CONFIGURATION AND CONFORMATION OF ALL FOUR COCAINES FROM NMR SPECTRA *

BY

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The configurations of (±)-allococaine and (±)-allopseudococaine have been determined, for the first time in an unambiguous way, by means of NMR spectroscopy. The known configurations of (±)-cocaine and (±)-pseudococaine receive independent confirmation.

The preferential conformation of the piperidine ring of the tropane nucleus is found to be the chair form in all four isomers, and also in the methyl esters of the four corresponding isomers of ecgonine.

The preparation of (±)-allococaine and (±)-allopseudococaine has been improved.

1. Introduction

(—)-Cocaine was subjected to an extensive chemical investigation after its isolation from leaves of *Erythroxylon coca* in 1860 by *A. Niemann* and *F. Wöhler* [1]. By means of complete hydrolysis, (—)-ecgonine is obtained from (—)-cocaine in addition to methanol and benzoic acid. Upon partial hydrolysis, benzoyl-(—)-ecgonine is formed, in addition to methanol. The structure of cocaine (and ecgonine) was clarified chemically and confirmed by *Willstätter*'s synthesis [2]. Also by a chemical method, the connection was established with (+)-pseudococaine and (+)-pseudoecgonine respectively, which can be formed from (—)-cocaine upon reaction with alkali.

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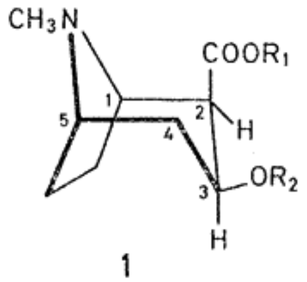
* This paper is to be considered as a continuation of studies on the stereochemistry of tropane alkaloids by one of us (*H. C. B.*). For the preceding paper see: *H. C. Beyerman, C. M. Siegmann, F. L. J. Sixma* and *J. H. Wisse*, The Sterical Structure of Tropinol and Pseudotropinol, Rec. Trav. Chim. **75,** 1445 (1956).

** The results of this investigation were communicated by one of us (*A. S.*) at the meeting of the Royal Netherlands Chemical Society, Division of Organic Chemistry, in Delft, October 13, 1967; Chem. Weekblad **63,** No. 39, B 418 (1967).

[1] *F. Wöhler*, Ann. **114,** 213 (1860); **121,** 372 (1862). For historical details see, *e.g.*, *E. Winterstein* and *G. Trier*, "Die Alkaloide", 2nd Ed., Berlin (1931), 311-313.

[2] The reader is referred to: *T. A. Henry*, The Plant Alkaloids, London, 4th Ed. (1949) 92-100. *H. L. Holmes*, in *R. H. F. Manske* and *H. L. Holmes*, The Alkaloids, I, Chapter 6, New York (1950). *G. Fodor*, in *R. H. F. Manske*, The Alkaloids, VI, Chapter 5, New York (1960). *H. G. Boit*, Ergebnisse der Alkaloid-Chemie bis 1960, Berlin (1961) 80-85. *G. Fodor*, in *R. H. F. Manske*, The Alkaloids, IX, Chapter 7, New York (1967).

Pseudococaine was found to be the C_2 epimer of cocaine. Further chemical investigation threw light on the relative configuration of cocaine (**1**) and pseudococaine (**2**) as shown in the Figure. In the recent past the absolute configuration of (−)-cocaine, and consequently also that of (+)-pseudococaine, was determined by means of a chemical correlation with L-glutamic acid [3]. The relative configuration was confirmed, and extended with conformational data, by means of an X-ray diffraction analysis of (−)-cocaine hydrochloride [4]. In this *crystal* the piperidine ring of the tropane nucleus has the chair form, with C_3 displaced less, and N displaced more, than usual from the plane of the ring. The benzoyloxy side-chain on C_3 is equatorial, and the methoxycarbonyl side-chain on C_2 is axial. The substituents are cis to each other and to the nitrogen atom.



