** isoshihunine.

The formation of isoshihunine (**8**) can be rationalized by the reaction sequence outlined in Scheme 5. In view of



SCHEME 5

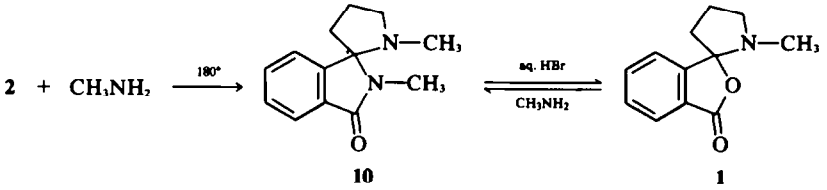
the failure of the various attempts to synthesize shihunine by the methods described, we have undertaken to examine the behavior of keto acid **2** in the presence of amines in spite of it's thermal instability. *Ortho*-carboxyphenyl cyclopropyl ketone was heated with aniline at 185° for 2 h.[24] From this reaction we have isolated in 50% yield N-phenyl-N-norshihunine (**9**), which



9

was identified by the similarity of its IR and NMR spectra, to those of shihunine.

In contrast to this heating of keto acid **2** with methylamine at 180°–190° in an autoclave for 2 h gave, in 30% yield, spiro[(1 - methylpyrrolidine) - 2 - 3′ - (2′ - methyl - 1′ - isoindolinone)] (**10**). Lactam **10** is a hygroscopic oil which was identified on the basis of its IR, NMR and mass spectra. It was characterized and



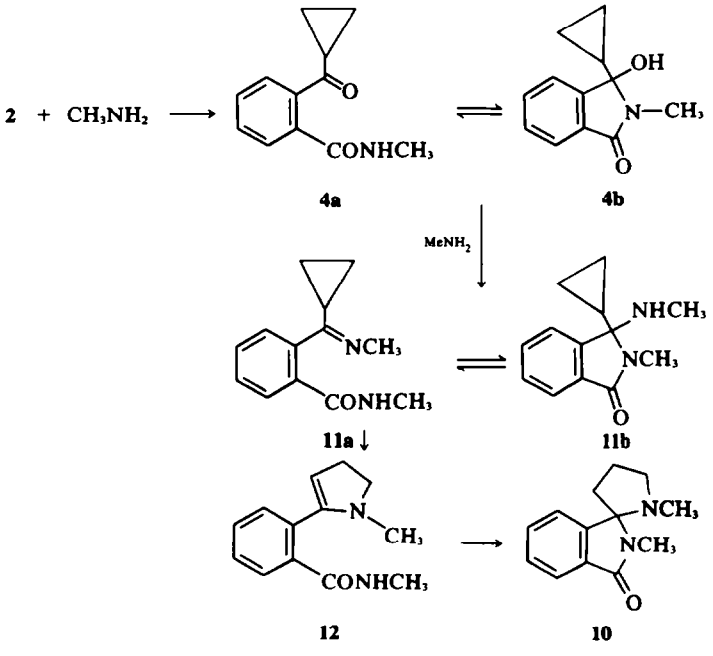
10 **1**

analyzed as picrate. Lactam **10** was converted to shihunine (**1**) in quantitative yield by refluxing 48% hydrobromic acid. The synthetic shihunine exhibited identical spectral characteristics with the natural product. It was converted to a picrate which was found identical as regard to m.p., mixed m.p., IR and mass spectra[25] with an authentic sample of shihunine picrate.*

It is reasonable to assume, in view of the formation of **9**, that the reaction of keto acid **2** and aniline proceeds according to Scheme 1. On the other hand the formation of lactam **10** may be accounted for by assuming that the reaction of keto acid **2** with methylamine leads first to the formation of the keto amide **4a**⇄**4b** (Scheme 6). Further reaction of **4** with methylamine would lead to the imino amide **11a** or its "ringtautomer" **11b**. Imino amide **11a**, may undergo the cyclopropyl ketimine→ pyrroline rearrangement to pyrroline derivative **12**, which is the "chain-tautomer" of lactam **10**. Alternatively lactam **10** may result from the reaction of shihunine with excess methylamine.

