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A SYNTHESIS OF LAUDANINE AND (±)-PSEUDOCODAMINE: RESOLUTION INTO THE OPTICAL ISOMERS

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Abstract—By application of the Bischler–Napieralski reaction, and protection of the phenolic hydroxyl group by benzoylation, laudanine and (±)-pseudocodamine were synthesized. The benzoyl bases were resolved easily with tartaric acid. (+)-Pseudocodamine belongs to the same series as (+)-laudanosine.

Laudanine and the laudanidines

LAUDANINE is a racemic phenolic alkaloid isolated from opium by Hesse,[1] who also showed its structural relationship to laudanosine. Späth[2] established that the phenolic hydroxyl was located in carbon 4′ of the benzyl group and assigned to it structure (IV; $R_1 = H$, $R_2 = CH_3$).

This structure was confirmed by the synthesis by Späth and Lang,[3] who employed the Bischler–Napieralski reaction for the formation of the *iso*quinoline ring. Protection of the phenolic hydroxyl group was provided by carbethoxylation. Laudanine was also obtained by demethylation of (±)-laudanosine, as was done by Späth and Burger[4] with hydrochloric acid and by Schöpf and Thierfelder[5] with aluminium chloride.

We report a new synthesis of laudanine by the Bischler–Napieralski reaction, in which the protection of the phenolic hydroxyl group is afforded by benzoylation. The 3′-benzoyloxy-4′-methoxyphenyl-N-2-(3,4-dimethoxyphenyl)ethylacetamide (I; $R_1 = PhCO$, $R_2 = CH_3$) was cyclized under the action of phosphorus pentachloride in cold chloroform solution, and 1-(3′-benzoyloxy-4′-methoxybenzyl)-3,4-dihydro-6,7-dimethoxy*iso*quinoline hydrochloride (II; $R_1 = PhCO$, $R_2 = CH_3$) was obtained in 80 per cent yield. It was transformed into the crystalline methiodide (III; $R_1 = PhCO$, $R_2 = CH_3$), which, when reduced with hydrogen, with platinum oxide as a catalyst, yielded the hydriodide of benzoyllaudanine, from which the crystalline benzoylated base (IV; $R_1 = PhCO$, $R_2 = CH_3$) was prepared. Hydrolysis of the benzoyllaudanine with hydrochloride acid afforded laudanine (IV; $R_1 = H$, $R_2 = CH_3$).

Properties, derivatives and color reactions of the synthetic product were in agreement with those described for natural laudanine. It was transformed into (±)-laudanosine (IV; $R_1 = R_2 = CH_3$) by treatment with diazomethane.

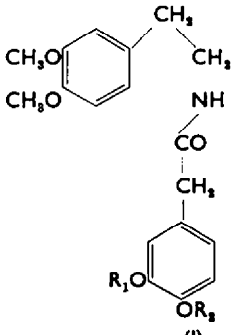
The laevorotatory isomer of laudanine is (−)-laudanidine, an alkaloid which was

[1] O. Hesse, *Liebigs Ann.* **153**, 47 (1870); *Ber. Dtsch. Chem. Ges.* **4**, 693 (1871)
[2] E. Späth, *Mh. Chem.* **41**, 297 (1920).
[3] E. Späth and N. Lang, *Mh. Chem.* **42**, 273 (1921).
[4] E. Späth and A. Burger, *Mh. Chem.* **47**, 733 (1926).
[5] Cl. Schöpf and K. Thierfelder, *Liebigs Ann.* **537**, 143 (1939).

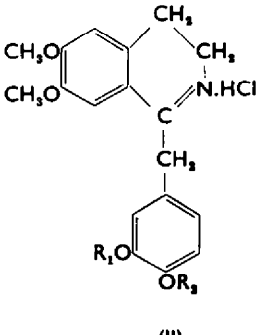
also isolated from opium by Hesse[6] and was shown by Späth and Seka[7] to be identical to the tritopine base of Kauder.[8]

Laudanine [(±)-laudanidine] could not be resolved by Hesse[9] nor by Späth and Burger[4] by employing optical active acids. The stereoisomeric laudanidines were prepared by the latter authors, by treating the optical isomers of laudanosine with hydrochloric acid. (−)-Laudanosine produced the natural (−)-laudanidine.

