Tetrahedron, 1960, Vol. 11, pp. 78 to 88. Pergamon Press Ltd. Printed in Northern Ireland

PAPILIONACEOUS ALKALOIDS—XXXVIII

CONTRIBUTION TO THE CHEMISTRY AND STEREOCHEMISTRY OF RETAMINE

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(*Received* 13 *April* 1960)

Abstract—Three new bases related to retamine are described: chlororetamine, isoretamine, and chloroisoretamine. Retamine and isoretamine are 8-hydroxy-(±)-sparteine epimers; chlororetamine is an 8-chloro-(±)-sparteine; chloroisoretamine is an 11-chloro-(±)-α-isosparteine. In the transformation of isoretamine to chloroisoretamine the rearrangement is explained by the modern concept of bridge carbonium ion.

IN previous papers[1], retamine has been formulated as 7- or 9-hydroxy-(+)-sparteine, the 7 and 9 positions of sparteine (I) being considered as equivalent. Ribas and Fraga[1b] have excluded position 8 for the hydroxyl group in retamine, as a ketone cannot be obtained by oxidation. Having also excluded the 6 and 11 positions owing to the failure of several reactions, the only remaining position for the tertiary hydroxyl group was 7 or 9.

Leonard and Marion *et al.*[2], however proved the structural formula of sparteine to be IIa, with the positions 7 and 9 no longer equivalent, and therefore, an investigation of the problem was undertaken. This work is summarized in the following table.

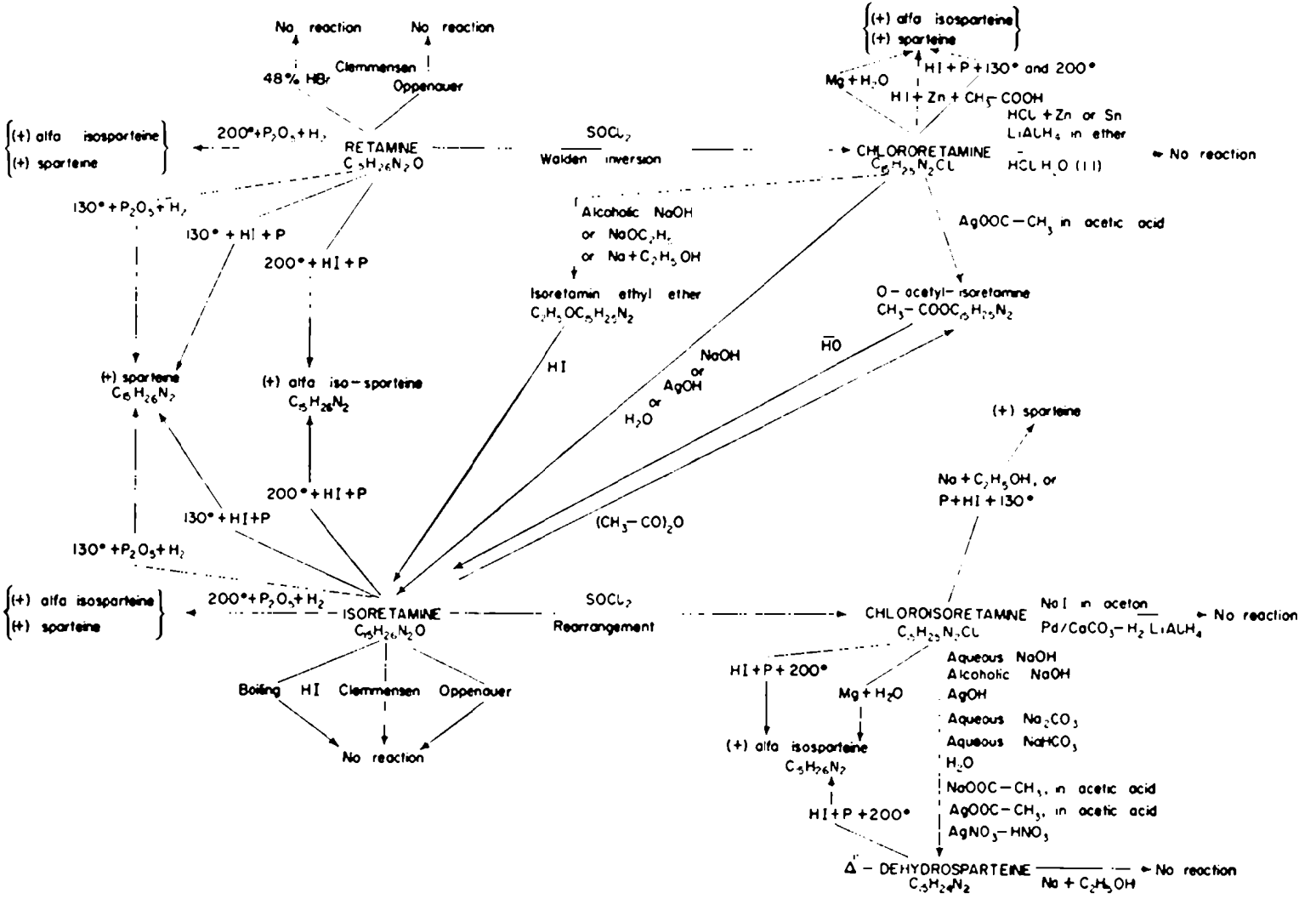
Chlororetamine, a new base, $C_{15}H_{25}N_2Cl$, was obtained by substitution of the hydroxyl group in retamine by chlorine. The carbon–nitrogen skeleton of retamine remains unchanged in this new base, as it can be transformed into a mixture of (+)-α-isosparteine (III) and (±)-sparteine (IIa) by the following methods: reduction with Zn dust and hydrobromic acid in acetic acid, reduction with red phosphorus and hydriodic acid, and hydrolysis of magnesium–chlororetamine formed by treatment of the new base with magnesium in anhydrous ether.

