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QUATERNISATION AND OXIDATION OF STRYCHNINE AND BRUCINE DURING PLANT EXTRACTION*

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Key Word Index—*Strychnos* spp.; Loganaceae; alkaloids; strychnine; brucine; quaternisation in CH_2Cl_2; oxidation.

Abstract—Use of $CHCl_3$ and CH_2Cl_2 for the extraction of amines and alkaloids may easily lead to the formation of artifacts. CH_2Cl_2 in particular reacts rapidly at laboratory temperature with strychnine and brucine forming quaternary salts. In connection with this, the TLC behaviour, NMR and MS properties of the chlorometho- and bromometho-halides and -picrates of strychnine and brucine are discussed. On standing, $CHCl_3$ solutions of strychnine yield not only a quaternary salt but also 16-hydroxystrychnine (pseudostrychnine) and strychnine *N*-oxide; brucine reacts similarly. When CH_2Cl_2 and $CHCl_3$ are to be used for the extraction of amines or alkaloids, it is advisable to ascertain whether or not they leave the compounds chemically unchanged.

INTRODUCTION

METHYLENE dichloride (CH_2Cl_2) and chloroform ($CHCl_3$) are water-immiscible organic solvents commonly used in the extraction procedures for amines and alkaloids. In considering which solvent to use in screening *Strychnos* species for alkaloids, CH_2Cl_2 was selected because of its lower b.p. and lesser tendency to form emulsions. Over 200 samples of African *Strychnos* species have already been successfully screened for alkaloids,[1] but when dealing with certain alkaloid-rich Asian species, it was observed that the crude CH_2Cl_2 extracts unexpectedly yielded crystals.[2] It was therefore decided to examine further the formation of these crystals and also the suitability of these two solvents for *Strychnos* alkaloids.

The separation of crystals from crude $CHCl_3$ extracts of *Strychnos henningsii* Gilg led to the discovery that strychnine (I, R = H) and brucine (I, R = OCH_3) apparently react with $CHCl_3$ to give quaternary salts which were thought to be the dichloromethochlorides (II) mainly on the basis of analytical data.[3] It has also been reported that strychnine reacts with $CHCl_3$ during assay procedures to form a dichloromethochloride.[4] Subsequently it was shown that $CHCl_3$ contains CH_2Cl_2 and CH_2ClBr as impurities and that strychnine formed the chloromethobromide (III) rather than the dichloromethochloride (II).[5] $CHCl_3$ itself does not react with strychnine.[5,6] The additional unexplained alkaloid spots noted during the PC investigation of strychnine and brucine can thus be attributed to the formation of chloromethobromides.[7]

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* Part I in a projected series "Artifacts Produced by Chloroform and Methylene Dichloride During the Extraction of Amines and Alkaloids".

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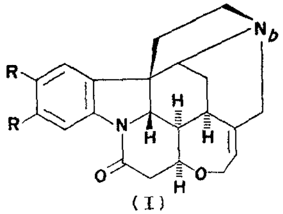
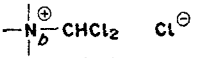
It has been shown that amines readily quaternise with CH_2ClBr in $CHCl_3$[8–10] and that ephedrine (IV) forms hydrochloride and hydrobromide salts together with 3,4-dimethyl-5-phenyloxazolidine (V).[11]

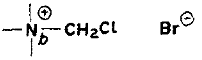


(I)



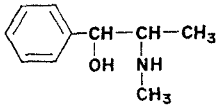
$-\overset{\oplus}{N}_b-CHCl_2 \quad Cl^{\ominus}$

(II)



$-\overset{\oplus}{N}_b-CH_2Cl \quad Br^{\ominus}$

(III)



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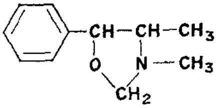
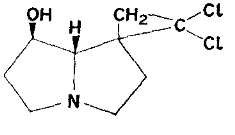


(V)

There are other reports in the literature about the formation of artifacts through the reaction of alkaloids with $CHCl_3$. For example, it has been suggested that 7β-hydroxy-1-spiro-(2′,2′-dichlorocyclopropyl)-8β-pyrrolizidine (VI) isolated from *Crotalaria goreensis* Guill. et Perr. is probably an artifact formed from 7β-hydroxy-1-methylene-8β-pyrrolizidine (VII) stored in the presence of $CHCl_3$.[12] More common is the production of quaternary salts; thus anhydrorosmarinecine (VIII) is stated to yield a dichloromethochloride when treated with $CHCl_3$.[13]