Heating of shihunine with methylamine at 180° resulted in its quantitative conversion to lactam **10**. In contrast heating lactam **4b** in an autoclave for 2 h at 180° gave no lactam **10**. Upon workup of the mixture it was found to contain, in addition to unreacted **4b**, a new compound of identical R_f value to that of **4b**. Although this compound could not be separated and purified it was identified as the amino lactam **11b** on the basis of its NMR and mass spectra. Heating **4b** with excess methylamine, for 24 h at 180°, gave an approximately 7:3 mixture of **4b** and **11b** as determined by NMR analysis. It is worthy of note that the examination of this latter reaction revealed the presence of approx. 30% of lactam **10**.

Consequently our results indicate, that although the reactions outlined in Scheme 6 may proceed at low rate, the major amount of lactam **10** formed in the reaction of **2**



SCHEME 6

*We wish to thank Prof. Y. Inubushi of Kyoto University for furnishing us with an authentic sample of shihunine picrate.

with methylamine, comes from the initially formed shihunine. Therefore it follows that shihunine is indeed formed in one-step from keto acid **2** and methylamine, as outlined in the original plan (Scheme 1).

EXPERIMENTAL*

o-Carboxyphenyl cyclopropyl ketone (**2**). To cyclopropyl magnesium bromide, prepared from 24·2 g (16·2 ml, 0·2 mol) bromocyclopropane and 4 g Mg (0·15 mol) in ether, was added 16 g (0·085 mol) dry cadmium chloride and the mixture was stirred for 2·5 h at room temp. To this mixture was added in one portion 15·8 g (0·08 mol) phthalic acid monochloride monomethyl ester with cooling. Stirring was continued for 90 min at room temp and for 1 h with reflux. After allowing the mixture to stand overnight at room temp it was decomposed by dil H_2SO_4 (100 ml, 15%). The phases were separated, the aqueous layer was extracted 4 times with ether, the combined ether soln was washed successively with water, 10% K_2CO_3 and water. After removal of the ether the residue was disolved in 200 ml MeOH containing 48 g KOH and left overnight at room temp. The MeOH was removed *in vacuo*, the residue was dissolved in water and extracted 3x with ether to remove neutral impurities, then it was acidified by dil H_2SO_4. The mixture was extracted 4x with ether. After drying over Na_2SO_4 and removing the ether the residue was dissolved in benzene and left overnight at room temp. The next day the benzene soln was filtered to remove the precipitated unreacted phthalic acid, and the benzene was evaporated to leave 12 g **2** as a crude oil. This compound decomposed upon heating above 100°. It is sufficiently pure for further work. IR (neat): 3300 1720–1610 cm^{-1}. UV (EtOH): 212 nm (log ϵ = 4·00), 229(3·96), 274(3·10). M.W.: Calcd. 190, found (M.S.) 190. NMR ($CDCl_3$,δ, 12·34 1H s, 8·75–7·80 1H m, 7·60–7·20 3H m, 2·35–1·90 1H m, 1·40–0·65 4H m.

3-Cyclopropyl-4,5-benzo-1,2 6H-oxazine was prepared from **2** and hydroxylamine hydrochloride with NaOAc in aqueous EtOH m.p. 95–97° from aqueous EtOH. IR (nujol): 1730, 1600 cm^{-1}. UV (EtOH): 221 nm (log ϵ = 4·25), 284 (3·24), 294 (3·21). M.W. calcd.: 187, found (M.S.): 187. NMR ($CDCl_3$): δ 8·70–8·40 1H m, 8·35–7·88 3H m, 2·55–2·00 1H m, 1·38–0·90 4H m. Found: C, 70·70; H, 5·19; N, 7·25. Calcd. for $C_{11}H_9NO_2$: C, 70·58; H, 4·81; N, 7·48%.

o-Carbomethoxyphenyl cyclopropyl ketone (**3**) was prepared by reacting **2** with diazomethane in ether, b.p. 106° at 0·1 mm, $n_D^{24.5}$ 1·5366. IR: (neat) 1725, 1625 cm^{-1}. UV (EtOH) 211 nm (log ϵ = 4·06), 230 (3·89), 275 (3·12). M.W. Calcd.: 204, found (MS) 204. NMR ($CDCl_3$): δ 7·90–7·60 1H m, 7·60–7·30 3H m, 3·87 3H s, 2·50–2·04 1H m, 1·40–0·90 4H m. (Found: C, 70·31; H, 5·83. Calcd. for $C_{12}H_{12}O_3$: C, 70·58; H, 5·88%).