The chlorine atom of the chlororetamine is readily substituted by the action of nucleophilic reagents (NaOH, AgOH, H_2O, etc.) giving rise to a second new base, isoretamine, $C_{15}H_{26}N_2O$, m.p. 162°, an isomer of retamine with the same carbon–nitrogen skeleton since (+)-sparteine and (±)-α-isosparteine are formed by reduction with red phosphorus and hydriodic acid at 130° and 200° respectively.

Both isoretamine and retamine on heating with P_2O_5 at 130° yield a dehydrobase, which can be hydrogenated to (±)-sparteine, and on heating either compound with the same reagent at 200° a mixture of dehydrobases is obtained which on hydrogenation gives (±)-α-isosparteine and (±)-sparteine. The hydroxyl group in retamine or

[1a] I. Ribas, A. Sánchez and E. Primo, *Anales fis. y quim.* **42**, 516 (1946); [b] I. Ribas and F. Fraga, *Anales Real Soc. Espan. Fis. y Quim.* **45B**, 1426 (1949); [c] F. Fraga and I. Ribas, *Ibid.* **46B**, 665 (1950).
[2a] N. J. Leonard and R. E. Beyler, *J. Amer. Chem. Soc.* **72**, 1316 (1950); [b] L. Marion and N. J. Leonard, *Canad. J. Chem.* **29**, 355 (1951); [c] L. Marion, *Bull. Soc. Chim. Fr.* 1193 (1954).

Table summary of retamine chemistry



isoretamine cannot be oxidized to a ketone by the Oppenauer method or with chromic acid.

These reactions showing similar chemical behaviour indicate that retamine and isoretamine are hydroxy-epimer compounds. Neither can be 7- or 9-hydroxy-sparteine as these positions do not allow epimer compounds.

The same conclusion is reached by the examination of the chemical activity of chlororetamine. Substitution of the chlorine by a hydroxyl group quantitatively is independent of the concentration of the nucleophilic reagent and even takes place with water. Therefore, this transformation into isoretamine is a first class nucleophilic substitution reaction (S_N1), which proceeds by a carbonium ion mechanism. But the carbonium ion formation is not consistent with the 7 and 9 positions, which contain bridged head carbons, unable to produce the required structure.[3]

Positions 6 and 11 for the hydroxyl group in the retamine are excluded as 11-(or 6-) hydroxy-sparteine should readily be dehydrated, show a ketone form or be reduced electrolytically, but retamine and isoretamine fail to give these reactions.

Molecular rotations, infra-red spectra, dehydration and the reactions of a new base, chloroisoretamine, indicate 8 as the only position for the hydroxyl group in retamine and isoretamine.

Molecular rotations. If from the molecular rotation (M_D) of retamine, or isoretamine, that of (+)-sparteine is substracted the contribution of the asymmetric centre at C_8 is obtained. The molecular rotation calculated from the value of this contribution is in perfect agreement with the experimental value.

Compound	$[\alpha]_D$	M_D (found)	M_D (calculated)
Retamine	+46·2°	−115	+115
Isoretamine	−14·2°	35	−35
(+)-Sparteine	−17°	−40	

M_D retamine − M_D (+)-sparteine = −115 − 40 = +75

M_D isoretamine − M_D (+)-sparteine = −35 − 40 = −75

Contribution of the asymmetric centre: ±75

Infra-red spectra. Cole *et al.*[4] found that the hydroxyl group of 3-hydroxysteroids exhibits a band between 995 and 1055 cm^{-1}, an axial hydroxyl group absorbing at 995–1035 cm^{-1}, and an equatorial one at 1035–1055 cm^{-1}; the difference being 20–40 cm^{-1}. The infra-red spectra of retamine, isoretamine, and the related (+)-sparteine and (+)-α-isosparteine, under identical conditions (4% in CS_2) show the following intensities:

Retamine	1007 (35%)	1025 (50%)	1050 (50%)		
Isoretamine	1007 (50%)	1027 (55%)	1047 (60%)		
Sparteine	1011 (50%)			1070 (55%)	
α-Isosparteine	1007 (30%)				1107 (30%)

The two bands shown in the spectra of retamine (1025, 1050 cm^{-1}) and isoretamine (1027, 1047 cm^{-1}) must be produced by the hydroxyl group as they do not occur in

[3] D. Bethell and V. Gold, *Quart. Rev.* **12**, 185 (1958).
[4] A. R. H. Cole, R. N. Jones and K. Dobriner, *J. Amer. Chem. Soc.* **74**, 5571 (1952).

the spectra of the related compounds. The frequency, difference and shape of the bands indicate that the lower one is due to an axial, and the higher to an equatorial hydroxyl. But as both retamine and isoretamine have only one hydroxyl group, this must be axial to one ring and equatorial to the other; and this feature can only occur at C_8 position.