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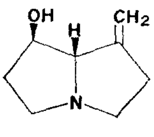

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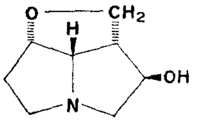
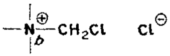


(VIII)

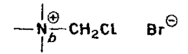
RESULTS

Contrary to the indications in the literature, strychnine and brucine dissolved in CH_2Cl_2 readily form heavy crops of crystals within 2 hr at laboratory temp. Examination of these crystals by TLC in solvent systems containing ammonia indicated that strychnine and brucine were absent but that in each case two major and more polar alkaloidal spots were present. As it appeared that mixtures of quaternary salts had been formed, in order to help in establishing their identity, the following quaternary salts of strychnine (I, R = H) and brucine (I, R = OCH_3) were prepared: (a) chloromethochloride (IX); (b) chloromethobromide (X); (c) bromomethochloride (XI); and (d) bromomethobromide (XII). The method of preparation is outlined in Scheme 1.



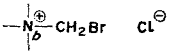
$-\overset{\oplus}{N}_b-CH_2Cl \quad Cl^{\ominus}$

(IX)



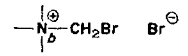
$-\overset{\oplus}{N}_b-CH_2Cl \quad Br^{\ominus}$

(X)



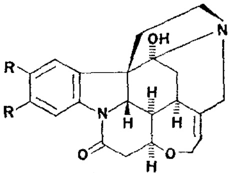
$-\overset{\oplus}{N}_b-CH_2Br \quad Cl^{\ominus}$

(XI)

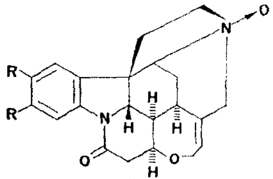


$-\overset{\oplus}{N}_b-CH_2Br \quad Br^{\ominus}$

(XII)



(XIII)



(XIV)

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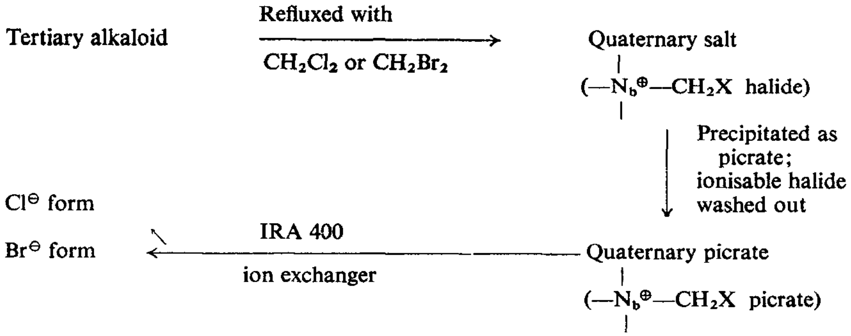

SCHEME 1. THE PREPARATION OF THE QUATERNARY SALTS (IX–XII) OF STRYCHNINE AND BRUCINE.

TLC of the quaternary picrates gave in each case only one alkaloidal spot, whereas TLC of the crystalline products resulting from the replacement of picrate by chloride or bromide gave two spots, the lower one having the same R_f as the spot obtained with the corresponding picrate. This indicated that despite the use of ammonia in the solvent, TLC of the quaternary halides resulted in double spot formation. Further evidence for this was obtained when the plates were sprayed with bromocresol purple. For each quaternary halide the lower spot was purple (quaternary hydroxide) whilst the upper spot was yellow (quaternary halide). Changes in TLC behaviour were noted when acid and alkali were added to aqueous solutions of the quaternary halides prior to developing the chromatogram. The addition of HCl to the chloromethochlorides resulted in one major alkaloidal spot corresponding in R_f to the upper spot of the chloromethochlorides, whilst the addition of HBr to the chloromethochlorides resulted in one major spot corresponding in R_f to the upper spot of the chloromethobromides. The addition of NaOH to the chloromethochloride resulted in one major spot corresponding to the lower chloromethochloride spot and to the single spot obtained with the chloromethopicrate. It was therefore concluded that on silica-gel with solvent systems containing ammonia the quartenary halides (IX–XII) of strychnine and brucine ran as two alkaloidal spots (corresponding to the quaternary hydroxide and the quaternary halide).

