Completion of the reaction was indicated by the absence of a black color (HgS). The reaction mixture was cooled and filtered. The filtrate was evaporated to dryness and the residue was dissolved in boiling MeCN (100 ml). Insoluble material was removed by filtration. The filtrate was concentrated and cooled to give 3.3 g of crystalline **6b**.

***N,N'*-Bis(2,6-dimethylphenyl)acetamidine (8c).** A solution of 2,6-dimethylaniline (50 g, 0.41 mol) in THF (50 ml) was treated slowly with Ac_2O (102 g, 1 mol). The mixture was stirred for 10 min and poured into ice-H_2O. The precipitated material was filtered, washed with H_2O, and recrystallized from EtOH to give 51 g (76%) of *N*-(2,6-dimethylphenyl)acetamide, mp 180–181°.

A solution of the above amide (50 g, 0.31 mol) in $CHCl_3$ (300 ml) at 0° was treated slowly during 20 min with $POCl_3$ (56.3 g, 0.37 mol) in $CHCl_3$ (70 ml). The mixture was stirred at 25° for 4 hr, treated with an excess of $MeNH_2$, and heated in an autoclave at 140° for 18 hr. Solvent was evaporated and the residue dissolved in H_2O. The aqueous solution was basified and extracted with $CHCl_3$. The extract was treated with activated C, filtered, and evaporated to a brown oil which crystallized on standing. A small sample, recrystallized from Et_2O, had mp 144–145°; the nmr spectrum of this material was consistent with **8c**. The remaining material was converted to the HCl salt by treatment with ethereal HCl. Recrystallization of the salt (45 g) from EtOH-Et_2O and Me_2CO gave 7.3 g of **8c** · HCl.

3-Acetyl-2-(2,6-dimethylphenylimino)tetrahydro-1,3-thiazine (9h). A solution of **9g** (10 g, 52.5 mmol) in Ac_2O (35 ml) was kept at 25° for 48 hr and then poured into ice-H_2O to decompose the excess Ac_2O. The mixture was extracted with C_6H_6 and the extract was washed with H_2O, $NaHCO_3$ solution, and brine and dried. Evaporation of the solvent left a viscous oil which slowly crystallized. After washing the residue with hexane, it was recrystallized to give 2.5 g of **9h**.

2-(2,6-Dimethylphenylamino)thiazole (10b). To a stirred and refluxing suspension of 2,6-dimethylphenylthiourea[9] (12 g, 66 mmol) in H_2O (50 ml) was added dropwise 1,2-dichloroethyl ethyl ether (10 g, 70 mmol). After 2 hr, the cooled mixture was basified (NaOH). The product was filtered and recrystallized from EtOH to give 10.1 g (75%) of **10b**.

2-(2,6-Dimethylphenylamino)benzothiazole (11). To a chilled solution of phenyl isothiocyanate (20 g, 0.148 mol) in EtOAc (60 ml) was added slowly 2,6-dimethylaniline (24.9 g, 0.21 mol). The mixture was refluxed for 25 min. The precipitated product, 1-(2,6-dimethylphenyl)-3-phenylthiourea (mp 203–205°), was collected by filtration (34.9 g, 91%).

A suspension of the above thiourea (25 g, 0.097 mol) in C_6H_5Cl (175 ml) was treated slowly with sulfuryl chloride[19] (17 g, 0.126 mol), keeping the reaction temperature below 50°. The mixture was maintained at 50° for 2.5 hr. The precipitated solid material was filtered, washed with C_6H_6, and dissolved in H_2O. After basifying the aqueous solution with NH_4OH, the precipitated product was filtered and recrystallized to give 10.35 g of **11**.

Acknowledgments. We thank Anna Helt, Frank Gruber, Jack H. Schlosser, and Joan S. Long for performing the pharmacological tests.