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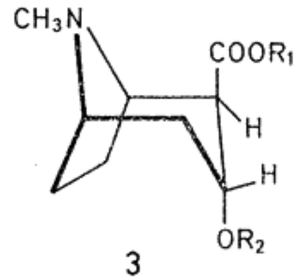

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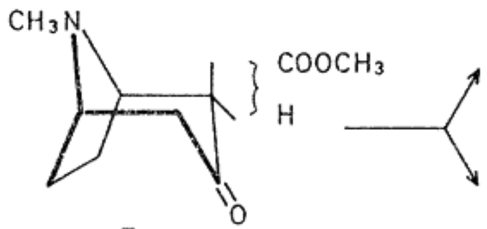

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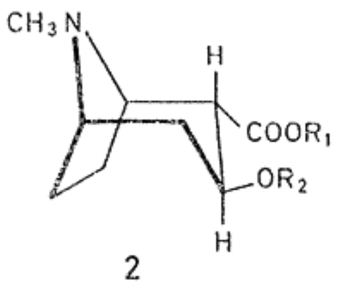

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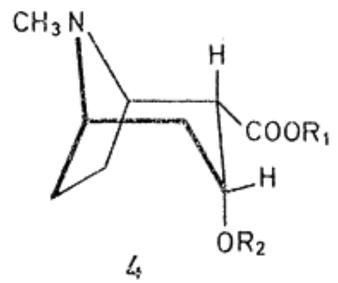

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Figure

1	Cocaine,	$R_1 = CH_3$ and $R_2 = CO \cdot C_6H_5$	3	Allococaine,	$R_1 = CH_3$ and $R_2 = CO \cdot C_6H_5$
	Ecgonine,	$R_1 = R_2 = H$		Alloecgonine,	$R_1 = R_2 = H$
2	Pseudococaine,	$R_1 = CH_3$ and $R_2 = CO \cdot C_6H_5$	4	Allopseudococaine,	$R_1 = CH_3$ and $R_2 = CO \cdot C_6H_5$
	Pseudoecgonine,	$R_1 = R_2 = H$		Allopseudoecgonine,	$R_1 = R_2 = H$

5 2-Methoxycarbonyltropinone

[3] *E. Hardegger* and *H. Ott*, Helv. Chim. Acta **38,** 312 (1955).
[4] *E. J. Gabe* and *W. H. Barnes*, Acta Cryst. **16,** 796 (1963).

A study of the structural formula **1** of cocaine reveals that the four asymmetrical centres in the bicyclic system give rise to eight isomers, to be arranged as four diastereoisomeric pairs. In addition to cocaine **1** and pseudococaine **2** (and the corresponding ecgonines) therefore two other racemic "cocaines" may also be expected. In the reaction product of the reduction of 2-methoxycarbonyltropinone (**5**) *R. Willstätter* found, in addition to ecgonine and ψ-ecgonine methyl esters, another substance, which he called "das dritte racemische Ecgonin" [5]. Much later, *Zeile* and *Schulz* converted a "third" ecgonine, which had been prepared according to *Willstätter*, into the methyl ester, and after treatment with benzoic anhydride in benzene obtained "das dritte racemische Cocain" [6]. *Findlay* [7] as well as *Preobrazhenskii et al.* [8] finally prepared the last two cocaines (and ecgonines). These racemates were called allococaine and allopseudococaine (and allo- and allopseudoecgonine).

In Table I we have listed the physical constants of the racemates of the last two cocaines (and ecgonines) found by *Findlay* [7] and by the Russian group [8]. From this, very considerable differences between them become apparent; the data of *Zeile* and *Schulz* [6] are completely different.

Various investigators, such as *Bose* and *Chaudhury* [9], *Findlay* [7], *Fodor* [10], and *Preobrazhenskii et al.* [8], gave a *tentative* assignment of the configuration to allococaine and allopseudococaine on the basis of chemical experiments. *Preobrazhenskii et al.* [11] investigated the formation of intramolecular hydrogen bonds in the methyl esters of the four isomeric ecgonines by means of infrared spectroscopy. Their assignment of the configurations of alloecgonine methyl ester and allopseudoecgonine methyl ester, and, consequently, of the corresponding cocaine isomers, rests completely upon the assumption that the piperidine ring of the tropane nucleus is in the chair form, an assumption for which there was no independent evidence.