Although TLC distinguished quaternary chloride from quaternary bromide, no effective TLC or PC system was developed for the separation of mixtures of the four quaternary halides of strychnine and brucine. It was hoped that NMR spectroscopy would enable the four quaternary halides (IX–XII) to be differentiated since the presence of a two-proton singlet well downfield in the spectra of the four quaternary halides of strychnine clearly demonstrated that N_b is quaternised, the additional group containing methylene, and that a bis-(strychnine)-methane derivative had not been formed. However, the close proximity of the signals for these two-proton singlets did not permit the use of 60 MHz NMR spectroscopy for identifying the components of mixtures of these quaternary strychnine salts. These values were: chloromethochloride δ 5·78; chloromethobromide δ 5·73; bromomethochloride δ 5·82; bromomethobromide δ 5·79.

Mass spectrometry of strychnine and brucine quaternary picrates (see Scheme 1) established the nature of the halogen atom on the N_b methylene and confirmed the expected identity and purity of these compounds. Prominent peaks for halogen and for halogen acid were obtained at m/e 35, 36, 37, 38 (Cl, HCl) for the chloromethopicrates and at m/e 79, 80, 81, 82 (Br, HBr) for the bromomethopicrates. The MS of strychnine chloromethochloride (IX), prepared via the picrate and ion-exchange (Scheme 1), showed that chlorine was the only halogen present. In addition, the molecular ion was found to be absent, but peaks at m/e 346 (16%, M^+–2HCl) and at m/e 334 (94%, M^+ for strychnine) were present. Similarly, the mass spectrum of strychnine bromomethobromide (XII) showed that bromine was the only halogen present. Again, no molecular ion was observed, but peaks at m/e 346 (2%, M^+–2HBr) and 334 (39%) were present. The spectra of strychnine chloromethobromide (X) and bromomethochloride (XI) are very similar but mass spectrometry will not distinguish between them if they are present in the same mixture. Both compounds showed peaks at m/e 346 (M^+–HCl–HBr), 334, 79, 80, 81, 82, 35, 36, 37 and 38. The MS of the corresponding brucine quaternary salts (IX–XII) were similar, with one important exception, viz. whether they contained ionisable or non-ionisable halide the three compounds containing chlorine gave prominent peaks at m/e 50 and 52 (CH_3Cl) and the three compounds containing bromine gave prominent peaks at m/e 94 and 96 (CH_3Br).

The crystals which formed so readily with strychnine and CH_2Cl_2, although giving two major alkaloidal spots on TLC (see above), were shown to consist of a single compound, strychnine chloromethochloride (IX). MS indicated that only chlorine was present; the presence of ionisable chlorine was confirmed by elution of the halide from CG 120 ion-exchanger followed by TLC examination and mass spectrometry of the picrate showed that non-ionisable chlorine was also present. The chemical shift of the two-proton singlet in the NMR spectrum, δ 5·78, was also consistent with the structure of strychnine chloromethochloride (IX).

Experiments with other *Strychnos* alkaloids indicate that CH_2Cl_2 and $CHCl_3$ do not react with pseudo alkaloids (16-hydroxystrychnine (XIII, R = H); 16-hydroxybrucine (XIII, R = OCH_3)) or with *N*-methyl-pseudo alkaloids (icajine, vomicine, novacine). CH_2Cl_2 solutions of emetine, reserpine, and quinine when left to stand show the presence of additional more polar alkaloidal spots on TLC.