References

(1) T. Jen, B. Dienel, F. Dowalo, H. Van Hoeven, P. Bender, and B. Loev, *J. Med. Chem.*, **16**, 633 (1973) (paper 5).
(2) A. Kreutzberger, *Progr. Drug. Res.*, **11**, 356 (1968).
(3) W. T. Comer and A. W. Gomoll, "Medicinal Chemistry," 3rd ed, Part II, A. Burger, Ed., Wiley-Interscience, New York, N.Y., 1970, Chapter 39, p 1019.
(4) W. Hoefte and W. Kobinger, *Arzneim.-Forsch.*, **16**, 1038 (1966).
(5) H. Schmitt, H. Schmitt, J. R. Boissier, J. F. Gindicelli, and J. Fichelle, *Eur. J. Pharmacol.*, **2**, 340 (1968).
(6) W. Graubner and M. Wolf, *Arzneim.-Forsch.*, **16**, 1055 (1966).
(7) T. Jen, B. Dienel, H. Bowman, J. Petta, A. Helt, and B. Loev, *J. Med. Chem.*, **15**, 727 (1972).
(8) B. Loev, T. Jen, and R. McLean, *Experientia*, **27**, 875 (1971).
(9) B. Loev, P. Bender, H. Bowman, A. Helt, R. McLean, and T. Jen, *J. Med. Chem.*, **15**, 1024 (1972).
(10) L. M. Jackman and T. Jen, *J. Amer. Chem. Soc.*, in press.
(11) (a) D. Greco, F. Olmsted, M. G. N. Masson, and A. C. Corcoran, *J. Lab. Clin. Med.*, 41, 729 (1953); D. M. Green, F. J. Saunders, N. Wahlgren, and R. L. Craig, *Amer. J. Physiol.*, **170**, 94 (1952); (b) K. S. Grimson, *Arch. Surg.*, **43**, 284 (1941).
(12) E. Lord, *Biometrika*, **34**, 56 (1947).
(13) S. A. Komarov, S. P. Bralow, and E. Boyd, *Proc. Soc. Exp. Biol. Med.*, **112**, 415 (1963).
(14) L. H. Werner and W. E. Barrett, *Med. Chem., Ser. Monogr.*, **7**, 357 (1967).
(15) O. Behner, H. Henecka, F. Hoffmeister, H. Kreiskolt, W. Meiser, H. W. Schubert, and W. Wirth, U. S. Patent 3,235,550 (1966).
(16) N. Lofgren, U. Ragnarsson, and K. Sjoberg, *Acta Chem. Scand.*, **17**, 1252 (1963).
(17) B. Loev and M. M. Goodman, *Chem. Ind. (London)*, 2026 (1967).
(18) H. Najer and R. Giudicelli, *Bull. Soc. Chim. Fr.*, 960 (1960).
(19) C. F. H. Allen and J. VanAllen, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N.Y., 1955, p 76.

Notes

Synthesis and Biological Actions of Fragmented Derivatives of Tetrahydroisoquinolines

Duane D. Miller,* William V. P. Merritt, Peter F. Kador, and Dennis R. Feller

Divisions of Medicinal Chemistry and Pharmacology, College of Pharmacy, The Ohio State University, Columbus, Ohio 43210.
Received August 16, 1974

Appropriately substituted tetrahydroisoquinolines have shown a variety of pharmacological actions including lipolytic,[1-4] bronchial relaxant,[5] and hypotensive activity.[3] In continuing our investigations of tetrahydroisoquinolines as agonists[1,2] and antagonists[6,7] in adrenergic systems we have initiated a program in determining the relationship of chemical structure to the production of biological actions. One portion of this program involves delineating the importance of an intact tetrahydroisoquinoline ring system for adrenergic activity with a goal toward the development of selective and/or potent β-adrenergic stimulants. This report is concerned with the modification of 1-benzyl-6,7-dihydroxytetrahydroisoquinoline (1) which is known to possess β-adrenergic activity.[1,2,8] The analogs prepared in this study may be considered tetrahydroisoquinolines in which the bond between C_4 and the aromatic ring is broken, as shown in 2. Modifications were also made in the catechol portion of the structure. It had been shown previously that elimination of either the 6- or 7-hydroxy group in I greatly reduced the bronchodilator activity.[8] In order to examine the importance of aromatic ring substitution in the fragmented derivative series, the