It was obvious that a definitive clarification of the configurations was required. At the same time it appeared desirable to gain an insight into the conformations of all four cocaines and the corresponding ecgonine methyl esters, this also in order to verify the assumptions and conclusions from the infrared spectroscopic analysis [11].

[5] *R. Willstätter, O. Wolfes* and *H. Mäder*, Ann. **434,** 111 (1923).
[6] *K. Zeile* and *W. Schulz*, Ber. **89,** 678 (1956).
[7] *S. P. Findlay*, J. Org. Chem. **21,** 711 (1956); **24,** 1540 (1959).
[8] *M. S. Bainova, G. I. Bazilevskaya* and *N. A. Preobrazhenskii*, Zhur. Obshch. Khim. **30,** 3258 (1960); English translation 3227.
[9] *A. K. Bose* and *D. K. R. Chaudhury*, Nature **171,** 652 (1953).
[10] *G. Fodor*, Experientia **11,** 129 (1955) and Reference 2.
[11] *M. S. Bainova, G. I. Bazilevskaya, L. D. Miroshnichenko, N. A. Preobrazhenskii*, Dokl. Akad. Nauk SSSR **157,** 599 (1964); English translation 703.

Table I

Data on some cocaines, ecgonines, and derivatives

Structure see Figure	This paper		*Findlay* [7]		*Preobrazhenskii* [8,11]	
	Name	M.p. °C	Name	M.p. °C	Name	M.p. °C
3	Allococaine	95-97	Allopseudo-cocaine	93-95	Allococaine	yellow oil
Hydrochloride	—	—		—		hygr. cryst. 103.5-132 (def. 128)
Picrate		161-162		161-162		
4	Allopseudo-cocaine	83-84	Allococaine	82-84	Allopseudo-cocaine	83-84 (def. 81.5)
Hydrochloride		209-210		201.5		177-178 (def. 176)
Picrate		213-214		178.5-180		172-174 (def. 170)
3	Alloecgonine	235 *	Allopseudo-ecgonine	243		
Hydrochloride		198-199		213		
4	Allopseudo-ecgonine	224 *	Alloecgonine	240-241		
Hydrochloride		—		231.5-233.5		
3	Alloecgonine methyl ester	79-80	Allopseudo-ecgonine methyl ester	80-80.5	Alloecgonine methyl ester	78.5-80
Hydrochloride		189-190		191.5-192		yellow oil
Picrate		135-136		135-136		126-131 (def. 125)
4	Allopseudo-ecgonine methyl ester	72-73	Alloecgonine methyl ester	81.5-83.5	Allopseudo-ecgonine methyl ester	82-83.5
Hydrochloride		193-194		—		188-189.5
Picrate		194-195		195-196 (203-203.5)		196-198 (def. 195)
Hydroacetate		107-109		108-110		

Zeile and *Schulz* [6]: Third racemic cocaine (0.5 H_2O) m.p. 156-157°; third racemic ecgonine methyl ester (0.5 H_2O) m.p. 203.5°.

* See experimental part.

We have found that both the configuration and the preferential conformation of *all four* racemic cocaines and those of the corresponding ecgonine methyl esters can be derived from the proton magnetic resonance spectra in a wholly satisfactory way. Considering the discrepancies in the published data of the compounds in question (Table I), the preparation of pure racemates was our first objective. In the tests for the absence of isomers in the different stages of preparation of the racemates, proton magnetic resonance spectroscopy proved to be invaluable.

2. Synthetic chemistry

Our starting material was racemic 2-methoxycarbonyltropinone (**5**). This compound is obtained most conveniently by the Robinson-Schöpf condensation of monomethyl β-ketoglutarate, obtained from β-ketoglutaric anhydride, with succindialdehyde and methylamine according to an extensive investigation of *Findlay* [12].