At laboratory temps strychnine reacts less rapidly in $CHCl_3$ than in CH_2Cl_2. Crystals slowly separate from $CHCl_3$ during the course of 14 days. TLC examination of these crystals again showed the apparent presence of two major alkaloidal spots, the R_f of the upper one indicating quaternary bromide. However, the picrate showed only one major spot on TLC, corresponding to the lower spot of compounds (IX–XII). MS of the crystals indicated that both chlorine and bromine were present, whilst mass spectrometry of the picrate showed that only chlorine was present, i.e. that the bromine present in the original crystals was in the ionisable form. Hence the crystals formed when strychnine is allowed to stand in $CHCl_3$ contain the chlorometho group and ionisable bromine. However, these results do not rule out the presence of ionisable chlorine. Elution of the halide from CG 120 ion-exchanger and TLC examination confirmed that only ionisable bromine was present. The two-proton singlet at δ 5·73 in the NMR spectrum of the $CHCl_3$ reaction product supports the occurrence of the $\equiv N^{\oplus}–CH_2X$ grouping and is consistent with its being the chloromethobromide (X). These results are therefore in agreement with those of Caws and Foster[5] who identified the crystals formed by strychnine in $CHCl_3$ as strychnine chloromethobromide and who also indicated that the chloromethobromide is the only quaternary product and that bromomethochloride, chloromethochloride, and dichloromethochloride are all absent.

However, TLC examination of the solution remaining after removal of the strychnine–$CHCl_3$ crystals showed that further alkaloidal constituents were present. In particular, the chromatograms revealed two prominent alkaloidal spots, one with a higher R_f and the other with a lower R_f than strychnine. The high R_f compound was separated by means of column chromatography and was identified by mass spectrometry as 16-hydroxystrychnine (pseudostrychnine (XIII, R = H)). This identification was confirmed by comparing the IR spectrum and the R_f on TLC in three solvents with those of authentic 16-hydroxystrychnine. The low R_f compound was separated by preparative TLC and identified as strychnine *N*-oxide (XIV, R = H) by MS and TLC comparison with authentic strychnine *N*-oxide.

Strychnine *N*-oxide[1,2,14] and 16-hydroxystrychnine[15–17] are regarded as natural products but the above results indicate that they might possibly be artifacts. Control experiments were therefore undertaken on strychnine using the conditions previously described for screening procedures.[1] TLC checks showed that under these conditions small amounts of quaternary halide were formed but that strychnine *N*-oxide and 16-hydroxystrychnine were absent. TLC examination of the 14-day-old solution remaining after the removal of brucine–chloroform crystals indicated that brucine *N*-oxide (XIV, R = OCH_3) and 16-hydroxybrucine (XIII, R = OCH_3) were present, thus showing its similarity in behaviour to strychnine.

Strychnine chloromethochloride and brucine chloromethochloride when injected intraperitoneally into mice showed very weak muscle relaxant effects with absence of tonic convulsions.[18]

DISCUSSION

Previous workers have shown that CH_2ClBr, an impurity in $CHCl_3$, reacts with amines and alkaloids forming artifacts during isolation procedures. This present work has demonstrated that with strychnine and brucine not only can the quaternary chloromethobromides be formed but also oxidation products, *N*-oxides and 16-hydroxy compounds. The use of CH_2Cl_2 as an alternative solvent to $CHCl_3$ cannot be recommended since quaternisation of strychnine and brucine is so rapid at laboratory temp. The problem of choosing a suitable solvent for these particular alkaloids is not solved because they tend not to be sufficiently soluble in other common laboratory solvents. The fact that crystals of chloromethobromide form only slowly with $CHCl_3$ whilst chloromethochloride formation with CH_2Cl_2 is so rapid means that $CHCl_3$ is to be preferred, but with the inevitable formation of small amounts of quaternary salt. CH_2ClBr can be removed from $CHCl_3$ by refluxing with strychnine and then redistilling the solvent; purified $CHCl_3$ obtained by this procedure does not react with strychnine or brucine. Strychnine and brucine chloromethochlorides and chloromethobromides decompose during GLC, the single peaks obtained having the same R_ts as the corresponding tertiary alkaloids. Hence, if extracts are examined only by GLC it may not be realised that quaternary artifacts are present. The formation of crystalline chloromethochlorides with CH_2Cl_2 can be used as a method for separating the normal bases from the pseudo and *N*-methyl-pseudo bases which occur naturally together. The weak muscle-relaxant properties of strychnine chloromethochloride and brucine chloromethochloride as contrasted with the convulsant properties of the tertiary alkaloids illustrates the fact that pharmacological evaluation of amines or alkaloids extracted by $CHCl_3$ or CH_2Cl_2 might well give results which are different from those expected with the original tertiary bases.