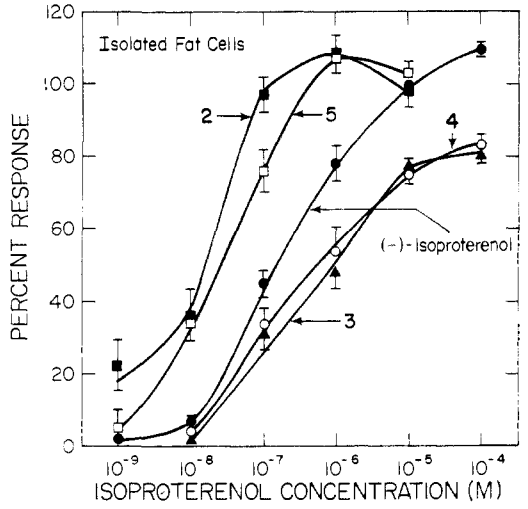
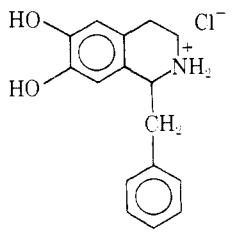
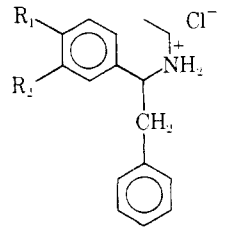


Figure 1. Influence of 2-5 on isoproterenol-induced glycerol release from isolated fat cells. Key: 2, ■-■; 5, □-□; (−)-isoproterenol, ●-●; 3, ▲-▲; and 4, ○-○. Concentration of each drug was 10^{-4} *M*. Values plotted represent the mean of $N = 4 \pm$ S.E. as indicated by the vertical line.

monophenolic compounds 3 and 4 along with the 3,4-dichloro derivative 5 were prepared and examined for their agonist and antagonistic activities in β-adrenergic tissues.

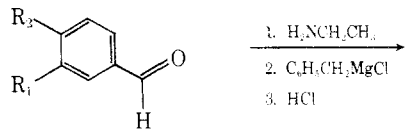


1



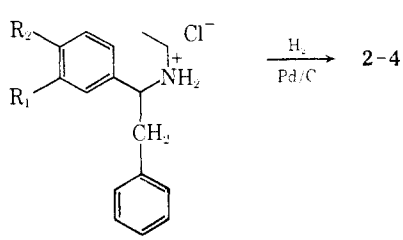
2, $R_1 = R_2 = OH$
3, $R_1 = OH$; $R_2 = H$
4, $R_1 = H$; $R_2 = OH$
5, $R_1 = R_2 = Cl$

Chemistry. The fragmented derivatives were synthesized by a condensation of aldehydes 6-9 with ethylamine in the presence of molecular sieves to give the desired imines,[9] which in turn were treated with phenylmagnesium



1. $H_2NCH_2CH_3$
2. $C_6H_5CH_2MgCl$
3. HCl

6, $R_1 = R_2 = OCH_2C_6H_5$
7, $R_1 = H$; $R_2 = OCH_2C_6H_5$
8, $R_1 = OCH_2C_6H_5$; $R_2 = H$
9, $R_1 = R_2 = Cl$



H_2, Pd/C → 2-4

10, $R_1 = R_2 = OCH_2C_6H_5$
11, $R_1 = H$; $R_2 = OCH_2C_6H_5$
12, $R_1 = OCH_2C_6H_5$; $R_2 = H$
5, $R_1 = R_2 = Cl$

Table I

Compd[a]	Mp, °C	Recrystn solvent	% yield
2	182	EtOH–Et_2O	88
3	178–180	MeOH–Et_2O	94
4	204–205	MeOH–Et_2O	85
5	229–231	MeOH–Et_2O	90
10	131–133	MeOH–Et_2O	63
11	200	MeOH–Et_2O	64
12	185–186	$CHCl_3$–Et_2O	70

[a] Analysis of C, H, and N was carried out on each of the synthesized compounds and variation did not exceed ±0.4% of the theoretical values.

chloride[10] to give the desired amines 5 and 10-12. Hydrogenolysis was carried out on compounds 10-12 to give the desired phenolic compounds 2-4 (Table I).