o-Butyryl benzoic acid was prepared by reacting di-n-propyl cadmium with phthalic anhydride according to De-Benneville.[9] It had m.p. 84–5° from benzene–light petroleum (40–60°) IR (nujol): 3290–3280, 1730, 1710 cm^{-1}. UV (EtOH): 227 nm (log ϵ = 3·90), 268 (3·01), 275 (2·99). NMR ($CDCl_3$): δ 7·92–7·30 4H m, 5·88 1H s, (OH), 2·25 2H t (J = 7·5 Hz), 1·70–1·17 2H m, 0·96 3H t (J = 6 Hz). (Found: C, 68·54; H, 6·04. Calcd. for $C_{11}H_{12}O_3$: C, 68·75; H, 6·25%).

Methyl o-butyryl benzoate was prepared by esterification of the corresponding acid with diazomethane, b.p. 100° at 0·1 mm, $n_D^{24.5}$ 1·5140. IR (neat) 1720, 1690 cm^{-1}; UV (EtOH): 212 (4·00), 229 (3·96), 274 (3·10); NMR ($CDCl_3$): δ 7·98–7·78 1H m, 7·60–7·20 3H m, 3·84 3H s, 2·85 2H t (J = 7·5 Hz), 2·10–1·43 2H m, 1·00 3H t (J = 6·8 Hz). (Found: C, 70·19; H, 6·96. Calcd. for $C_{12}H_{14}O_3$: C, 69·90; H, 6·79%).

2 - *Methyl* - 3 - *hydroxy* - 3 - *cyclopropyl* - 1 - *isoindolinone* (**4b**). 1 g of **3** dissolved in 10 ml ethereal methylamine soln. After standing overnight at room temp the ppt was collected and recrystallized from chloroform-light petroleum (40–60°) to afford 0·9 g of **4b** m.p. 184–186°. IR (nujol): 3250, 1675 cm^{-1}; UV (EtOH): 212·5 nm (log ϵ = 4·08), 220 s (3·99), 237 s (3·83), 246 (3·59); NMR ($CDCl_3$): 7·07–7·30 4H m, 4·22 1H s (OH), 2·75 3H s, 1·13–0·3 5H m. (Found: C, 70·63; H, 6·29; N, 6·89. Calcd. for $C_{12}H_{13}NO_2$: C, 70·93; H, 6·40; N, 6·90%).

2 - *Methyl* - 3 - (3 - *chloropropylidene*) - 1 - *isoindolinone* (**5a**). Dry HCl was introduced into a soln of 0·1 g **4b** in 6 ml EtOH free chloroform for 2 min at r.t. After removal of the chloroform the residue was recrystallized from light petroleum. (90°–100°) to give 0·109 mg product m.p. 97°–99°; IR (nujol): 1710–1650 cm^{-1}; UV (MeOH): 225 nm (log ϵ = 3·30), 243 s (2·86), 260 (3·00), 270 s (2·95), 311 (2·82); NMR ($CDCl_3$) δ 7·92–7·19 4H m, 5·35 1H t (J = 7·5 Hz), 3·86–3·39 2H m, 3·17 3H s, 3·32–2·80 2H m (Found: C, 65·17; H, 5·54; Cl, 15·65; N, 6·03. Calcd. for $C_{12}H_{12}ClNO$: C, 65·15; H, 5·43; Cl, 15·83; N, 6·33%).

2 - *Methyl* - 3 - (3 - *bromopropylidene*) - 1 - *isoindolinone* (**5b**). A soln of 0·15 g **4b** in 2 ml EtOH free chloroform was shaken with 5 ml 48% HBr for 1 min. After separation of the layers, the aqueous soln was extracted with chloroform. The combined chloroform soln was evaporated after drying to leave 0·18 product m.p. 96–7° from light petroleum (90–100°); IR (nujol): 1700, 1690, 1650 cm^{-1}; UV (MeOH): 225 (4·17), 261 (3·99), 270 s (3·95), 312 (3·83) NMR ($CDCl_3$): δ 7·93–7·33 4H m, 5·43 1H t (J = 7·5 Hz), 3·80–2·80 4H m, 3·27 3H s. (Found: C, 53·93; H, 4·26; Br, 30·40; N, 5·06. Calcd. for $C_{12}H_{12}BrNO$: C, 54·13; H, 4·51; Br, 30·08; N, 5·26%).

