acid, the solvent was evaporated to leave the acid **21** as a gum to which a mixture of acetic acid (5 ml) and concentrated hydrochloric acid (5 ml) was added. The mixture was refluxed for 7 days until carbon dioxide had ceased to be evolved. After being allowed to stand overnight, crystals formed were collected by filtration and then suspended in chloroform. The chloroform suspension was shaken with 10% ammonia, washed with water, and dried over Na_2SO_4. Evaporation of the chloroform yielded a powder, which was recrystallized from methanol to give naucléfine (**4**, 26 mg, 10%) as yellow needles, mp 285–290 °C (lit.[4] mp 285–290 °C), whose uv [(EtOH) 390, 372, 300, 290, 250, and 220 nm], ir [(KBr) 3500 (NH), 1650 (C=O), 1610 and 1538 cm^{-1}], NMR [(Me_2SO-d_6) δ 4.92 (2 H, t, J = 7 Hz, 5-CH_2), 6.96–7.70 (6 H, m, indole aromatic protons and 14- and 20-CH), 8.56 (1 H, d, J = 6.5 Hz, 21-CH), and 9.25 (1 H, s, 17-CH)] spectra were superimposable on those of natural product.

B. A mixture of the azaisocarbostyril **20** (300 mg), concentrated hydrochloric acid (5 ml), and glacial acetic acid (5 ml) was refluxed for 7 days after standing overnight. Crystals formed were collected and worked up as above to give naucléfine (**4**, 28 mg, 15%) as yellow needles, mp 285–290 °C, which was identical with the above product prepared by method A.

Acknowledgments. We are indebted to Dr. T. R. Govindachari for a gift of gentianine, Dr. J. D. Phillipson and Dr. H. T. Cheung for providing a gift of natural angustine and its spectra, and Professor F. Hotellier for providing the spectral data of naucléfine. We are also grateful to Professor T. Nambara and Dr. K. Shimada for taking HPLC and Mmes. R. Kobayashi, A. Satoh, and C. Koyanagi, Misses R. Suenaga, E. Nagoaka, Y. Yokohama, and H. Koizumi, and Mr. K. Kawamura for microanalyses and spectral measurements.

Registry No.—**1**, 40041-96-1; **4**, 57103-51-2; **6**, 439-89-4; **7**, 57110-40-4; **8**, 59054-51-2; **9**, 59054-52-3; **10**, 57110-41-5; **11**, 59054-53-4; **14**, 57155-81-4; **16**, 59054-54-5; **17**, 5444-01-9; **18**, 58790-51-5; **19**, 38824-07-6; **20**, 58752-34-4; **21**, 58752-35-5; ethyl oxalate, 95-92-1; tryptamine, 61-54-1; ethyl formate, 109-94-4.

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(16) NMR (Me_2SO-d_6 at 90 °C) δ 4.49 (2 H, t, J = 7 Hz, 5-CH_2), 5.73 (1 H, dd, J = 11.5 and 2 Hz, 18-CH), 6.90 (1 H, dd, J = 18 and 2 Hz, 18-CH), 8.87 (1 H, s, 21-H), and 9.26 (1 H, s, 17-CH).

A Novel Cleavage of Aryl Benzyl Ethers and Allyl Aryl Ethers by Sodium Bis(2-methoxyethoxy)aluminum Hydride. An Alternative Synthesis of Pentazocine