The selection of configurations. Formulae IV, IIb and IIc are proposed for retamine isoretamine and chlororetamine respectively. No epimer for chlororetamine is possible since the C_8 position is hindered by the axial C_{12}-hydrogen atom of the D-ring. With Catalin molecular models (Waltham, Essex) it is clearly seen that the voluminous chlorine atom has no room at this hindered position for epimer formation. Isoretamine, obtained from chlororetamine by hydrolysis, must be the less hindered epimer IIb, leaving configuration IV for retamine. A Walden inversion at C_8 must occur in the change of retamine to chlororetamine; but the configuration at C_8 is preserved in going from the chlororetamine to isoretamine. The molecular rotation changes are in good agreement:

$$M_D \text{ retamine} - M_D (+)\text{-sparteine} = +75$$
$$M_D \text{ chlororetamine} - M_D (+)\text{-sparteine} = -28{\cdot}4$$
$$M_D \text{ isoretamine} - M_D (+)\text{-sparteine} = -75$$

The mechanism for these reaction changes is as follows: the action of thionyl chloride on retamine should give rise to chlorosulphite (V), which is possible according to the Catalin molecular models, and the decomposition of this intermediate (V) with simultaneous attack of the chloride ion, from the less hindered side, should bring about the formation of chlororetamine (IIc). Although this compound reacts with nucleophilic reagents by the intermediate of carbonium ion (VI), it always gives isoretamine (IIb) or the corresponding derivative (IId, IIe) because steric hindrance precludes the formation of an epimer.

Chloroisoretamine and its chemical behaviour. Chloroisoretamine, a new base, $C_{15}H_{25}N_2Cl$, m.p. 90°, isomeric with chlororetamine and with the same carbon-nitrogen skeleton, is obtained from isoretamine dihydrochloride on treatment with thionyl chloride. It reacts with nucleophilic reagents to give Δ^{11}-dehydrosparteine (VII), whose structure has been established.[5] As chlororetamine under the same conditions undergoes a substitution, this reaction establishes the chlorine atom at C_{11} in chloroisoretamine.

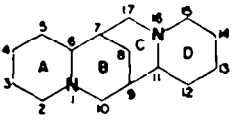
There are two possible configurations for 11-chlorosparteine represented by VIII and IX. Formula VIII is preferred as the chlorine atom is *axial* respecting to both rings C and D and is *trans* with regard to the fourth N_{16} valency, and therefore the four centres participating in the reaction are in the same plain. This structure is supported by the fact that chloroisoretamine readily undergoes elimination reactions, $\Delta^{11,16}$-dehydrosparteinium (X) hydrochloride being produced by heating chloroisoretamine with water on a steam bath. Moreover, its infra-red spectrum shows bands at 800 cm^{-1} and 3457 cm^{-1}, which are typical of the α-isosparteine conformation to which VIII belongs. The fact that chloroisoretamine is a crystalline solid, like α-isosparteine, and not a liquid like chlororetamine and sparteine, is in agreement with the same statement.

[5] N. J. Leonard, P. D. Thomas and V. W. Gash, *J. Amer. Chem. Soc.* 77, 1552 (1955).

In the formation of chloroisoretamine the action of thionyl chloride on isoretamine should give the chlorosulphite (XI); but the steric hindrance of the epimer position of this intermediate forbids the chloride ion attack at C_8. This attack must then take place at C_{11}, with the migration of a hydrogen from C_{11} to C_8, the elimination of SO_2Cl, and the formation of chloroisoretamine.

The intermediate formation of a bridged carbon-hydrogen ion between C_8-C_{11}, usual in policyclic bridged compounds,[6] may facilitate the 1:3-interaction between C_{11}-C_8. Furthermore, the reaction causes a Walden inversion at C_{11}, so that the chloroisoretamine is the 11-chloro-(+)-α-isosparteine (or 6-chloro-(+)-α-isosparteine, VIII).

Dehydration and other reactions common to retamine and isoretamine. An explanation of these reactions is only possible if the hydroxyl group is located at C_8. Both 8-hydroxysparteines are unable to form a double bond between C_7-C_8 or C_8-C_9 by the elimination of one molecule of water, as the formation of these double bonds requires a valency plain structure at C_7 or C_9, prevented by the rigid tetrahedric



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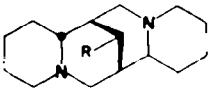
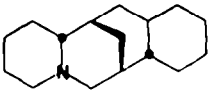
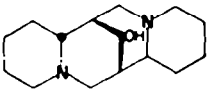


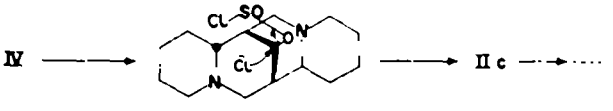
II a R=H II d R=CH_3COO
II b R=HO II e R=C_2H_5O
II c R=Cl II f R=C_6H_5COO