The 2-methoxycarbonyltropinone was converted by catalytic hydrogenation and epimerization into the methyl ester of allopseudoecgonine and of alloecgonine. Benzoylation of these compounds yielded allopseudococaine **4** and allococaine **3** (Figure). We did not succeed in reproducing the directions of the Soviet workers [8]. A reproduction of the intricate prescriptions of *Findlay* [7] at first involved us in difficulties. After having made a number of modifications, which appear from the experimental part, we succeeded in obtaining the desired compounds in the pure form. In this connection it is to be noted that we prefer the nomenclature used by the Russian workers for allo- and allopseudococaine [8,11], which is different from that of *Findlay* [7], for reasons which will appear later. Reasonable agreement was found to exist between the data as found by us and those given by *Findlay* [7] (Table I).

The deviations from the data of the Russian group [8] may have been caused by handling mixtures of isomeric ecgonines. The different data of *Zeile* and *Schulz* [6] are inexplicable to us.

3. Proton magnetic resonance spectra

The application of proton magnetic resonance spectroscopy to configurational and conformational problems is often based on the correlation of values of coupling constants between vicinal protons with the torsional angle between the carbon-hydrogen bond directions. In this connection use is made of equations introduced by *Karplus* [13].

In the case of the cocaines and ecgonines, three proton-proton couplings are of great importance for this type of analysis, *viz.* one between the

[12] *S. P. Findlay*, J. Org. Chem. **22,** 1385 (1957).
[13] *M. Karplus*, J. Chem. Phys. **30,** 11 (1959).

protons on C_2 and C_3, and two between the proton on C_3 and the two protons on C_4. Owing to the presence of a methoxycarbonyl substituent on C_2 and a hydroxyl or benzoyloxy substituent on C_3 a sufficient difference in the chemical shift for the protons on C_5 and C_3 of the tropane nucleus has arisen, so that the signals of these protons are observed separately.

In view of the sensitivity of the parameters in the Karplus equations to the nature of the substituents [14,15], values derived from related compounds are very desirable. For the ecgonine methyl esters we chose tropine and pseudotropine as model substances, for the cocaines we chose tropine benzoate and pseudotropine benzoate (tropacocaine), the configuration of which is known [16].

A difficulty might have occurred in the analysis of the C_3 proton signal owing to strong coupling between the geminal protons on C_4, a phenomenon which is observed with pseudotropine under certain conditions [17]. With the ecgonine methyl esters and the cocaines it was established by spin decoupling that no strong coupling occurred. Owing to the sufficient differences in chemical shift a first-order analysis could be applied. With pseudotropine and its benzoate the coupling constants for the proton on C_3 were found by analysis of the absorption signal as X-part of an AA'BB'X-system [18]. The relevant data from the spectra have been listed in Tables II and III. For the calculation of the torsional angles the values for the parameters in the Karplus equations, as given by *Williamson* and *Johnson* [14], were used. These give the best correlation if it is taken into account that the *sum or the difference* of the two torsional angles between the C_3—H bond and the two C_4—H bonds must be about 120°. The values for the torsional angles are listed in Table IV.

From a comparison of the data for the ecgonine methyl esters and the corresponding cocaines it is at once obvious that no essential change of the conformation of the six-membered ring is to be found when the hydroxyl group has been benzoylated. All the conclusions as to the conformations of the cocaines on the basis of the values found for the torsional angles are also valid to the corresponding ecgonine methyl esters.

[14] *K. L. Williamson* and *W. S. Johnson*, J. Am. Chem. Soc. **83,** 4623 (1961).
[15] *R. J. Abraham, L. D. Hall, L. Hough* and *K. A. McLauchlan*, J. Chem. Soc. **1962,** 3699; *L. D. Hall*, Chem. Ind. London **1963,** 950.
[16] *J. W. Visser, J. Manassen* and *J. L. de Vries*, Acta Cryst. **7,** 288 (1954); see also other papers mentioned in Reference 2 and in the first Reference in this paper marked with one asterisk.
[17] *R. J. Bishop, G. Fodor, A. R. Katritzky, F. Soti, L. E. Sutton* and *F. J. Swinbourne*, J. Chem. Soc. (C) **1966,** 74.
[18] *J. Parello, P. Longevialle, W. Vetter* and *J. A. McCloskey*, Bull. Soc. Chim. France [5], **30,** 2787 (1963).