We have found that benzoyllaudanine can be resolved easily by treatment with D-tartaric acid. (+)-Benzoyllaudanidine D-tartrate was obtained, from which the optically active benzoylated base was prepared. Hydrolysis gave (+)-laudanidine. When L-tartaric acid was employed, (−)-laudanidine was obtained. They were identified, by the identity of their physical constants and derivatives, with those described in the literature.



(I)



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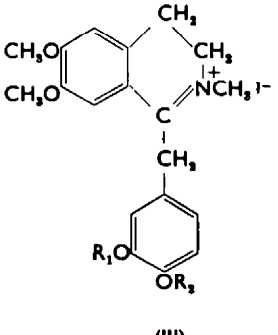
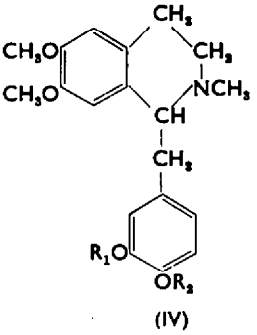
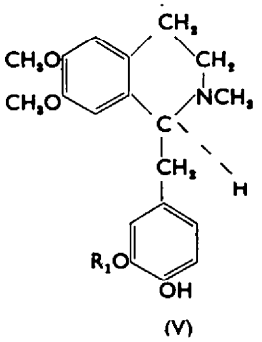


(III)



(IV)



(V)

Pseudocodamine

(±)-Pseudocodamine is a racemic phenolic base, which like laudanine and the laudanidines was isolated by Burger[10] from the products formed by the treatment of laudanosine with hydrochloric acid. Burger assigned to it structure (IV; $R_1 = CH_3$, $R_2 = H$), because by ethylation and oxidation 4-ethoxy-3-methoxybenzoic acid was obtained.

[6] O. Hesse, *Liebigs Ann.* **282**, 208 (1894).
[7] E. Späth and R. Seka, *Ber. Dtsch. Chem. Ges.* **58**, 1272 (1925).
[8] E. Kauder, *Arch. Pharm. Berl.* **228**, 419 (1890).
[9] O. Hesse, *J. Prakt. Chem.* [2], **65**, 42 (1902).
[10] A. Bürger, Dissertation, Vienna (1927); A. Bürger, *The Alkaloids* (Ed. R.H.F. Manske and H. L. Holmes) Vol. IV, p. 63. Academic Press, New York (1954).

This structure has been confirmed by a synthesis following similar lines to those described for (±)-laudanine. (±)-Benzoylpseudocodamine (IV; $R_1 = CH_3$, $R_2 = PhCO$) was prepared by identical reactions (I → II → III → IV; $R_1 = CH_3$, $R_2 = PhCO$). The active benzoylpseudocodamines were obtained by resolution of the racemic benzoyl base with D-tartaric and with L-tartaric acid. Acid hydrolysis of the resolved benzoyl bases gave (+)-pseudocodamine and (−)-pseudocodamine. The racemic and the optical active forms of pseudocodamine have the same melting point (130–131°), which does not change when the optical isomers are mixed in different proportions.

(±)-Pseudocodamine was transformed into (+)-laudanosine by treatment with diazomethane. Carbon atom 1 in (+)-pseudocodamine has the structure shown in formula (V). In the nomenclature of Cahn *et al.*,[11] (+)-pseudocodamine is (1 *S*)-1-(4′-hydroxy-3′-methoxybenzyl)-6,7-dimethoxy*iso*quinoline.

EXPERIMENTAL

All the ultraviolet spectra were recorded in 96 per cent ethanol. M.p. are uncorrected.

*Benzoyliso**homovanillic acid.** iso*Homovanillic acid (10 g) was dissolved in 100 ml of 6 per cent sodium hydroxide solution, 7·0 ml of benzoyl chloride was added and the mixture was shaken well until the odour disappeared. The solution was cooled and acidified with 2 N hydrochloric acid, when an oil, which crystallized easily, was precipitated. The solid was centrifuged, and then washed three times, by centrifugation, with 15 ml of 96 per cent ethanol, to dissolve the benzoic acid formed. It melted at 125–127° and weighed 15·7 g (96 per cent). It could be used without further purification for the preparation of the chloride. For analysis it was recrystallized from ethanol, to give prisms melting at 128°, which were soluble in ether, acetone, chloroform and acetic acid, but less soluble in methanol and benzene (Found: C, 67·94; H, 4·78. Calc. for $C_{16}H_{14}O_5$: C, 67·12; H, 4·95 per cent).