2 - *Methyl* - 3 - (3 - *iodopropylidene*) - 1 - *isoindolinone* (**5c**). This compound was prepared by the method described for **5b** using 57% HI. The product had m.p. 92·5–93° from light petroleum (90–100°); IR (nujol): 1710–1670 cm^{-1}; UV MeOH: 225 (4·25), 263 (4·10), 270 s (4·08), 3·31 (3·99); NMR ($CDCl_3$): δ 7·88–7·15 4H m, 5·13 1H t, 3·46–2·83 4H m, 3·08 3H s. (Found: C, 45·87; H, 3·98; I, 40·08; N, 4·77. Calcd for $C_{12}H_{12}INO$: C, 46·00; H, 3·86; I, 40·57; N, 4·47%).

3-(3-Chloropropylidene) phthalide (**7**). A soln of 0·15 g **2** and 2·5 ml freshly distilled $SOCl_2$ in 10 ml EtOH free chloroform is stirred overnight at r.t. After removal of the solvent and excess $SOCl_2$ the residue is distilled *in vacuo*, b.p. 149° at 0·1 mm. Recrystallization of the distillate from light petroleum (40–60°) gave 0·1 g product m.p. 68°–70°; IR (nujol): 1780 cm^{-1}; UV (MeOH): 220 s (3·95), 237·5 (4·10), 260 (4·08), 269 s (3·94), 307 (3·58); NMR ($CDCl_3$): δ 7·93–7·27 4H m, 5·78 1H t (J = 7·5 Hz), 3·70 2H t (J = 6 Hz), 2·85 2H dt. (Found: C, 63·11; H, 4·36; Cl, 16·76. Calcd. for $C_{11}H_9ClO_2$: C, 63·30; H, 4·31; Cl, 17·02%).

Spiro[tetrahydrofuran - 2 - 3' - (2' - methyl - 1' - isoindolinone)], Isoshihunine (**8**). 0·4 g of **7** was dissolved in 10 ml 33% ethanolic methylamine solution, and the soln was kept overnight at room temp. After removal of the solvent the residue was separated by thick layer chromatography (silica gel-chloroform) to yield 0·17 g product, m.p. 75–7° from light petroleum (40–60°); IR (nujol): 1685, 1207 cm^{-1}; NMR ($CDCl_3$): 8·00–7·30 4H m, 4·50–4·10 2H m, 3·01 3H s, 2·60–2·20 4H m. (Found: C, 70·79; H, 6·70; N, 6·94. Calcd. for $C_{12}H_{13}NO_2$: C, 70·93; H, 6·40; N, 6·89%).

N-Phenyl-N-norshihunine (**9**). 0·3 g of **2** was heated with 0·8 ml aniline at 185–190° for 2 h. After removal of the excess aniline by vacuum distillation, the residue was separated by thick layer

*All b.ps and m.ps are uncorrected. NMR spectra were measured by a Jeol C-60H instrument, all chemical shifts are given in ppm downfield from TMS. IR spectra were measured on a Perkin Elmer Model 237 Spectrophotometer. UV spectra were measured on a Unicam SP 800A Spectrophotometer in EtOH or MeOH. Mass spectra were obtained by a Varian MAT CH5 mass spectrometer at 70 eV using a direct inlet system. Microanalyses were carried out by the Hebrew University Microanalytical Laboratory.

chromotography (silica gel-chloroform). Isolation gave 0·16 g product, m.p. 156–7° from ether-light petroleum (90–100°); IR (KBr): 1750, 1600; NMR ($CDCl_3$): δ 8·06–6·26 9H m, 4·16–3·35 2H m, 2·70–2·03 4H m; M.W. Calcd: 265, found (MS 265. (Found: C, 76·65; H, 5·63; N, 5·28. Calcd. for $C_{17}H_{15}NO_2$: C, 76·98; H, 5·66; N, 5·28%).