III



IV



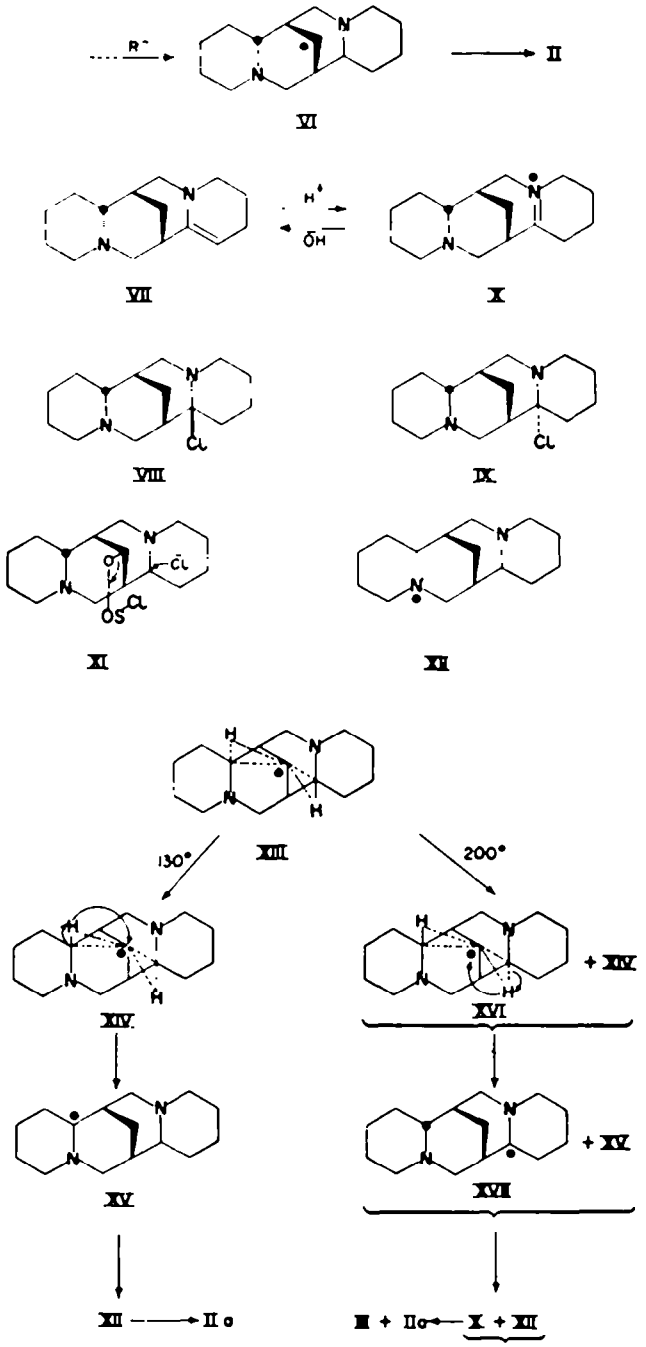
V

structures produced by the convergence of three hexagonal rings (bridgehead carbons). The 8-hydroxysparteines are, therefore, not easy dehydrated; but under vigorous conditions a carbonium ion at C_8 may be formed. This spreads a bridge between the carbons and hydrogens of the 6 and 11 positions (XIII) giving rise to a bridged carbon-hydrogen ion. At low temperature, this bridged ion should react by picking up the twice axial hydrogen at C_6 (XIV) and donating to this position the whole positive charge, with the formation of the classical ion XV. At high temperature, the bridged ion reacts at C_{11} (XVI), in the same way, giving the carbonium ion XVII. Both classical carbonium ions XV and XVII will be converted in the usual way into the enamonium salts XII and X, which on hydrogenation yield (+)-sparteine (IIa) and (+)-α-isosparteine (III) respectively.

The retamine and isoretamine reductions with red phosphorus and hydriodic

[6] T. P. Nevell, E. de Salas and C. L. Wilson, *J. Chem. Soc.* 1188 (1939); [7] J. D. Roberts, C. C. Lee and W. H. Saunders, *J. Amer. Chem. Soc.* 76, 4501 (1954); [8] S. Winstein and M. Shatavsky, *Chem. & Ind.* 56 (1956); [9] A. Gagneux and C. A. Grob, *Helv. Chim. Acta* 42, 1753 (1959).

acid, producing at 130° (+)-sparteine and at 200° (+)-α-isosparteine, are similarly explained by bridged hydrogen–carbonium ion formation. In the first case the bridged ion operates at C_6 and the reduction product is (+)-sparteine, and in the second case at C_{11}, producing (+)-α-isosparteine on reduction.



EXPERIMENTAL

Melting points are uncorrected. Unless specified to the contrary, the reaction products were isolated by ether extraction from an aqueous solution, made alkaline with sodium hydroxide or ammonia. The ether extracts were dried with sodium sulphate (or potassium carbonate) and evaporated on a steam bath.