*Benzoyliso**homovanillyl chloride.* Benzoyl*iso*homovanillic acid (10 g) was boiled in a water bath with 50 ml of thionyl chloride for 1 hr. The excess of reagent was removed by distilling under vacuum and the oily residue was kept in a vacuum desiccator over potassium hydroxide. Crystallization of the chloride started very soon and was finished in a few hours. Recrystallized from light petroleum (boiling range 80–90°), 11 g of prisms melting at 86° was obtained; the product was soluble in ether, acetone and chloroform (Found: Cl, 11·11. Calc. for $C_{16}H_{13}Cl.O_4$: Cl, 11·49 per cent).

3′-Benzoyloxy-4′-methoxyphenyl-N-2-(3,4-*dimethoxyphenyl)ethylacetamide* (I; R_1 = PhCO, $R_2 = CH_3$). Benzoyl*iso*homovanillyl chloride (10 g) was dissolved in 40 ml of purified chloroform. The solution was cooled to below 5° and then slowly added to a chloroform solution of 6 g of 3,4-dimethoxyphenylethylamine, also at 5°. The resulting solution was maintained at this temperature for 10 min, and then 25 ml of N sodium hydroxide solution was added to make the aqueous layer alkaline. This was separated by decanting, and the chloroform solution was washed three times with 2 N hydrochloric acid and then with water. After drying, the chloroform was evaporated in vacuum, and the oily residue crystallized in a few hours on standing in

[11] R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia* **12**, 81 (1956).

a desiccator. Recrystallized from 60 ml of absolute ethanol, 14 g (96 per cent) of the amide was obtained as needles melting at 106°, λ_{max} 276–278 mμ (log ε 3·85), soluble in acetone and chloroform, but less soluble in ether. For analysis it was recrystallized from ethanol and still had m.p. 106° (Found: C, 67·58; H, 5·98; N, 3·07. Calc. for $C_{26}H_{27}NO_6.H_2O$: C, 66·79; H, 6·25; N, 3·00 per cent).

1-(3′-*Benzoyloxy*-4′-*methoxybenzyl*)-3,4-*dihydro*-6,7-*dimethoxy*isoquinoline *hydrochloride* (II; R_1 = PhCO, R_2 = CH_3). 3′-Benzoyloxy-4′-methoxyphenyl-N-2-(3,4-dimethoxyphenyl)ethylacetamide (10 g) was dissolved in 100 ml of chloroform, the solution was cooled to 2–3° and 20 g of solid phosphorus pentachloride was slowly added. After the addition was finished, cooling was continued for 3 hr and then the mixture was kept at room temperature (20–25°). A yellow precipitate was formed in the first 24 hr and it did not increase in bulk. After 4 days, 40 g of ice was added, and the chloroform was removed by distilling under vacuum. A brown-yellow solid and water remained in the flask. The water was removed by decantation and the solid was partially dried in a desiccator and then 50 ml of a mixture (1:1) of ethanol and 2 N hydrochloric acid was added. The hydrochloride crystallized very easily as white needles, which after some cooling were filtered off and recrystallized from absolute ethanol (yield 8·2 g; 80 per cent), m.p. 232°. After recrystallization several times from ethanol it had m.p. 233°, λ_{max} 278 mμ (log ε 3·9), 306–307 mμ (3·87) (Found: C, 66·47; H, 5·58; N, 2·83; Cl, 6.95. Calc. for $C_{26}H_{25}NO_5.HCl$: C, 66·72; H, 5·59; N, 2·99; Cl, 7·57 per cent).

1-(3′-*Benzoyloxy*-4′-*methoxybenzyl*)-3,4-*dihydro*-6,7-*dimethoxy*isoquinoline *methiodide* (III; R_1 = PhCO, R_2 = CH_3). The hydrochloride (3 g) was suspended in a mixture of 30 ml of water and 30 ml of ethyl ether. A saturated solution of sodium hydrogen carbonate was added to alkalinity, and the free base was extracted with ether. The well dried ether extract was evaporated and the oily residue was boiled with 24 ml of methyl iodide. After a few minutes crystals of the methiodide began to be precipitated. After 30 min the heating was stopped and the excess of methyl iodide was removed by evaporation under vacuum. The orange crystalline solid residue was well dried and recrystallized several times from absolute ethanol to give long yellow needles (yield 3·1 g; 92 per cent), m.p. 224° (Found: C, 54·91; H, 4·51; I, 20·51. Calc. for $C_{26}H_{25}NO_5.CH_3I.H_2O$: C, 54·81; H, 5·05; I, 21·46 per cent).