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EXPERIMENTAL

MS were determined on an AEI MS 902 high-resolution mass spectrometer at 70 eV; 60 MHz NMR spectra were determined in DMSO (hexadeuterated) with TMS as internal reference; the IR spectra were taken in Nujol; GLC was carried out with a Perkin–Elmer F11 equipped with FID and a Hitachi–Perkin–Elmer recorder using a 60 cm × 3 mm i.d. glass column packed with 5% SE 52 on Varaport 30; the carrier gas was N_2 at 13 psi and the column temperature was 225°; the CH_2Cl_2 was redistilled and the $CHCl_3$ was AR grade and was taken from freshly opened bottles; the TLC was done with plates coated with silica-gel G (Merck) and run in the systems: (A) EtOAc–*iso*-PrOH–5·5% NH_3 (45:35:20); (B) EtOAc–*iso*-PrOH–conc. NH_3 (80:15:5); (C) EtOAc–*iso*-PrOH–conc. NH_3 (100:2:1); (D) Me_2CO–*n*-BuOH–conc. NH_3–H_2O (65:20:10:15); alkaloids were detected by Dragendorff reagent and halide by 0·1% bromocresol purple in 90% EtOH containing a trace of dilute NH_3.

Preparation of strychnine and brucine chloromethochlorides (IX), *chloromethobromides* (X), *bromomethochlorides* (XI) *and bromomethobromides* (XII). 10 g alkaloid was dissolved in 1·5 l. CH_2Cl_2 and the needle crystals were collected after 2 days and well washed with CH_2Cl_2; yield of strychnine quaternary salt 12·0 g, of brucine salt 5·7 g. 10 g alkaloid was dissolved in 3 l. C_6H_6, 25 ml CH_2Br_2 was added and the whole refluxed for 24 hr; after cooling for 3 hr, the needle crystals were collected; yield of strychnine quaternary salt 9·2 g, of brucine salt 13·0 g. 1 g aliquots of these quaternary salts were dissolved in H_2O and aqueous picric acid added until no further ppt. formed. The picrates were well washed with H_2O and crystallized as needle crystals from Me_2CO–H_2O.

MS at 220°: *Strychnine chloromethopicrate*, *m/e* 35 (22%), 36 (100%), 37 (6%), 38 (42%), 334 (28%), 346 (4%); *strychnine bromomethopicrate*, *m/e* 79 (32%), 80 (100%), 81 (32%), 82 (100%), 334 (35%), 346 (5%); *brucine chloromethopicrate*, *m/e* 35 (18%), 36 (100%), 37 (7%), 38 (33%), 50 (24%), 52 (14%), 394 (28%), 406 (2%); *brucine bromomethopicrate*, *m/e* 79 (37%), 80 (63%), 81 (37%), 82 (63%), 94 (100%), 96 (80%), 394 (59%), 406 (0·4%).

The picrates were dissolved in the minimum volume of aqueous Me_2CO and eluted with H_2O from Amberlite IRA 400 ion-exchange resin columns in the chloride or the bromide form. The eluate was evaporated to dryness under reduced pressure and crystallized from H_2O to yield: *Strychnine chloromethochloride*, 0·56 g; NMR, two-proton singlet δ 5·78; MS, *m/e* 35 (18%), 36 (100%), 37 (6%), 38 (50%), 334 (94%), 346 (16%); *strychnine chloromethobromide*, 0·82 g; NMR, two-proton singlet δ 5·73; MS, *m/e* 35 (10%), 36 (100%), 37 (5%), 38 (36%), 79 (28%), 80 (76%), 81 (28%), 82 (76%), 334 (56%), 346 (8%); *Strychnine bromomethochloride*, 0·70 g; NMR, two-proton singlet δ 5·82; MS, *m/e* 35 (12%), 36 (100%), 37 (6%), 38 (42%), 79 (17%), 80 (40%), 81 (17%), 82 (40%), 334 (94%), 346 (22%); *strychnine bromomethobromide*, 0·77 g; NMR, two-proton singlet δ 5·79; MS, *m/e* 79 (37%), 80 (100%), 81 (37%), 82 (100%), 334 (39%), 346 (2%). R_fs in system A: two spots for each compound: lower spot 0·14, upper spot for chlorides 0·24, for bromides 0·28; strychnine 0·59. For all four compounds the R_t was identical with that of strychnine, 4 min.