The chromatography, on Whatman No. 1 paper, was performed according to conditions by Munier[7]. Sparteine and α-isosparteine however, always gave the same spots under these conditions, but they could be separated on Whatman No. 1 paper salted with a buffered solution of citric acid (0·1 M; 11·18 ml)-disodium phosphate (0·2 M; 8·82 ml), or citric acid (0·2 N; 100 ml) sodium citrate (50 ml 0·2 N NaOH) at pH 4·4 in both cases and developed with n-butanol-water (Sparteine R_f - 0·22; α-isosparteine R_f - 0·33).

Retamine (IV). The retamine, m.p. 166°, was isolated from *Retama sphaerocarpa Boiss.*,[1a] and recrystallized from ethanol. $[\alpha]_D^{20}$ + 46·2° (*c* 1·017; absolute ethanol).

Chlororetamine (IIc).

Retamine (1·0 g) dissolved in conc HCl (1·2 ml) was converted to the dihydrochloride by removal of water (*in vacuo* on a steam bath). Thionyl chloride (1·3 ml) was added, and the solution heated at 85–90° for 50 min. After addition of ice-water, the base, an oil (1·05 g) was converted into the following salts:

(a) The *monoperchlorate* crystallized from methanol had m.p. 243–244° dec. (Found: C, 48·9; H, 7·1; N, 7·9; Cl, 19·1. $C_{15}H_{25}N_2Cl{\cdot}ClO_4H$ requires: C, 48·8; H, 7·1; N, 7·6; Cl, 19·0%).

(b) *Chlororetamine monochlorozincate*. To chlororetamine (0·22 g of the oil) dissolved in ethanol (0·5 ml) 3 N chlorozincic acid (0·25 ml) was added, yielding white crystals of chlororetamine monochlorozincate (0·31 g) m.p. 318–320° dec. (Found: Cl, 29·6; $C_{15}H_{25}N_2Cl{\cdot}Cl_4ZnH_2$ requires: Cl, 29·7%).

(c) *Chlororetamine dipicrate*. This was obtained by mixing an aqueous solution of chlororetamine monochlorozincate with saturated solution of picric acid, and had m.p. 208° dec. from ethanol. (Found: C, 45·9; H, 4·4. $C_{15}H_{25}N_2Cl{\cdot}2C_6H_3N_3O_7$ requires: C, 44·6; H, 4·3%).

Chlororetamine. This was obtained, in the usual way, from monoperchlorate as a colourless oil, with a strong basic reaction. $[\alpha]_D^{21}$ + 4·3° (*c* 2·3; absolute ethanol).

Isoretamine (IIb).

Chlororetamine (1·06 g) was converted into its monochlorozincate (1·4 g) and heated with water (50 ml) on a steam bath for 45 min. The isoretamine (0·85 g) recrystallized from acetone m.p. 162°; sublimation point 120–125°/0·05 mm $[\alpha]_D^{21}$ −14·2° (*c* 1·02%; absolute ethanol). (Found: C, 71·9; H, 10·65; N, 10·9. M. wt. by Rast, 236. $C_{15}H_{26}N_2O$ requires: C, 71·9; H, 10·5; N, 11·2%. M. wt. 250).

(a) *Isoretamine monoperchlorate*. Crystallized from methanol, m.p. 195°. (Found: C, 51·6; H, 7·7; N, 23·0. $C_{15}H_{26}N_2O{\cdot}ClO_4H$ requires: C, 51·4; H, 7·7; N, 22·8%).

(b) *Isoretamine diperchlorate*. To the base dissolved in methanol, 70% solution of perchloric acid was added till Congo red changed to blue. The product crystallized from methanol, m.p. of the anhydrous salt 230–232° dec. (Found: C, 39·5; H, 6·1. $C_{15}H_{26}N_2O{\cdot}2ClO_4H$ requires: C, 39·9; H, 6·25%).

(c) *Isoretamine dipicrate* crystallized from ethanol as bright yellow needles, m.p. 195°. (Found: C, 45·75; H, 4·6. $C_{15}H_{26}N_2O{\cdot}2C_6H_3N_3O_7$ requires: C, 45·76; H, 4·6%).

(d) *Isoretamine monohydriodide*. Isoretamine (0·52 g) in warm absolute ethanol (2·5 ml) was treated with 3·0 ml hydriodic acid (sp. gr. = 1·7) and the product (0·44 g) crystallized from methanol, m.p. 246°. (Found: I, 33·7. $C_{15}H_{26}N_2O{\cdot}HI$ requires I, 33·5%).

(e) *Isoretamine chloromercuriate*. To isoretamine (0·3 g) in ethanol conc HCl (0·25 ml) and 5% mercuric chloride was added and the product (0·75 g), crystallized from 10% HCl, had m.p. 250° dec (Found: Hg, 32·85; Cl, 23·2. $C_{15}H_{26}N_2O{\cdot}Cl_4HgH_2{\cdot}H_2O$ requires: Hg, 32·7; Cl, 23·15%).

(f) *Isoretamine monochlorozincate*. Isoretamine (0·27 g) in ethanol (1 ml) was treated with 3 N chlorozincic acid (0·4 ml) and the product (0·51 g), crystallized from water, had m.p. 318° dec (Found: Cl, 29·8; H_2O, 3·78. $C_{15}H_{26}N_2O{\cdot}Cl_4ZnH_2{\cdot}H_2O$ requires: Cl, 29·7; H_2O, 3·77%).