1-(3′-*Benzoloxy*-4′-*methoxybenzyl*)-6,7-*dimethoxytetrahydro*isoquinoline *hydriodide* (*benzoyllaudanine hydriodide*). The methiodide (2 g) was suspended in 200 ml of absolute ethanol and reduced with hydrogen at 60° and 2 atmospheres, with 400 mg of platinum oxide as catalyst. After 2 hr the methiodide had dissolved. The solution was allowed to cool at room temperature while the reduction was continued for 2 hr more. In some experiments white needles of the hydriodide separated during this last phase of the reaction. They were dissolved by warming the solution, the platinum filtered off and the alcohol was removed by evaporating under vacuum to 50 ml. The crystalline hydriodide was collected after cooling (yield 1·7 g; 85 per cent), m.p. 183°, which did not increase after further crystallizations (Found: C, 56·09; H, 5·26; I, 21·75. Calc. for $C_{27}H_{29}NO_5.HI$: C, 56·38; H, 5·24; I, 22·05 per cent).

Benzoyllaudanine (IV; R_1 = PhCO, R_2 = CH_3). The hydriodide (500 mg) was suspended in a mixture of 10 ml of water and 10 ml of ethyl ether, the suspension was made alkaline with sodium hydrogen carbonate solution, and the base was extracted with ether. By evaporation of the ether extracts, 336 mg of crystalline

benzoyllaudanine (yield 95 per cent), m.p. 154–155°, were obtained. After recrystallization several times from absolute ethanol, it formed prisms, m.p. 156–157°, λ_{max} 284 mμ (log ε 3·87), soluble in cold acetone, chloroform and ether, but less soluble in methanol benzene and dioxan (Found: C, 72·39; H, 6·49; N, 3·15. Calc. for $C_{27}H_{29}NO_5$: C, 72·46; H, 6·53; N, 3·13 per cent).

The crystals gave a reddish color with concentrated nitric acid and a negative reaction with ferric chloride, Millon's reagent and Folin and Ciocalteu's reagent. Benzoyllaudanine does not couple with diazotized *p*-nitroaniline.

Laudanine (IV; $R_1 = H$, $R_2 = CH_3$). To 200 mg of benzoyllaudanine, 20 ml of concentrated hydrochloric acid was added and the suspension was heated to 70° in a water bath, for 45 min. The base dissolved easily and, when the heating was finished, the cooled solution was extracted with ether to remove the benzoic acid. It was then made alkaline with sodium hydrogen carbonate solution and extracted again with ether. The ether extracts were dried and evaporated, when an oily residue was left, which crystallized as soon as a drop of absolute ethanol was added. By filtering, 180 mg of crystals melting 163–164°, with sintering from 159°, were obtained. After several recrystallizations from absolute ethanol, fine needles melting at 164–165° were collected, λ_{max} 284 mμ (log ε 3·78) (Found: N, 4·32. Calc. for $C_{20}H_{25}NO_4$: N, 4·08 per cent). From the product a picrate, obtained as rectangular prisms from ethanol, m.p. 176–177°, and an oxalate, obtained as prisms from water, m.p. 110°, were prepared. Laudanine melts at 163–164°,[5] its picrate 176·5–177·5°[3] and the oxalate 110°.[12]

Synthetic laudanine gives a green-blue color with ferric chloride, a reddish one with nitric acid and with concentrated sulfuric acid, and a blue color with Folin and Ciocalteu's reagent. Millon's reaction is negative. It couples with diazotized *p*-nitroaniline.

(±)-*Laudanosine* (IV; $R_1 = R_2 = CH_3$). Methylation of the synthetic laudanine, in ether solution, with diazomethane gave (±)-laudanosine, m.p. 113–114°, which did not give any depression when mixed with crystals of authentic laudanosine, m.p. 113–114°.

(+)-*Benzoyllaudanidine* D-*tartrate*. Benzoyllaudanine (300 mg) was dissolved in 6 ml of absolute ethanol, 100 mg of D-tartaric acid was added and the suspension was heated to boiling, when all the materials dissolve. On cooling, a solid separated, which after standing several hours at 5°, was filtered off and recrystallized from absolute ethanol (yield 95 mg), m.p. 159–160°. After several recrystallizations from the same solvent, rectangular prisms were obtained, m.p. 160–161°, $[\alpha]_D^{22°}$ +50·5° ± 2° (*c*, 0·4 in chloroform) (Found: C, 61·71; H, 5·97; N, 2·35. Calc. for $C_{31}H_{35}NO_{11}$: C, 62·30; H, 5·86; N, 2·34 per cent).