Biological Results and Discussion. Compounds 1-5 were evaluated for β-adrenergic activity in isolated systems of guinea pig trachea and rat adipose tissue. We have previously shown that tetrahydroisoquinolines including compound 1 are potent stimulators of lipolysis.[1,2] In preliminary experiments, we observed that the fragmented derivatives 2-5 were unable to elicit a lipolytic response, whereas 1 shows significant lipolytic activity in the isolated fat cell preparation (pD_2 value of 1 = 5.7). However, compounds 2-5 at 10^{-4} *M* were able to modify glycerol release in the presence of (−)-isoproterenol (see Figure 1). It was noted that compounds 2 and 5 potentiated the lipolytic response to isoproterenol whereas compounds 3 and 4 blocked isoproterenol-induced lipolysis. The potentiation of the dose-response curve of isoproterenol in the presence of 2 and 5 is analogous to the parallel shift to the left in the dose-response curves of catecholamines preincubated with phosphodiesterase inhibitor.[11,12] We plan to examine the interaction of 2 and 5 in partially purified phosphodiesterase preparations at a later date. Further studies will also be necessary to delineate the site of interaction for the antilipolytic activity possessed by 3 and 4.

The comparative bronchial relaxant actions of 1-5 and isoproterenol are summarized in Table II. The order of bronchial relaxant activity observed in this series was (−)-isoproterenol ≫ 1 ≈ 2 = 3 = 4 > 5. The observation that (−)-isoproterenol is more potent than 1 in this β-adrenergic system is in agreement with the earlier reports of Yamato, *et al.*,[5] and Iwasawa and Kiyomoto.[8] Our studies further indicate that the presence of an intact THI nucleus is not a prerequisite for bronchial relaxant activity. This is supported by the fact that all of the fragmented derivatives investigated possessed significant activity which, with the exception of 5, was comparable to the parent tetrahydroisoquinoline (1). These observations are in contrast to the data obtained for 1-5 on lipolysis (see Table II).

The profile of adrenergic activity observed with 1 and 2 in several β-receptor systems is summarized in Table III. The data demonstrate that 1 and 2 are equally active in the isolated tracheal strip preparation, whereas 2 is significantly less active than 1 in guinea pig atrial and isolated fat cell preparations. Our findings show that fragmentation of the tetrahydroisoquinoline nucleus can lead to compounds that exhibit selective β-adrenergic activity.

Experimental Section

Melting points (uncorrected) were determined on a Thomas-Hoover melting point apparatus. Spectral data were obtained using a Perkin-Elmer 257 infrared spectrophotometer and a Varian A-60A nuclear magnetic resonance spectrometer. Analyses

Table II. Comparative Effects of (−)-Isoproterenol and Tetrahydroisoquinoline Analogs (Compounds 1–5) on Guinea Pig Trachea

Compd tested	N^a	$pD_2 \pm$ S.E.[b]
1	7	4.42 ± 0.26
2	8	4.11 ± 0.06
3	7	4.26 ± 0.11
4	6	4.26 ± 0.13
5	4	3.66 ± 0.17
(−)-Isoproterenol	20	8.20 ± 0.09

[a] N is equal to the number of experiments. [b] pD_2 values defined as $-\log ED_{50}$.

were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Analytical results for elements indicated were within ±0.4% of the theoretical values.

General Procedure. A mixture of 0.10 mol of aldehyde (Aldrich Chemical Co.) and 0.30 mol of anhydrous ethylamine (Eastman) along with 20 g of molecular sieves (Linde 4A) in 250 ml of benzene was stirred overnight. The molecular sieves were removed by filtration and washed with 100 ml of benzene. The combined benzene solutions were evaporated *in vacuo* to give a quantitative yield of a light brown oil with an absorption in the 1640-cm^{-1} region of the infrared spectra (C=N). No free aldehyde could be detected using either ir or nmr spectroscopy. The light brown imine was dissolved in 250 ml of anhydrous ether† and added dropwise to a stirred solution of benzylmagnesium chloride prepared from 4.6 g (0.2 g-atom) of magnesium, 25.2 g (0.20 mol) of benzyl chloride, and 400 ml of ether. Stirring was continued for 3 hr at room temperature. A solution of 10.6 g (0.2 mol) of ammonium chloride in 200 ml of water was added cautiously to the reaction mixture. The organic layer was separated and the aqueous layer was then extracted with two portions of 200 ml of ether. The combined ether layers were dried (Na_2SO_4) and evaporated *in vacuo* to give a brown oil. Chromatography on silica gel (Brinkman silica gel 60) with $CHCl_3$–ethanol (3:1) afforded the desired amine. The amine was dissolved in 30 ml of $CHCl_3$ and added to 500 ml of anhydrous ether saturated with hydrogen chloride gas. The mixture was stirred magnetically for 1 hr and the solid hydrochloride collected by filtration. The appropriate hydrochloride salt **10–12** (0.01 mol) was dissolved in 250 ml of hot absolute ethanol and after cooling 500 mg of 10% Pd/C was added to the solution. The mixture was placed on a Parr shaker for 8 hr at 40 psi at 25°. After removal of the Pd/C by filtration the solution was concentrated *in vacuo* to a volume of approximately 15 ml. Ether was added until the solution became cloudy and cooled overnight in a refrigerator. The resulting hydrochloride salt was isolated by filtration (see Table I).