[7a] R. Munier, *Bull. Soc. Chim. Fr.* 852 (1952); [b] R. Munier, *Bull. Soc. Chim. Biol.* 35, 1225 (1953).

(g) O-*acetyl-isoretamine* (IId) *monoperchlorate*. Isoretamine (0·10 g) was heated with acetic anhydride (1·0 ml) on a steam bath for 30 min, acetic anhydride removed by distillation *in vacuo*, methanol (0·4 ml) and 70% perchloric acid added till neutral. The product crystallized from methanol as rhombic plates, m.p. 206–208°. (Found: C, 51·1; H, 7·1; N, 7·2. $C_{18}H_{28}N_2OCOCH_3 \cdot ClO_4H$ requires: C, 51·9; H, 7·4; N, 7·1%).

(h) O-*benzoyl-isoretamine* (IIf) *dihydrochloride*. Isoretamine (0·18 g) in dry benzene (0·7 ml) was refluxed with benzoyl chloride (0·5 ml) for 2 hr. The benzoyl base, an oil (0·16 g) in ethanol (2·6 ml), was treated with a few drops HCl and ether (20 ml) and the O-benzoyl-isoretamine dihydrochloride crystallized (0·14 g), m.p. 213–215° (anhydrous product). (Found: Cl, 16·2. $C_{18}H_{28}N_2OCOC_6H_5 \cdot 2H$ Cl requires: Cl, 16·6%).

Chloroisoretamine (VIII).

This new base was obtained from isoretamine following the technique for chlororetamine from retamine. Isoretamine dihydrochloride (from isoretamine, 2·0 g, and hydrochloric acid, 2·4 ml), well dried, was heated with thionyl chloride (2·4 ml) at 85–90° for 1 hr. The reaction product crystallized from acetone as white prismatic needles (1·2 g), m.p. 90°; sublimation point 80–85°/0·05 mm; $[\alpha]_D^{21}$ · 31·3° (*c* 2·17; absolute ethanol). (Found: C, 66·97; H, 9·5; Cl, 13·0. $C_{18}H_{25}N_2Cl$ requires: C, 67·0; H, 9·3; Cl, 13·2%).

(a) *Chloroisoretamine dipicrate*. Chloroisoretamine (0·05 g) dissolved in the smallest amount ethanol, was treated with saturated ethanolic solution of picric acid till Congo red paper turned blue. The salt (0·09 g) recrystallized from ethanol, m.p. 208–209°. (Found: C, 44·9; H, 4·7. $C_{18}H_{25}N_2Cl \cdot 2C_6H_3N_3O_7$ requires: C, 44·6; H, 4·3%).

(b) *Chloroisoretamine monoperchlorate*. The base in methanol was treated with perchloric acid till just acid, and adjusting the pH with ammonia to 8. By partial evaporation of the solvent, the reaction product crystallized. Recrystallization from methanol–acetone gave colourless prisms m.p. 196–197°. (Found: C, 49·2; H, 6·9. $C_{18}H_{25}N_2Cl \cdot ClO_4H$ requires: C, 48·8; H, 7·1%).

(c) *Chloroisoretamine diperchlorate*. Chloroisoretamine (0·06 g), dissolved in the minimum of methanol, was treated with 20% perchloric acid till acid. The salt was recrystallized from methanol as white needles, m.p. 255–256°. (Found: C, 37·4; H, 5·6. $C_{18}H_{25}N_2Cl \cdot 2ClO_4H$ requires: C, 38·4; H, 5·8%).

Chemical Behaviour of Retamine, Isoretamine and Related Compounds

1. *Negative reactions*

Retamine and isoretamine were recovered unchanged after being submitted to the following reactions: Oppenauer oxidation, silver hydroxide oxidation, Clemmensen reduction, reaction with boiling 57% hydriodic acid (1 hr), and treatment with boiling 48% hydrobromic acid (6 hr).

2. *Dehydrations*

(a) *Retamine dehydration at* 130° *with phosphorus pentoxide*. Retamine (0·5 g) mixed with phosphorus pentoxide (4·5 g) was heated at 130° for 4 hr. After addition of ice, the reaction product, a basic oil (0·26 g), in N hydrochloric acid (25 ml), was hydrogenated over Adams catalyst (0·037 g) for 2 hr. The solution was made alkaline with 33% NaOH and steam distilled. In the distillate (300 ml) the base was precipitated with excess picric acid. The crude picrate (0·27 g) recrystallized from methanol as (+)-sparteine dipicrate (0·12 g), m.p. 205°, identical with an authentic specimen (mixed m.p., infra-red spectrum, and R_f number, AcONa paper. Ba15. R_f 0·82).

(b) *Retamine dehydration with phosphorus pentoxide at* 200°. Retamine (0·1 g) and P_2O_5 (1·0 g) was heated at 200–220° for 6 hr and the product, after hydrogenation, gave a mixture (0·06 g) of 2 bases: one, in larger proportion, was identified as α-isosparteine by R_f number, and the other identified, in the same way, as (−)-sparteine.