Table II

NMR-spectral data of 3-benzoyloxytropane derivatives

Compound	Solvent	Chemical shifts, δ-values (ppm)						Vicinal coupling constants (cps)			
		H_1	H_2	H_3	H_5	CH_3N	CH_3O	$J_{2\,3}$	$J_{3\,4ax}$	$J_{3\,4eq}$	$J_{1\,2}$
Tropine benzoate	CCl_4	3.08	— [a]	5.25	3.08	2.25	—	—	5	1-2	—
Pseudotropine benzoate	$CDCl_3$	3.22	— [a]	5.28	3.22	2.33	—	—	9.8	7.5	—
Cocaine	$CDCl_3$	3.55	3.03	5.27	3.27	2.21	3.71	6.0	11.6	6.0	3
Pseudococaine	$CDCl_3$	3.50	3.15	5.58	3.25	2.41	3.63	10.4	10.4	6.8	3
Allococaine	$CDCl_3$	3.65	2.82	5.67	3.17	2.25	3.76	1-2	5	1-2	3
Allopseudococaine	$CDCl_3$	3.50	3.15	5.65	3.15	2.33	3.53	5	5	1-2	—

[a] Signals not identified.

Table III

NMR-spectral data of 3-hydroxytropane derivatives

Compound	Solvent	Chemical shifts, δ-values (ppm)						Vicinal coupling constants (cps)			
		H_1	H_2	H_3	H_5	CH_3N	CH_3O	$J_{2\,3}$	$J_{3\,4ax}$	$J_{3\,4eq}$	$J_{1\,2}$
Tropine	$CDCl_3$	3.07	— [a]	3.99	3.07	2.25	—	—	5	1-2	—
Pseudotropine	$CDCl_3$	3.17	— [a]	3.88	3.17	2.30	—	—	9.8	7.0	—
Ecgonine methyl ester	$CDCl_3$	3.60	2.75	3.85	3.19	2.20	3.75	5.4	—	—	3
Pseudoecgonine methyl ester	$CDCl_3$	3.45	2.70	4.13	3.21	2.38	3.73	10.0	10.0	7.0	3
Alloecgonine methyl ester	$CDCl_3$	3.57	2.62	4.37	3.08	2.18	3.70	1-2	5	1-2	3
Allopseudoecgonine methyl ester	$CDCl_3$	3.42	2.90	4.27	3.08	2.30	3.73	5	5	1-2	3

[a] Signals not identified.

Table IV

Torsional angles in tropane derivatives
(Calculated [14] from: $J = 16\cos^2\varphi$ for $90° \leqslant \varphi \leqslant 180°$
$J = 10\cos^2\varphi$ for $0° \leqslant \varphi \leqslant 90°$)

Observed coupling constant (cps)	Allowed torsional angles	
	$J_0 = 16$ cps	$J_0 = 10$ cps
1-2	104-111	72-63
5	124	45
5.4	126	43
6.0	128	39
6.8	131	35
7.0	132	33
7.5	133	30
9.8	142	14
10.0	143	0
10.4	145	—
11.6	148	—

4. Discussion and conclusions

(a) *Cocaine and Pseudococaine (Ecgonine and Pseudoecgonine methyl esters)*

Since the configurations of these two isomers are known [2], proton magnetic resonance spectroscopy here yields an independent confirmation not only of these configurations, but also of the preferential conformations. A comparison of the values for the torsional angles between the C_3—H bond and the two C_4—H's with the corresponding angles in pseudotropine benzoate (Table IV) shows that the benzoyloxy group must occupy the same position in all three compounds. The conclusion that pseudotropine benzoate occurs mainly in a chair form on the basis of the angles found [18] applies equally to cocaine (**1**) and pseudococaine (**2**). In this chair form the benzoyloxy group occupies the equatorial position.

From the ratio of the coupling constants between H_3 and H_{4ax} and between H_3 and H_{4eq} it can be deduced according to *Lambert et al.* [19] that the chair form in cocaine is less flattened than in pseudococaine, and in pseudococaine less again than in pseudotropine benzoate. The deviations are highly symmetrical, considering the identical values for corresponding

[19] *J. B. Lambert*, J. Am. Chem. Soc. **89**, 1836 (1967); *J. B. Lambert, R. G. Keske* and *D. K. Weary*, J. Am. Chem. Soc. **89**, 5921 (1967).

couplings between the proton on C_3, the proton on C_2, and the two protons on C_4.