Pharmacological Testing. Isolated Guinea Pig Tracheal Strip Preparation. Guinea pigs of either sex weighing 300–500 g were killed by a sharp blow on the head. The trachea of each animal was isolated and cleaned free of fatty tissue. From each guinea pig, two spiral tracheal strips were prepared and mounted in a 12-ml jacketed muscle chamber containing a physiological solution maintained at 37° through which a mixture of 95% O_2–5% CO_2 was bubbled. Drug-induced effects were recorded on a Grass polygraph (Model 7C) *via* a force displacement transducer. Strips were allowed to equilibrate for 1–1.5 hr before each experiment under a tension of 1 g. Carbachol (3×10^{-7} M) was used to increase the tone of each preparation and cumulative dose–response curves were obtained in the presence of each drug. Individual plots of tracheal relaxation, expressed as a per cent of the maximum relaxation obtained with 10^{-5} M isoproterenol added at the end of each experiment *vs.* log molar concentration of each drug, were prepared and the ED_{50} values determined individually. Compounds were tested in the concentration range of 10^{-8}–3×10^{-4} M.

Isolated Right Atrial Preparation. Guinea pigs of either sex were killed by a sharp blow on the head. The atrium was dissected from extraneous tissue and placed in a 12-ml jacketed muscle bath. The atrium was allowed to equilibrate for a 1-hr period in a physiological solution maintained at 37° through which a mixture of 95% O_2–5% CO_2 was bubbled. The increase in atrial rate was recorded on a Grass polygraph (Model 7C) *via* a force displacement transducer.

In each experiment, the atrium was exposed to a test dose of a drug and the atrial rate recorded during a 3-min period. Individual recordings were made at 1- and 3-min intervals. Cumulative dose–response curves were obtained for each analog. The data were plotted on a log scale and the chronotropic responses expressed in terms of the maximum response obtained in the presence of 10^{-5} M isoproterenol added at the end of each experiment. ED_{50} values were determined from individual plots. Compounds were tested in the concentration range of 10^{-8}–3×10^{-4} M.

Isolated Fat Cells. Epididymal fat tissue obtained from nonfasted male Sprague–Dawley rats weighing 200–250 g was used. Fat cells were isolated by the method of Rodbell[13] after digestion of adipose tissue with crude collagenase (Worthington) in a Krebs bicarbonate buffer containing 3% bovine serum albumin.

Incubation mixtures contained 0.2 ml of fat cell suspension, test drug, and Krebs bicarbonate–albumin solution in a total volume of 2.5 ml. Drugs were tested in the concentration range of 10^{-8}–3×10^{-4} M. Flasks were incubated in air at 37° for 1 hr. In other experiments designed to examine analogs as antagonists, drugs (10^{-4} M) were preincubated for 15 min prior to the addition to varying concentrations of (−)-isoproterenol. All reactions were terminated by the addition of an equal volume of 10% TCA and the amount of glycerol released was measured by procedures described previously.[14,15]

In each experiment, a maximal release of glycerol was obtained in the presence of 10^{-6} M isoproterenol and this maximal figure was used to calculate the dose–response relationships obtained in this study.

Drugs. All drugs were prepared in normal saline containing 0.05% sodium metabisulfite.