(c) *Isoretamine dehydrations with phosphorus pentoxide at* 130° *and* 200°. These two dehydrations under similar conditions gave the same results as retamine, grouped together in Table 1.

3. *Reductions*

(a) *Retamine reduction with hydriodic acid and red phosphorus at* 200°. Retamine (0·1 g), red phosphorus (0·1 g) and hydriodic acid (1 ml; sp. gr. 1·7) were heated in a sealed tube at 200° for 50 hr. The reaction product was a mixture of a crystalline solid (0·04 g) and oil. The solid was

identified as (+)-α-isosparteine by comparison its m.p. 95–115° and R_f number with an authentic sample (NaOAc paper. Ba2. R_f = 0·82; KCl paper. Bc2. R_f = 0·76), and m.p. of its dipicrate 219–220° dec. The oil, a complex mixture, on paper chromatography (NaOAc paper. Ba2) showed, at least, four spots: one of them coincided with that of α-isosparteine (R_f = 0·82) and a second with that of Δ^{11}-dehydrosparteine (R_f = 0·55).

TABLE 1. DEHYDRATIONS WITH P_2O_5

Product to be dehydrated	Heating temp. and time	Hydrogenated dehydrobase	Identified
Retamine	130°, 4 hr	(±)-sparteine	as dipicrate
Isoretamine	130°, 4 hr	(±)-sparteine	as dipicrate
Retamine	200°, 6 hr	(±)-α-isosparteine and (±)-sparteine	by its R_f
Isoretamine	200°, 6 hr	(±)-α-isosparteine and (±)-sparteine	by its R_f

TABLE 2. REDUCTIONS WITH HYDRIODIC ACID AND RED PHOSPHORUS

Product to be reduced	Heating temp. and time	Reduction product	Identification
Retamine	200°; 50 hr	(−)-α-isosparteine	M.p.; dipicrate; R_f
Isoretamine	200°; 50 hr	(±)-α-isosparteine	M.p.; dipicrate; diperchlorate; R_f
Retamine	130°; 100 hr	(−)-sparteine	Dipicrate; monoperchlorate; dihydrobromide; bisulphate
Isoretamine	130°; 100 hr	(+)-sparteine	Dipicrate; R_f
Chlororetamine	200°; 50 hr	(±)-α-isosparteine and (+)-sparteine	M.p.; R_f Dipicrate; R_f
Chloroisoretamine	200°; 50 hr	(+)-α-isosparteine	M.p.; dipicrate; R_f
Chlororetamine	130°; 100 hr	(±)-α-isosparteine and (+)-sparteine	R_f R_f
Chloroisoretamine	130°; 100 hr	(+)-sparteine	Dipicrate; R_f

(b) *Isoretamine reduction with boiling hydriodic acid and red phosphorus.* Isoretamine (0·25 g), red phosphorus (0·6 g) and hydriodic acid (6 ml; sp. gr. 1·7) was refluxed for 100 hr. After treatment with zinc dust (0·5 g), the product, an oil (0·28 g), in pet ether (25 ml b.p. 50–70°) was chromatographed on alumina (10 g). Elution with pet ether gave (+) sparteine identified as dipicrate (0·13 g), m.p. 204–205°, by comparison with an authentic specimen.

(c) *Other reductions of related compounds with hydriodic acid and red phosphorus.* Many other reductions were carried out under similar conditions and with similar results, which are grouped together in Table 2.

(d) *Chloroisoretamine reduction through the respective Grignard compound.* Magnesium (0·1 g) in anhydrous ether (8 ml) was treated with bromobenzene (0·47 g). After the reaction had proceeded, chloroisoretamine (0·27 g) was added and the mixture refluxed for 13 hr. The reaction product, hydrolysed by dil HCl, was an oil (0·20 g) from which (+)-α-isosparteine (0·06 g) was isolated and identified by its m.p. 95–110°, picrate m.p. 218° dec, and perchlorate m.p. 264° dec.

(e) *Chlororetamine reduction through the respective Grignard compound.* When the reaction between magnesium (0·14 g) and ethyl bromide (0·38 ml) in anhydrous ether (15 ml) had started,

TABLE 3

Starting compound	Reagent	Reaction conditions	Reaction product
Chlororetamine (0·68 g)	10% NaOH/EtOH	10 days, room temp. or 15 min steam bath	Isoretamine (0·54 g)
Chloroisoretamine (0·25 g)	10% NaOH/EtOH	90 min steam bath	Δ^{11}-Dehydrosparteine (0·21 g diperchlorate)
Chlororetamine (0·10 g)	H_2O (Cu_2Cl_2 trace)	1 hr; steam bath	Isoretamine (0·08 g)
Chloroisoretamine (0·13 g)	H_2O (Cu_2Cl_2 trace)	30 min; steam bath	Δ^{11}-Dehydrosparteine (0·3 g dipicrate)
Chlororetamine (0·22 g monoperchlorate)	AgOAc/AcOH (0·09 g/5 ml)	reflux. 15 min	O-Acetyl-isoretamine (0·16 g monoperchlorate)
Chloroisoretamine (0·16 g)	AgOAc/AcOH (0·08 g/5 ml)	reflux. 15 min	Δ^{11}-Dehydrosparteine (0·15 g diperchlorate)
Chlororetamine (0·10 g)	AgOH/EtOH	4 hr; room temp.	Isoretamine (0·08 g)
Chloroisoretamine (0·10 g)	AgOH/EtOH	45 min; steam bath	Δ^{11}-Dehydrosparteine (0·08 g free base)
Chlororetamine	NaOEt/EtOH	2½ hr; steam bath	Isoretamine ethyl ether (see below)
Chloroisoretamine	NaOEt/EtOH	2 hr; steam bath	Δ^{11}-Dehydrosparteine