(−)-*Benzoyllaudanidine* L-*tartrate*. The mother-liquors of the preparation of the D-tartrate were evaporated to dryness. The residue was dissolved in water, and the solution made alkaline with sodium hydrogen carbonate solution and extracted with ether. The ether solution, after being dried and evaporated, left a residue of 150 mg, which was dissolved in 3 ml of boiling absolute ethanol with 50·4 mg of L-tartaric acid. On cooling, a precipitate was obtained, which, after several crystallizations from

[3] O. Hesse, *Liebigs Ann.* Suppl. 8, 277 (1872), from Beilstein's *Handbuch der Org. Chem.* (4th Ed.) Vol. 21, p. 210. Springer, Berlin (1935).

absolute ethanol, was obtained as rectangular prisms, m.p. 160–161°, $[\alpha]_D^{22°}$ −50·3° ± 1·6° (*c*, 0·34 in chloroform).

(+)-*Benzoyllaudanidine*. (+)-Benzoyllaudanidine D-tartrate (400 mg) was dissolved in 15 ml of saturated sodium hydrogen carbonate solution and the base was extracted with ether. The ether, dried and evaporated, gave an oil that crystallized easily on the addition of one drop of methanol or absolute ether. After being recrystallized several times from ethanol, 240 mg of prisms melting at 144–145° (dec.) were collected, $[\alpha]_D^{22°}$ +63·2 ± 1·4° (Found: C, 72·19; H, 6·48; N, 3·07. Calc. for $C_{27}H_{29}NO_5$: C, 72·46; H, 6·53; N, 3·13 per cent).

(−)-*Benzoyllaudanidine*. Five-hundred milligrams of (−)-benzoyllaudanidine L-tartrate gave 305 mg of (−)-benzoyllaudanidine, m.p. 144–145°, $[\alpha]_D^{22°}$ −63·9 ± 1·6°.

By dissolving equimolecular quantities of the optical isomers of benzoyllaudanidine in boiling absolute ethanol, the racemic (±)-benzoyllaudanidine, m.p. 156–157°, was obtained.

(+)-*Laudanidine* (IV; $R_1 = OH$, $R_2 = CH_3$). (+)-Benzoyllaudanidine (100 mg) was heated for 45 min at 70° with 10 ml of concentrated hydrochloric acid. After cooling, the solution was extracted with ether. The aqueous layer was diluted, made alkaline with sodium hydrogen carbonate solution and extracted again with ether. After drying and evaporating, the oily residue crystallized on the addition of one drop of methanol. On recrystallization several times from methanol, 67 mg of small prisms, m.p. 184–185° (vacuum), were obtained, $[\alpha]_D^{22°}$ −94·8 ± 1·4° (*c*, 0·4 in chloroform) (Found: C, 70·01; H, 7·46; N, 4·07. Calc. for $C_{20}H_{25}NO_4$: C, 69·95; H, 7·33; N, 4·08 per cent. For the (+)-laudanidine obtained from laudanosine, Späth and Burger[4] give m.p. 184–185°.

(+)-*Laudanidine picrate* was obtained as prisms from ethanol, m.p. 174–175° (Found: C, 54·92; H, 4·79; N, 9·87. Calc. for $C_{20}H_{25}NO_4.C_6H_3N_3O_7$: C, 54·54; H, 4·93; N, 9·79 per cent.

(−)-*Laudanidine*. One-hundred milligrams of (−)-benzoyllaudanidine was hydrolyzed in the same way as the dextrorotatory isomer. After recrystallization several times from methanol, 69 mg of crystals, m.p. 184–185° (vacuum), were obtained, $[\alpha]_D^{22°}$ −94·7° ± 1·3. The picrate had m.p. 174–175°.

(±)-*Laudanidine* (*laudanine*). Ten milligrams of each optical isomer of laudanidine was dissolved in boiling absolute ethanol. On cooling, the racemic form crystallized, m.p. 164–165°; picrate, m.p. 176–177°.