The value of the coupling constant between the proton on C_3 and that on C_2 provides a definite answer about the configuration of the substituent on C_2. In cocaine the methoxycarbonyl group is in the axial position, in pseudococaine in the equatorial position, so that the configuration already known is confirmed (Figure).

b) Allococaine and Allopseudocoeaine (Allo- and Allopseudoecgonine methyl ester)

Pseudococaine **2** is the C_2 epimer of cocaine **1**. We prefer a nomenclature in which for allococaine **3** the configuration of the methoxycarbonyl group on C_2 corresponds to that in cocaine and, consequently, that in allopseudococaine **4** to that in pseudococaine, in conformity with *Preobrazhenskii et al.* [8,11] and contrary to *Findlay* [7] (Figure).

In view of the fact that in cocaine and pseudococaine the benzoyloxy group on C_3 has the same configuration and corresponds to that in pseudotropine benzoate, the configuration of that group in allococaine and allopseudococaine must differ from it and correspond to that in tropine benzoate.

The correspondence of the values of the coupling constants between the proton on C_3 and those on C_2 and C_4 for tropine benzoate, allococaine, and allopseudococaine implies that allococaine and allopseudococaine have broadly the same conformation as tropine benzoate, for which the chair form was concluded to be present [18]. A coupling constant of 5 cps between the equatorial proton on C_3 and the proton on C_2 implies that this proton must occupy the *axial* position and, consequently, the methoxycarbonyl group the equatorial position. The compound for which this situation is found is *allopseudococaine* **4** in our nomenclature.

The configurations and preferential conformations of all four isomeric cocaines can be determined on the basis of the proton magnetic resonance spectra. A comparison with the spectra of the methyl esters of all four ecgonines shows that there is no appreciable difference in conformation: all the compounds are preferentially in a conformation showing much resemblance to a chair form which has been deformed more or less.

Experimental part

The elemental analyses have been performed by Mr. *M. van Leeuwen* of this Laboratory (Table V).

The melting points were determined with a Leitz hot-plate on a miscroscope, unless marked with an asterisk, when the m.p. was determined with the sample contained in a glass capillary in a copper block with an Anschütz thermometer.

Proton magnetic resonance spectra were obtained with a Varian A-60 spectrometer equipped with a V-6058 A spin-decoupler and a C-1024 time-averaging computer. The compounds were dissolved (10% w/v) in deuteriochloroform. Chemical shifts are given in ppm relative to tetramethylsilane as internal standard (δ-values).

Table V

Elemental analyses of some cocaines and derivatives

Compound	M.p. °C	Formula	Molecular weight	Calc. %			Found %		
				C	H	N	C	H	N
Allopseudococaine	83-84	$C_{17}H_{21}NO_4$	303.35	67.31	6.98	4.62	67.4	7.0	4.5
Allococaine	95-97	$C_{17}H_{21}NO_4$	303.35	67.31	6.98	4.62	67.3	7.0	4.5
Picrate of allopseudococaine	213-214	$C_{23}H_{24}N_4O_{11}$	532.46	51.88	4.54	10.53	51.6	4.7	10.5

Preparation of 2-methoxycarbonyltropinone

2-Methoxycarbonyltropinone was prepared according to *Findlay* [12], *inter alia* by Mr. *C. J. Agasi* in the Laboratory of Verenigde Pharmaceutische Fabrieken, Apeldoorn. The material was crystallized from aqueous acetone. We used samples with m.p. 86-97°, m.p. 89-92°, and m.p. 88-93°. All samples contained varying amounts of water according to Karl Fischer titrations. *Findlay* mentions m.p. 96-98° (monohydrate), m.p. 93-96° (dihydrate), m.p. 97.5-98° (trihydrate), and m.p. 101-104° after previous melting, cooling, and reheating.