chlororetamine (0·2 g) in ether (10 ml) was added and the mixture refluxed for 2 hr. After acidic hydrolysis, the product (0·18 g) in pet ether (40 ml) was chromatographed on alumina (8 g) and the first 8 fractions eluted with the same solvent, gave a colourless oil (0·055 g) which was converted into (+)-sparteine dipicrate, m.p. 204–205°. The last fractions eluted with pet ether/benzene (10/1) gave a solid, which after sublimation (0·01 g) was converted in picrate m.p. 215–216° dec and identified as α-isosparteine dipicrate.

(f) *Chlororetamine reduction with zinc dust and hydrobromic acid in acetic acid.* Chlororetamine (0·25 g), hydrobromic acid (2 ml; sp. gr 1·38), zinc dust (1·5 g) and acetic acid (10 ml) were refluxed for 20 hr. The reaction product, an oil (0·21 g). treated with acetone, gave crystals (0·03 g) of (·)-α-isosparteine. The oil separated from the crystalline solid in pet ether (50 ml; b.p. 50–70°) was chromatographed on alumina (10 g). The 6 first fractions eluted with the same solvent, gave an oil (0·035 g) identified as (+)-sparteine by mixed m.p. of its dipicrate (204°).

(g) *Chloroisoretamine reduction with sodium and ethanol.* Chloroisoretamine (0·25 g) in absolute ethanol (25 ml) was treated with sodium (3 g). The reaction product, steam distilled was precipitated with picric acid. The precipitate (0·52 g), after recrystallization from acetone, was identified as (+)-sparteine dipicrate, m.p. 204–205°. The identification was confirmed by m.p. and mixed m.p. of its perchlorate (170°) with (+)-sparteine monoperchlorate.

(h) *Attempted reduction of chlororetamine with sodium and ethanol.* Chlororetamine (0·56 g) in anhydrous ethanol (50 ml) was treated with sodium (6 g). The product worked up as in the foregoing preparation gave only an impure picrate. The base (0·32 g) from the crude picrate (0·90 g) in methanol, was treated with 20% perchloric acid till acid. The reaction product, crystallized from methanol, m.p. 232° dec, was identified with *isoretamine ethyl ether* (IIe) *diperchlorate* by its mixed m.p. and R_f number (NaOAc paper. Ba2. R_f · 0·88–KCl paper. Bc10. R_f 0·64–Monopotassium phosphate paper. n-Butanol/water. R_f 0·60).

4. *Chlororetamine nucleophilic substitutions and chloroisoretamine eliminations*

The same nucleophilic reagents, causing substitutions in chlororetamine, bring about eliminations with chloroisoretamine. Chlororetamine always yields isoretamine when treated with nucleophilic reagents containing the $H\bar{O}$ ion, whereas chloroisoretamine always affords Δ^{11}-dehydrosparteine with the same reagents.

Table 3 gives comparative experiments:

Chlororetamine reaction with sodium alcoholate. Chlororetamine monoperchlorate (0·5 g) was added to a solution of sodium (2 g) in anhydrous ethanol (30 ml). The solution was heated for 2½ hr and steam distilled. To the distillate (750 ml), perchloric acid was added (blue colour with Congo red) and the *isoretamine ethyl ether* (IIe) *diperchlorate* (0·48 g), crystallized from methanol, had m.p. 233–234° dec (Found: C, 42·8; H, 6·8; N, 5·6. $C_{16}H_{28}N_2OC_2H_5 \cdot 2ClO_4H$ requires: C, 42·6; H, 6·7; N, 5·8%).

The free base, an oil b.p. 125–127°/0·1 mm, was converted into *isoretamine ethyl ether monoperchlorate*, m.p. 155–156° (Found: C, 54·5; H, 7·4; N, 7·2. $C_{16}H_{28}N_2OC_2H_5 \cdot ClO_4H$ requires: C, 53·9; H, 8·2; N, 7·4%).

Cleavage of isoretamine ethyl ether diperchlorate (0·20 g) with boiling hydriodic acid (4 ml; sp. gr. 1·7) gave isoretamine (0·03 g) m.p. 161°.

Acknowledgements—We thank Professor Nelson J. Leonard (Urbana, Illinois, U.S.A.) for specimens of $\Delta^{11(16)}$-dehydrosparteinium diperchlorate and α-isosparteine, kindly sent to us, Dr. Guillermo García-Muñoz for his magnificent help in carrying out some reductions in sealed tube, Dr. J. Calderón, of Instituto "Alonso Barba" (Madrid), for many microanalysis, and Dr. J. Morcillo, of Instituto "A. G. de Rocasalano" (Madrid), for the infra-red spectra.