Benzoylhomovanillic acid. Homovanillic acid (10 g) were dissolved in 100 ml of 6 per cent sodium hydroxide solution and treated with 8·5 g of benzoyl chloride. When benzoylation was complete, 2 N hydrochloric acid was added to pH 3·5. A precipitate was produced, which was filtered off and washed well with water, and the benzoic acid was separated by boiling the solid with 10 ml of water and filtering the solution while hot. By repeating the extraction, an insoluble product, m.p. 167°, was obtained, which was recrystallized from absolute ethanol (yield 13·7 g; 88 per cent), m.p. 169° (Berlin *et al.*[13] give m.p. 169°).

Benzoylhomovanillyl chloride. Benzoylhomovanillic acid (10 g) was boiled with 25 ml of thionyl chloride for 1 hr. The excess of thionyl chloride was removed by distillation and the oily residue was well dried in a desiccator. It was then dissolved in 20

[13] A. Ya. Berlin, S. M. Sherlin and T. A. Serebrennikova, *Zhur. Obshchei Khim.* **19**, 759 (1949); *Chem. Abstr.* **44**, 1058 (1950).

ml of boiling benzene and after cooling, 140 ml of light petroleum boiling range (66–73°) was slowly added and the solution was set aside in a cool room overnight. The chloride crystallized as needles, which were filtered off (yield 8·1 g). The mother-liquors were concentrated to 80 ml and a new crop of chloride (1·5 g) was obtained. The chloride was recrystallized by dissolving in benzene and adding light petroleum when 9·2 g (77 per cent) of product was obtained as prisms, m.p. 64° (Berlin *et al.*[13] give m.p. 66–67°).

4′-Benzoyloxy-3′-methoxyphenyl-N-2-(3,4-*dimethoxyphenyl*)*ethylacetamide* (I; $R_1 = CH_3$, $R_2 = PhCO$). To 6 g of 3,4-dimethoxyphenylethylamine dissolved in 40 ml of chloroform and cooled to 0–5°, 10 g of benzoyl homovanillyl chloride, dissolved in 40 ml of chloroform, was slowly added, the temperature being kept low. After 10 min, 60 ml of N sodium hydroxide was added. The chloroform layer was decanted and well washed with 2 N hydrochloric acid and water. It was then dried and distilled under vacuum. The oily residue crystallized on standing in a desiccator. It was recrystallized from absolute ethanol to give 14·2 g (95 per cent) of needles, m.p. 97°. For analysis it was recrystallized several times from absolute ethanol, m.p. 98°, soluble in acetone and acetic acid, λ_{max} 276 mμ (log ε 3·84) (Found: C, 67·33; H, 6·34; N, 2·91. Calc. for $C_{26}H_{27}NO_6.H_2O$: C, 66·79; H, 6·25; N, 3·00 per cent).

*1-(4′-Benzoyloxy-3′-methoxybenzyl)-3,4-dihydro-6,7-dimethoxy*isoquinoline *hydrochloride* (II; $R_1 = CH_3$, $R_2 = PhCO$). To 5 g of the amide, dissolved in 50 ml of chloroform and cooled to 0–5°, 10 g of phosphorus pentachloride was slowly added. The temperature was kept at 5° and after 3 hr the suspension was left at room temperature for 4 days. During the first day a precipitate appeared that did not increase in bulk in the remaining time. Then 20 g of crushed ice was added and the mixture was evaporated under vacuum to remove the chloroform. Water and an insoluble solid remained. The water was separated by decanting and the solid was dried. It was dissolved in 60 ml of absolute ethanol and 60 ml of 2 N hydrochloric acid was added. Fine needles of the hydrochloride were obtained, which after recrystallization several times from absolute ethanol (yield 4·5 g; 79 per cent) had m.p. 149°, λ_{max} 276 mμ (log ε 3·94), 308–310 mμ (log ε 3·84) (Found: C, 66·50; H, 6·01; N, 2·89; Cl, 6·95. Calc. for $C_{26}H_{25}NO_5.HCl$: C, 66·72; H, 5·59; N, 2·99; Cl, 7·57 per cent).

*1-(4′-Benzoyloxy-3′-methoxybenzyl)-3,4-dihydro-6,7-dimethoxy*isoquinoline *methiodide*. The hydrochloride (4 g) was suspended in 40 ml of water, 20 ml of ethyl ether was added and the suspension was made alkaline by addition of saturated sodium hydrogen carbonate solution. The free base passed into the ether and the extraction was repeated several times. The pooled ether extracts were dried and evaporated to dryness. The colorless residue was dried in a desiccator, 32 ml of methyl iodide was added and the solution was heated to boiling. After 5 min a yellow precipitate appeared and after 30 min the heating was stopped, the excess of methyl iodide was evaporated under vacuum and the residue was crystallized from 200 ml of absolute ethanol, m.p. 198–199°. After three crystallizations from the same solvent the m.p. was 205–206°, as yellow irregular prisms, united to rosettes (yield 3·6 g; 80 per cent) (Found: C, 56·29; H, 5·12; N, 2·49; I, 22·44. Calc. for $C_{26}H_{25}NO_5.CH_3I$: C, 56·56; H, 4·88; N, 2·44; I, 22·15 per cent).