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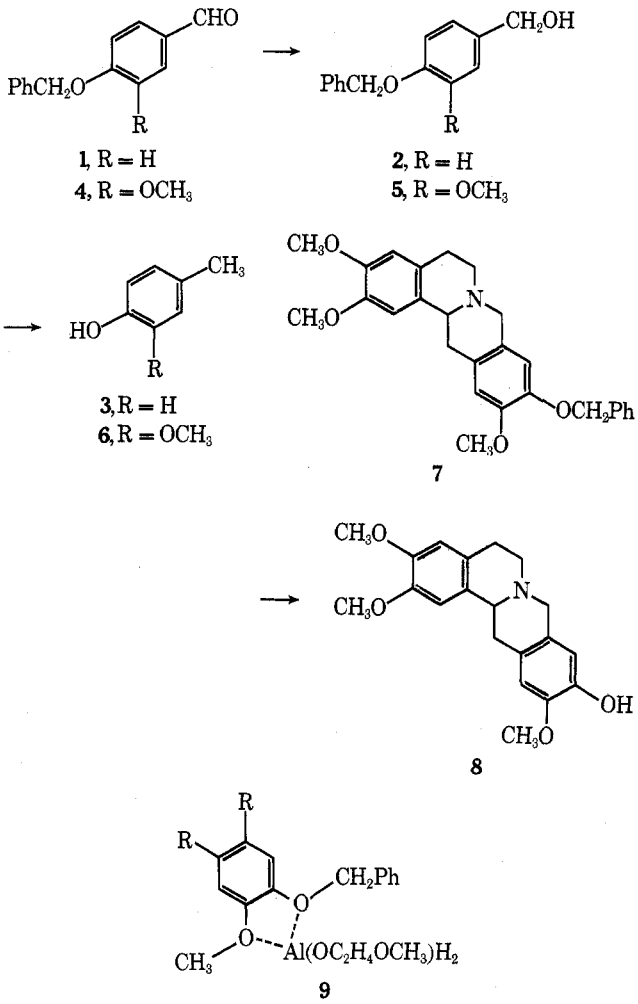
Refluxing with sodium bis(2-methoxyethoxy)aluminum hydride in xylene causes an effective cleavage of benzyl or allyl ether. Using this reaction, pentazocine (**10**) was synthesized as follows. Hydrogenolysis of 3-benzyl-1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-6,11-dimethyl-3-benzazocin-4-one (**11**) with palladium on charcoal, followed by condensation of the resulting secondary amide (**12**) with dimethylallyl bromide gave the *N,O*-bis(dimethylallyl) compound (**15**), which yielded pentazocine (**10**) on refluxing with sodium bis(2-methoxyethoxy)aluminum hydride in xylene. The conversion of 3-benzyl-1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocinium bromide (**17**) into pentazocine was examined under various conditions.

Although several examples of the hydrogenolysis of various types of organic compounds using complex metal hydrides have been reported, there are few synthetic applications.[1-3] Since sodium bis(2-methoxyethoxy)aluminum hydride, commercially available, has many advantages over other complex metal hydrides, the hydrogenolysis with sodium bis(2-methoxyethoxy)aluminum hydride have been studied. In this paper we now wish to report effective cleavages of aryl benzyl ethers or allyl aryl ethers with sodium bis(2-methoxyethoxy)aluminum hydride and alternative synthetic methods of pentazocine (**10**), a nonnarcotic analgesic, applying this reagent.

Debenzylation of the compounds having a methoxyl group at a vicinal carbon with sodium bis(2-methoxyethoxy)aluminum hydride proceeded more smoothly than that of the benzyl ether on monooxygenated aryl group. Thus, refluxing of 4-benzyloxybenzaldehyde (**1**) with an excess of the reagent in xylene for 6 h gave mainly 4-benzyloxybenzyl alcohol (**2**), and *p*-cresol (**3**) was obtained as a sole product by the same treatment as above for 60 h. On the other hand, when 4-benzyloxy-3-methoxybenzaldehyde (**4**) was refluxed with an excess of sodium bis(2-methoxyethoxy)aluminum hydride in xylene, creosol (**6**) was formed together with a small amount of 4-benzyloxy-3-methoxybenzyl alcohol (**5**) after 6 h, and creosol (**6**) was homogeneously obtained after 10 h. Treatment of 10-benzyloxy-5,6,13,13a-tetrahydro-2,3,11-trimethoxy-8*H*-dibenzo[*a,g*]quinolizine (**7**)[4] under the same conditions for 6 h caused the cleavage of the benzyl ether to afford the phenolic tetrahydroprotoberberine (**8**)[4] in an excellent yield (Scheme I).