The four corresponding salts of brucine had MS data similar to those of the corresponding strychnine compounds except that the three compounds containing chlorine showed prominent peaks at *m/e* 50, 52; the three compounds containing bromine showed prominent peaks at *m/e* 94, 96. R_fs in system A: two spots for each compound: lower spot 0·12, upper spot for chlorides 0·23, for bromides 0·25; brucine 0·48. For all four compounds the R_t value was identical with that of brucine, 12 min.

Identification of ionisable halide. 50 mg quaternary halide salt was dissolved in H_2O and eluted from a CG 120 ion-exchange column with H_2O. The eluate was concentrated and examined by TLC using system D: R_f values $Cl^{\ominus}$ 0·25, $Br^{\ominus}$ 0·40. The strychnine and brucine quaternary halides (IX) and (XI) contained only $Cl^{\ominus}$ with no $Br^{\ominus}$, while (X) and (XII) contained only $Br^{\ominus}$ with no $Cl^{\ominus}$.

Reaction of strychnine in methylene dichloride. The quaternary salt was prepared as above; NMR, two-proton singlet δ 5·78; MS, *m/e* 35, 36, 37, 38 (Cl, HCl), absence of bromine; ionisable halide (see above) only $Cl^{\ominus}$; R_f values system A: 0·14, 0·24; R_t 4 min, in agreement with the data for *strychnine chloromethochloride*.

Reaction of strychnine in $CHCl_3$. (a) 10 g strychnine was refluxed for 10 hr with 100 ml $CHCl_3$; yield of quaternary salt 1·93 g. The product was identical with the quaternary salt from (b). (b) 10 g strychnine in 100 ml $CHCl_3$ was allowed to stand at laboratory temp for 14 days; yield of quaternary salt 1·69 g. NMR, two-proton singlet δ 5·73; MS, *m/e* 35, 36, 37, 38 (Cl, HCl), 79, 80, 81, 82 (Br, HBr); R_fs in system A: 0·14, 0·28; ionisable halide (see above) only $Br^{\ominus}$: *picrate* MS, *m/e* 35, 36, 37, 38, (Cl, HCl), absence of bromine; in agreement with *strychnine chloromethobromide*. The mother liquors from (b) were concentrated to dryness; yield 9·8 g. R_fs in system A: 0·90, 0·59, 0·42. (i) 500 mg aliquot was chromatographed on a silica-gel (Woelm) column, the material eluted with EtOAc–*iso*-PrOH (97:3) was taken to dryness and crystallised; yield 30 mg. MS, *m/e* (215°) 130 (15%), 143 (17%), 144 (15%), 185 (100%), 334 (6%), 350 (93%, M^+), in agreement with 16-*hydroxystrychnine*; the IR spectrum and TLC properties were identical with those of an authentic sample, R_fs in systems A: 0·90; B: 0·60; C: 0·27. (ii) 200 mg aliquot was separated by preparative TLC using system B. The lower band was extracted and the residue crystallised from H_2O; yield 48 mg. MS, *m/e* 130 (21%), 143 (18%), 144 (18%), 185 (4%), 334 (100%), 350 (33%, M^+), in agreement with *strychnine* N-*oxide*; the IR spectrum and TLC properties were identical with those of an authentic sample; R_f value in system A: 0·42.

Reaction of brucine in chloroform. 200 mg brucine in 25 ml $CHCl_3$ was allowed to stand at laboratory temp for 14 days: yield of quaternary salt 95 mg; TLC examination of the crystals showed two spots, R_f values in system A: 0·12, 0·25, consistent with brucine chloromethobromide. TLC examination of the mother-liquors showed the presence of alkaloidal spots with R_fs identical with those of 16-hydroxybrucine and brucine *N*-oxide.

Muscle-relaxant activity. Intraperitoneal injections of the quaternary salts into mice gave the following results: *Strychnine chloromethochloride*: (a) 100 mg/kg, death within 6–9 min, muscle relaxation, no tonic convulsions, (b) 50 mg/kg, moderate muscle-relaxant effects from 5 to 20 min after injection, animals survived, (c) 30 mg/kg, no observable effects. *Brucine chloromethochloride*: (a) 200 mg/kg, death within 30 min, muscle relaxation, (b) 100 mg/kg, no observable effects.

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