*1-(4′-Benzoyloxy-3′-methoxybenzyl)-6,7-dimethoxytetrahydro*isoquinoline *hydriodide*. The dihydro*iso*quinoline methiodide (2 g) was dissolved in 150 ml of boiling absolute ethanol, the solution was cooled, 300 mg of platinum oxide was added and it was

reduced with hydrogen at a pressure of 2 atmospheres. After 30 min, a precipitate of crystalline white needles appeared, which increased with time. After 6 hr the hydrogenation was stopped, the crystalline precipitate was dissolved by heating and the platinum was filtered off. After being kept overnight at 5°, a new crystalline precipitate was obtained, which was filtered off and washed well with absolute ethanol (yield 1·85 g; 92 per cent), m.p. 165–166°, the melting point remained constant after recrystallization from ethanol (Found: C, 56·87; H, 5·92; N, 2·59; I, 22·38. Calc. for $C_{27}H_{29}NO_5.HI$: C, 56·38; H, 5·24; N, 2·46; I, 22·05 per cent).

(±)-*Benzoylpseudocodamine* The hydriodide (500 mg) was suspended in water, saturated sodium hydrogen carbonate solution was added to alkalinity and the liberated base was extracted with ether. The ether extracts were well dried and evaporated in vacuum, to leave a yellowish crystalline residue (343 mg), m.p. 131–132°. It was recrystallized in poor yields from absolute ethanol, when white rectangular prisms with a constant m.p. of 134–135° were obtained. They gave a negative test for phenols (Folin, Molish and diazotized *p*-nitroaniline) and a slight positive Burger's test for pseudocodamine, possible because of small hydrolysis of the benzoyl group; λ_{max} 282 mμ (log ε 3·87) (Found: C, 72·99; H. 6·50. Calc. for $C_{27}H_{29}NO_5$: C, 72·46; H, 6·53 per cent).

(±)-*Pseudocodamine* (IV; $R_1 = CH_3$, $R_2 = H$). The benzoyl base (150 mg) was suspended in 15 ml of concentrated hydrochloric acid and heated for 45 min at 70° in a water bath. The base dissolves easily. After heating, the solution was extracted with ether, to remove the benzoic acid. It was then diluted with water and made alkaline with sodium hydrogen carbonate solution, and the base was extracted with ether. The ether extracts were united, washed with water, dried and evaporated. The yellowish crystalline residue was crystallized several times from *cyclo*hexane, when white needles united to rosettes, of constant m.p. 131–132°, were obtained; the product was very soluble in methanol, ethanol, acetone and chloroform, but less soluble in benzene and *iso*propyl ether. It gives a positive Folin and Cinocalteu reaction and couples with diazotized-*p*-nitroaniline. When dissolved in concentrated sulfuric acid, a violet color appears on adding a small crystal of potassium dichromate (Burger's reaction); Millon's reaction is negative; λ_{max} 284 mμ (log ε 3·78) (Found: C, 69·90; H, 7·05; N, 4·18. Calc. for $C_{20}H_{25}NO_4$: C, 69·95; H, 7·33; N, 4·08 per cent).

Burger[10] gives m.p. 129–130° for the (±)-pseudocodamine prepared from (±)-laudanosine.

(±)-Pseudocodamine picrate was prepared in the usual way in ethanol solution to give rectangular plates, m.p. 156–157°, with sintering from 153° (Found: C, 54·69; H, 5·24; N, 9·85. Calc. for $C_{20}H_{25}NO_4.C_6H_3N_3O_7$: C, 54·54; H, 4. 93; N, 9·79 per cent).

The hydriodide was obtained as needles from ethanol, m.p. 213–214° (Found: C, 50·86; H, 5·57; I, 26·27. Calc. for $C_{20}H_{25}NO_4.HI$: C, 50·95; H, 5·52; I, 26·94 per cent).