Methyl ester of allopseudoecgonine

In a one-litre flask 9.00 g (– 14.9% = 7.66 g; 38.9 mmoles; m.p. 96-97°; water content 14.9%) of 2-methoxycarbonyltropinone, dissolved in 195 ml of glacial acetic acid and 30 ml of water, was hydrogenated for 6 days with magnetic stirring at 1 at and 35° with 750 mg of platinum oxide (Adams' catalyst) until no more hydrogen was absorbed.

After filtration, the colourless solution was evaporated at 40° in the rotary vacuum evaporator; the yellow, oily residue (15 g) was dissolved in 15 ml of water, and to this solution a solution of 50 ml of potassium carbonate, saturated in water, was added dropwise with stirring. The suspension was rapidly filtered with suction and extracted eight times with 40-ml portions of ether. The combined ethereal layers were dried over magnesium sulfate, evaporated at 30° (7.25 g), and dissolved in a mixture of 20 ml of acetone, 56 ml of ether, and 1.8 ml of glacial acetic acid. After 3 hours the white crystalline *hydroacetate* of the methyl ester of allopseudoecgonine was filtered off and dried at 30 mm over phosphorus pentoxide. Yield: 6.75 g (26.0 mmoles; 67%), m.p. 107-109°.

The hydroacetate (6.0 g; 23.2 mmoles) was dissolved in 33 ml of water. After 33 ml of saturated potassium carbonate had been cautiously added dropwise, the suspension was rapidly extracted eight times with 40-ml portions of ether. The combined ethereal layers were dried over magnesium sulfate, evaporated at 30°, dried at 0.2 mm over phosphorus pentoxide, and crystallized from 10 ml of petroleum ether (60-80°). Yield: 3.75 g (18.8 mmoles; 81%), m.p. 72-73° (Total yield 54%).

Melting point of the *picrate* of the methyl ester of allopseudoecgonine (from methanol): 194-195°.

Methyl ester of alloecgonine

The methyl ester of allopseudoecgonine (4.7 g; 23.6 mmoles) was hydrolysed and epimerized by boiling it for 4 hours in 30 ml of water, was subsequently evaporated at 60°, and was dried at 0.2 mm, first over concentrated sulfuric acid and then over phosphorus pentoxide (if the preparation is not quite dry, the allo isomer cannot be separated from the allopseudo compound).

The white residue (4.3 g) was boiled for a few minutes in 10 ml of ethanol dried over molecular sieves (4 A), and was filtered while hot. This process was repeated nine times more. The combined filtrates were evaporated under reduced pressure at 30° and the residue was crystallized five times (20 ml of super-dry ethanol per gram was used; dissolution at boiling temperature and cooling to – 20°). Yield: 1.42 g (7.7 mmoles), m.p. 235° *. From the mother liquors 1.3 g (7.0 mmoles), m.p. 230° * was obtained. Total yield: 2.72 g (14.7 mmoles; 62%) of alloecgonine. The product, which was insoluble in dry ethanol, was found to be allopseudoecgonine (0.32 g; 1.7 mmoles), m.p. 224° * (mixed m.p. with alloecgonine 218-220° *; m.p. hydrochloride 221-222° *; mixed m.p. with hydrochloride of alloecgonine 190-201° *).

Alloecgonine (1.38 g; 7.5 mmoles) was dissolved in 3.2 ml of 8% HCl in dry methanol, evaporated in the rotary vacuum evaporator at 30°, and crystallized from dry ethanol. The alloecgonine hydrochloride thus obtained (1.36 g; m.p. 198-199° *) was dissolved

with exclusion of moisture in 75 ml of 8% HCl in dry methanol and boiled for four hours. After evaporation at 30° and drying over phosphorus pentoxide at 20 mm, the white residue was dissolved in 10 ml of water, treated with 20 ml of saturated potassium carbonate solution in water, and rapidly extracted ten times with 30-ml portions of ether. The combined ethereal layers were dried over magnesium sulfate, evaporated under reduced pressure at 30°, and dried at 0.2 mm over phosphorus pentoxide. The white solid residue was crystallized from petroleum ether (60-80). Yield: 0.93 g (4.7 mmoles; 63%), m.p. 79-80° (total yield: 39%).