Spiro[(1 - *methylpyrrolidine*) - 2 - 3' - (2' - *methyl* - 1' - *isoindolinone*)] (**10**). A soln of 5 g keto acid in 25 ml liquid methylamine was heated in an autoclave at 180°–185° for 2 h. After evaporation of the excess methylamine the residue was taken up in chloroform. The chloroform soln was extracted 4 times with 10% HCl. Each portion of aqueous acidic extract was basified by addition of K_2CO_3 separately and extracted 4 times with chloroform. The combined chloroform extracts were dried over Na_2SO_4 and evaporated. The residue was first purified by passing it in a chloroform solution over a column of basic alumina (activity II). The product obtained from the chromatography was converted to a picrate, which was recrystallized from MeOH. The purified product was recovered from its picrate by passing it through an alumina column, it was obtained as a hygroscopic oil (1·5 g); IR (neat): 1685–1650 cm^{-1}; NMR ($CDCl_3$): δ 7·90–7·56 1H m, 7·56–7·20 3H m, 3·40–3·05 2H m, 2·95 3H s, 2·35–1·95 4H m, 1·85 3H s, M.W. Calcd. 216, found (M.S.) 216. *Picrate of* **10**, m.p. 161–162° from MeOH; IR (KBr): 1710, 1625, 1605, 1565, 1550 cm^{-1}; Mass spectrum[25] shows molecular ions of picric acid (m/e = 229) and of **10** (m/e 216). (Found: C, 51·49; H, 4·19; N, 15·59. Calcd. for $C_{19}H_{19}N_5O_8$: C, 51·24; H, 4·27; N, 15·73%).

Shihunine (**1**). A soln of 75 mg of **10** in 7 ml of 48% HBr was refluxed for 4 h. After dilution with water the soln was extracted 3 times with chloroform. The aqueous soln was basified with K_2CO_3 and extracted 4x with chloroform. The alkaline chloroform extract was dried, evaporated and the residue was separated by preparative thin layer chromatography (alumina-chloroform), to yield 70 mg shihunine that was dried *in vacuo* and crystallized m.p. 78–79° from n-hexane-ether (lit[2]. m.p. 78·5–79·0°); IR (neat): 1750 cm^{-1}; NMR ($CDCl_3$): δ 8·00–7·30 4H m, 3·40–3·00 2H m, 2·50–2·00 4H m, 2·10 3H s; M.W. Calcd: 203, Found (M.S.) 203.

Shihunine picrate. crystallized from MeOH m.p. (depending on rate of heating) 154–155·5°, and 159–160° (lit. 154–155·5°[3] and 163–164°[2]) no depression of the mixed m.p. of an authentic sample; IR (nujol): 1724, 1690, 1622, 1605, 1563, 1546 cm^{-1}. Mass spectra of our picrate and that of the authentic sample were identical.[25] Both spectra showed molecular peaks of picric acid (m/e = 229) and of shihunine (m/e = 203).

Reaction of shihunine with methylamine. A soln of 0·13 g shihunine in a few ml liquid methylamine was heated in an autoclave at 180° for 2 h. After evaporation of the methylamine and separation of the mixture on a TLC plate (silica-chloroform) a 0·11 g yield of **10** was obtained. It was found identical with **10** obtained previously by comparing their chromatographic behavior, IR, NMR and mass spectra.

Reaction of **4b** *with methylamine* (a) A soln of 0·31 g **4b** in liquid methylamine was heated in an autoclave at 180° for 2 h. The examination of the product by TLC showed the absence of compound **10**. The main band obtained by preparative TLC (R_f identical with that of **4b**) was isolated, to yield 0·25 g oil. Mass spectrum showed two molecular ions: m/e = 203 and m/e = 216. NMR ($CDCl_3$) showed a spectrum identical with that of **4b** containing two additional signals: δ 2·90 (N–CH_3 lactam of **11b** and 1·84 (N–CH_3 amine of **11b**) of equal intensity. By comparing the intensities of the lactamic N–CH_3 signals (of **4b** at 2·74 and of **11b** at 2·90) the composition of the mixture was estimated to be 30:70 **11b**:**4b**. Further attempts to purify this mixture resulted in increasing the proportion of **4b** in the mixture, presumably indicating hydrolysis of **11b** to **4b**.

–(b) A soln of a mixture of **4b** and **11b** in liquid methylamine was heated at 180° in an autoclave for 24 h. Separation of the product mixture by thin layer chromatography (silica-chloroform) gave 30% of **10** identified by comparison of its IR and NMR spectra with those of the product obtained above. The main band on the plate was found to be essentially identical with the product obtained in the previous experiment.

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