(+)-*Benzoylpseudocodamine* D-*tartrate*. *rac*.-Benzoylpseudocodamine (300 mg) was dissolved in 6 ml of warm absolute ethanol and a solution of 100 mg of D-tartaric acid in 6 ml of warm absolute ethanol was added. On cooling, a crystalline precipitate appeared, which was filtered off and recrystallized six times from absolute ethanol to give rectangular plates, m.p. 186–187°, with sintering from 183°, $[\alpha]_D^{22°}$ −40·7 ± 2° (*c*, 0·38 in chloroform) (Found: C, 61·47; H, 5·95; N, 2·41. Calc. for $C_{31}H_{35}NO_{11}$: C, 62·30; H, 5·86; N, 2·34 per cent).

(−)-*Benzoylpseudocodamine* L-*tartrate*. From the mother-liquors of the separation

of (+)-benzoylpseudocodamine D-tartrate, the base was extracted with ether in the usual way. By evaporation of the ether extracts, 100 mg of a residue was obtained and purified by recrystallization from ethanol, when 100 mg of a product m.p. 132° was obtained. This was dissolved, together with 34 mg of L-tartaric acid, in 2 ml of boiling absolute ethanol. On cooling, rectangular plates separated, which were filtered off and recrystallized four times from absolute ethanol, m.p. 186–187°, sintering from 183°, $[\alpha]_D^{22°}$ −41·1° ± 2° (*c*, 0·38 in chloroform).

(+)-*Benzoylpseudocodamine.* (+)-Benzoylpseudocodamine D-tartrate (500 mg) was suspended in 20 ml of water, and the suspension was made alkaline with sodium hydrogen carbonate and extracted with ether. The ether extracts on evaporation gave (+)-benzoylpseudocodamine, which was recrystallized several times from methanol to give long rectangular plates (yield 290 mg; 88 per cent), m.p. 134°, $[\alpha]_D^{22°}$ 35·3 ± 1·4° (*c*, 0·4 in chloroform).

(−)-*Benzoylpseudocodamine.* (−)-Benzoylpseudocodamine L-tartrate (300 mg) was treated as described for the dextrorotary isomer, when the yield was 180 mg (90 per cent) of (−)-benzoylpseudocodamine, m.p. 133–134°, $[\alpha]_D^{22°}$ −34·8° ± 2° (*c*, 0·6 in chloroform).

(+)-*Pseudocodamine.* (+)-Benzoylpseudocodamine (150 mg) was hydrolyzed as has been described for the racemic benzoyl base. After elimination of the benzoic acid, the ether extracts gave on evaporation an oil, which crystallized when a drop of absolute ether was added; a crude product was obtained, m.p. 124–125,° which after three crystallizations from *cyclo*hexane gave long prisms, m.p. 131–132°, $[\alpha]_D^{22°}$ +24·7° ± 2° (*c*, 0·46 in chloroform, soluble in cold methanol, ethanol and acetone, but less soluble in ether (Found: C, 69·85; H, 7·22; N, 4·06. Calc. for $C_{20}H_{25}NO_4$: C, 69·95; H, 7·33; N, 4·08 per cent).

The picrate was obtained as rectangular plates, m.p. 194–195° (from ethanol) (Found: C, 54·68; H, 4·58; N, 9·59. Calc.: C, 54·54; H, 4·93; N, 9·79 per cent).

(+)-*Laudanosine from* (+)-*pseudocodamine.* (+)-pseudocodamine (100 mg) was dissolved in 10 ml of ether, treated with a solution of diazomethane and left overnight at 5°. After destruction of the excess of diazomethane with acetic acid, the ether was evaporated and the solid residue was extracted with boiling light petroleum (boiling range 30–60°). On cooling prisms united to rosettes, m.p. 81°, were obtained, which were recrystallized several times from light petroleum (boiling range 30–60°), m.p. 89°, $[\alpha]_D^{22°}$ +52·2° ± 1·3° (in chloroform. (+)-Laudanosine has m.p. 89° and $[\alpha]_D$ +52° (in chloroform).

(−)-*Pseudocodamine.* (−)-Benzoylpseudocodamine (150 mg) was hydrolyzed in a similar way to the *dextro* isomer, when 115 mg of the crude base, m.p. 126°, were obtained, which after several recrystallizations from *cyclo*hexane had m.p. 131–132°, the picrate was obtained as rectangular plates, m.p. 194–195° (from ethanol), $[\alpha]_D^{22°}$ − 24·4° ± 2°.

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