Melting point of the *picrate* of the methyl ester of alloecgonine (from acetone): 135-136°.

Melting point of the *hydrochloride* (from methanol-ether); 189-190°.

Allococaine

In a 3-ml flask 0.7 ml of a solution of 1 ml of freshly distilled benzoyl chloride in 5 ml of pyridine was slowly added, with exclusion of moisture and with stirring, to 250 mg (1.26 mmoles) of methyl ester of alloecgonine at 0°. After 30 minutes' stirring at 0°, the reaction mixture was stored for 17 hours at room temperature. The pale orange-yellow mixture was evaporated at 25° until it was dry. The residue was treated with 10 ml of methanol-ether (1 : 4) in order to remove the insoluble methyl ester of alloecgonine hydrochloride (purified by dissolution in 1 ml of methanol and precipitation with 7 ml of ether: 80 mg, 0.34 mmol, 27%, m.p. 189-190°).

The filtrate was evaporated under reduced pressure at 30°. The pale yellow residue (300 mg) was treated with 2 ml of saturated sodium bicarbonate in water and rapidly extracted six times with 4-ml portions of ether. The combined ethereal layers were dried over magnesium sulfate, evaporated in the rotary vacuum evaporator at 25°, dried at 0.2 mm over phosphorus pentoxide (176 mg; m.p. 82-90°), and crystallized three times from petroleum ether (60-80). Yield: 105 mg (0.35 mmol; 38%), m.p. 95-97°.

Melting point of the *picrate* of allococaine (from methanol): 161-162°.

Allopseudococaine

In a round-bottom flask of 10 ml, provided with a magnetic stirrer and a $CaCl_2$-tube, 1.9 g (9.55 mmoles) of methyl ester of allopseudoecgonine was dissolved in 4.75 ml of pyridine (dried over potassium hydroxide). At 0°, with exclusion of moisture, 0.48 ml (0.58 g; 4.13 mmoles) of freshly distilled benzoyl chloride was added dropwise. After 15 minutes' stirring at 0°, 0.71 ml (0.85 g; 6.05 mmoles) of benzoyl chloride was added to the orange-yellow solution and the reaction mixture was stored for 8 hours at room temperature. In the dark brown reaction mixture white crystals had been formed, which were separated by adding first 4 ml of dry ether and then 4 ml of absolute methanol (if methanol is added first, the crystals dissolve), filtering, and washing the crystals once with 4 ml of methanol-ether (1 : 1) and then three times with 3-ml portions of ether.

These crystals (470 mg) were crystallized twice from methanol-ether (1 : 1) and twice from absolute methanol. Yield: 96 mg (m.p. 193-194°). This product was found to be the methyl ester of allopseudoecgonine hydrochloride. At least 4% therefore had not reacted.

The dark brown pyridine layer was evaporated in the rotary vacuum evaporator at 40° and then dissolved in 5 ml of methanol. To the solution 50 ml of ether was added and the mixture was stored for 2 days at −20°. The pale brown precipitate (1.36 g; m.p. 177-179°) was crystallized three times from methanol-ether (2 : 1). Yield: 446 mg (1.27 mmoles; 14%) of allopseudococaine hydrochloride, m.p. 209-210°.

Allopseudococaine hydrochloride (350 mg; 1.00 mmol) was suspended in 2.5 ml of saturated potassium carbonate in water and extracted 15 times with 3-ml portions of ether. Later it was found that instead of potassium carbonate it was preferable to use

sodium bicarbonate solution. The combined ethereal layers were dried over magnesium sulfate, evaporated at room temperature, and the crystalline residue (286 mg) was crystallized three times from petroleum ether (40-60°). Yield: 107 mg (0.35 mmoles; 35%) of allopseudococaine, m.p. 83-84° (mixed m.p. of allococaine and allopseudococaine: 60-73°; total yield: 5%).

The *picrate* of allopseudococaine melted at 213-214° (from methanol, and after drying over P_2O_5 for 3 days at 10 mm and 110°). *Findlay*[7] described a picrate which contained alcohol and melted at 178.5-180°.