Table III. Comparative Adrenergic Effects of 1-Benzyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (**1**) and *N*-Ethyl-1-(3,4-dihydroxyphenyl)-2-phenethylamine (**2**)[a]

Tissue	$pD_2 \pm$ S.E.	Intrinsic act.
Rat adipose tissue		
Compound **1**	5.75 ± 0.15	1.0
Compound **2**		*b*
Guinea pig atria		
Compound **1**	6.28 ± 0.24	1.0
Compound **2**	3.65 ± 0.02	1.0
Guinea pig trachea		
Compound **1**	4.42 ± 0.26	0.7[c]
Compound **2**	4.11 ± 0.06	0.7[c]

[a] Values represent the mean of N = 4–6 experiments. [b] No lipolytic activity was observed for this compound of concentrations ranging from 10^{-8} to 3×10^{-4} M. [c] All analogs (1–5) were unable to produce a maximum relaxation of the trachea preparation at the highest concentration used (3×10^{-4} M).

Acknowledgments. The authors wish to thank Mrs. R. Venkatraman for her excellent biological assistance. We also thank Drs. T. Takayanagi and M. S. Moriga of Tanabe Seiyaku Co., Ltd. (Japan), for the supply of 1-benzyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline and Dr. S. Archer for the supply of (−)-isoproterenol used in this study. The work was supported by a grant from the National Institutes of Health (NS 10896). W. V. P. Merritt was supported as an Undergraduate Research Participant of NSF (GY-10651) and P. F. Kador was supported as a NIH Predoctoral Trainee (3-T01-GM1949-05S).

References

(1) R. F. Shonk, D. D. Miller, and D. R. Feller, *Biochem. Pharmacol.*, **20**, 3403 (1971).
(2) D. R. Feller, R. F. Shonk, and D. D. Miller, *J. Pharm. Pharmacol.*, **22**, 869 (1970).
(3) P. Holtz, K. Stock, and E. Westerman, *Nature (London)*, **203**, 656 (1964).

†Anhydrous tetrahydrofuran was found to be a superior solvent for dissolving the ethylimine of *p*-benzyloxybenzaldehyde.

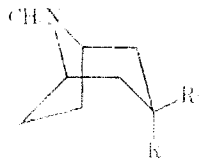
(4) G. Fassina, D. E. Toth, and R. Santi, *Progr. Biochem. Pharmacol.*, 3, 277 (1967).
(5) E. Yamato, M. Hirakura, and S. Sugasawa, *Tetrahedron Suppl.*, 8 (part I), 129 (1966).
(6) O. S. Lee, J. A. Mears, D. D. Miller, and D. R. Feller, *Eur. J. Pharmacol.*, in press.
(7) A. M. Hjort, E. J. DeBeer, J. S. Buck, and L. O. Randall, *J. Pharmacol. Exp. Ther.*, 76, 64 (1942).
(8) Y. Iwasawa and A. Kiyomoto, *Jap. J. Pharmacol.*, 17, 143 (1967).
(9) K. Taguchi and F. H. Westheimer, *J. Org. Chem.*, 36, 1570 (1971).
(10) R. B. Moffett, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 605.
(11) O. S. Lee, M.S. Thesis, The Ohio State University, 1972.
(12) L. DeSantis, D. Feller, and P. Patil, *Eur. J. Pharmacol.*, in press.
(13) M. Rodbell, *J. Biol. Chem.*, 239, 375 (1964).
(14) T. Nash, *Biochem. J.*, 55, 416 (1953).
(15) M. Lambert and A. C. Neish, *Can. J. Res.*, 23, 83 (1950).

β-Cocaine

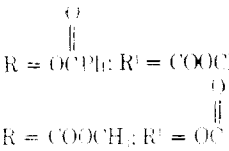
Robert L. Clarke* and Sol J. Daum

Sterling-Winthrop Research Institute, Rensselaer, New York 12144. *Received July 19, 1971*

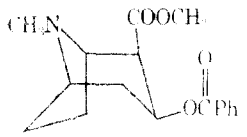
The present paper is the final chapter of a story of some 78 years duration in the chemical literature. In 1896 Willstätter[1] prepared a cocaine analog from 1αH,5αH-tropan-3-one called "α-cocaine." He published the correct structure for the tropane ring system 2 years later[2] and showed both substituents of α-cocaine to be on carbon-3 (structure **1a** or **1b**). Only one isomer was found. The compound produced no numbness of the tongue, an outstanding property of its relative, cocaine (**2**). Consideration of the fact that cocaine contains an equatorial 3-benzoyloxy group would lead one to assume that the nonanesthetic α-cocaine probably is represented by structure **1a** with its benzoyloxy group bent away from the amine side of the molecule rather than by **1b** wherein this group is equatorial.[3]



1a, R = OCPh; R' = COOCH$_3$



b, R = COOCH$_3$; R' = OCPh

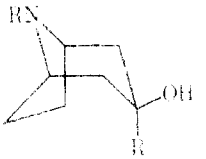


2

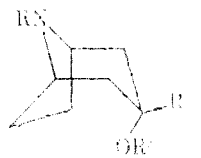
Foster and Ing[4] noted that the lack of local anesthetic activity observed with α-cocaine was based only on a topical test (production of tongue numbness) and surmised that it might show activity by subdermal infusion. They repeated Willstätter's synthesis, *i.e.*, tropanone → cyanohydrin → hydroxy acid → hydroxy ester → α-cocaine, again found the single isomer, and, together with Varagić,[5] demonstrated that it was one-third to one-eighth as active as cocaine in the guinea pig wheal test.[6] It was active but did not have the cocaine activity profile. The biological results certainly gave no satisfactory basis for structural assignment.

Heusner[3] settled the matter chemically, showing that α-cocaine is actually **1b**. He used 1αH,5αH-nortropan-3-one as a starting material, isolated a single crystalline cyanohydrin isomer and converted it ultimately to α-cocaine. Therefore, the matters of structure and activity were settled but no isomeric cyanohydrin had been found which could lead to "β-cocaine" (**1a**).

In this laboratory the cyanohydrin of 8-benzyl-1αH,5αH-nortropan-3-one was prepared. When the viscous, oily product could not be induced to crystallize, the crude material was hydrolyzed (concentrated HCl) and esterified (CH$_3$OH·HCl). The resulting mixture yielded 40% of recovered 8-benzyl-1αH,5αH-nortropan-3-one, 16% of methyl 8-benzyl-3β-hydroxy-1αH,5αH-nortropane-3α-carboxylate (*N*-benzylnor-α-ecgonine methyl ester, **3b**), and 20% of methyl 8-benzyl-3α-hydroxy-1αH,5αH-nortropane-3β-carboxylate (*N*-benzylnor-β-ecgonine methyl ester, **4b**).



3a, R = PhCH$_2$; R' = CN
b, R = PhCH$_2$; R' = COOCH$_3$
c, R = H; R' = COOCH$_3$



4a, R = PhCH$_2$; R' = CN; R'' = H
b, R = PhCH$_2$; R' = COOCH$_3$; R'' = H
c, R = PhCH$_2$; R' = COOCH$_3$; R'' = COPh
d, R = H; R' = COOCH$_3$; R'' = COPh
e, R = CH$_3$; R' = COOCH$_3$; R'' = COPh

The structures of isomers **3b** and **4b** were provisionally assigned on the basis of their nmr spectra. The nmr spectrum of **4b** showed a rather sharp (nonbonded) OH peak with δ 3.13 ppm and a benzylic singlet deshielded by COOMe at 3.62 ppm. The spectrum of **3b** showed a very diffuse bonded OH mound and a nondeshielded benzylic singlet at 3.45 ppm. The structures of these isomers were then firmly established by debenzylation of **3b** to the known nor compound **3c**[3] which was compared directly with an authentic sample (from 1αH,5αH-nortropan-3-one) kindly furnished by Dr. M. R. Bell of this Institute.

In seeking an explanation for the unexpected appearance of this α-hydroxy-β-carboxylic ester, it was recalled that the cyanohydrins from both 1αH,5αH-tropan-3-one and 1αH,5αH-nortropan-3-one are crystalline products which separate quickly and in high yield. If HCN addition under the extant reaction conditions is sufficiently reversible and if precipitation of crystalline β-hydroxy-α-nitrile simply shifts the equilibrium in its favor, simple filtration of the gratifyingly large yield of cyanohydrin would have precluded obtaining the other isomer. All workers to date used *crystalline* cyanohydrin. The happenstance of noncrystallinity of our cyanohydrin products seems to have allowed isolation of the isomer of opposite configuration.