Scheme I



Alkoxyaluminum hydride, such as $AlH_2(OC_2H_4OCH_3)$, would be reversibly formed from sodium bis(2-methoxyethoxy)aluminum hydride in solution as other complex metal hydrides.[5,6] We believe that the alkoxyaluminum hydrides play an important role as Lewis acid for the present hydrogenolysis and the debenzylation of the compounds having vicinal methoxyl group proceeded easily because of the formation of the complex as **9**.

This hydrogenolysis seemed to be useful for the debenzylation or deallylation of the compound which is labile to acid or catalytic hydrogenolysis. Recently we reported a synthetic method of producing pentazocine (**10**) from tyrosine.[7] The last stages have been further elaborated by application of this reagent.

Hydrogenolysis of the amide (**11**) in the presence of 10% palladium on charcoal under hydrogen in acetic acid at 80 °C gave the secondary amide (**12**), mp 275–277 °C, in 98% yield. Refluxing **12** with benzyl chloride in the presence of potassium carbonate in methanol afforded, in 78% yield, the *O*-benzyl ether (**13**), mp 194 °C, which reacted with dimethylallyl bromide in the presence of sodium hydride in dry dioxane to yield the *N*-dimethylallyl compound (**14**), mp 151–152 °C, in 90% yield. Refluxing **14** with sodium bis(2-methoxyethoxy)aluminum hydride in dry xylene for 60 h gave pentazocine (**10**) in 55% yield (Scheme II). All the physical properties of the synthetic pentzocine were identical with those of the authentic sample.[8]

When the above secondary amide (**12**) was heated with dimethylallyl bromide in the presence of sodium hydride in dry dioxane, the *N,O*-bis(dimethylallyl) compound (**15**), mp 129–131 °C, was obtained in 76% yield. Treatment of **15** with sodium bis(2-methoxyethoxy)aluminum hydride in hot xylene for 42 h gave pentazocine (**10**) in 62% yield. This procedure, **11** → **12** → **15** → **10**, was the best transformation of the amide (**11**) into pentazocine (**10**) (46% overall yield from **11**).

The rate of O-debenzylation or deallylation was slower than that of reaction for the amide group. Thus, refluxing the *N,O*-bis(dimethylallyl) compound (**15**) with sodium bis(2-methoxyethoxy)aluminum hydride in dry benzene for 5 h yielded mainly the amine (**16**) together with a small amount of pentazocine (**10**). Further treatment of **16** with sodium bis(2-methoxyethoxy)aluminum hydride in xylene for 42 h gave pentazocine (**10**).

Conversion of the quaternary salt (**17**), obtained from the amine (**18**) and dimethylallyl bromide, into pentazocine (**10**) had already been carried out under several conditions by one of the authors.[8-10] Refluxing **17** with sodium bis(2-methoxyethoxy)aluminum hydride in xylene for 17 h yielded pentazocine (**10**) and the amine (**18**) in 10.5 and 42.5% yield, respectively. Furthermore, heating **17** with triphenylphosphine in dry acetonitrile at 130–140 °C in a sealed tube[11] and a treatment of **17** with sodium *n*-propylmercaptide in hexamethylphosphoric triamide at 0 °C[12] also furnished pentazocine (**10**) in 18 and 8% yield, respectively, along with the amine (**18**) in 58 and 19.6% yield, respectively.

Experimental Section

All melting points were uncorrected. Ir spectra were taken with a Hitachi 215 recording spectrometer. NMR spectra were measured with JNM-PMX-60 and JNM-PS-100 spectrophotometers with tetramethylsilane as internal standard; mass spectra were taken with a Hitachi RMU-7 spectrometer. Sodium bis(2-methoxyethoxy)aluminum hydride (70%) in benzene (Wako Chemicals) was used for the following reactions.

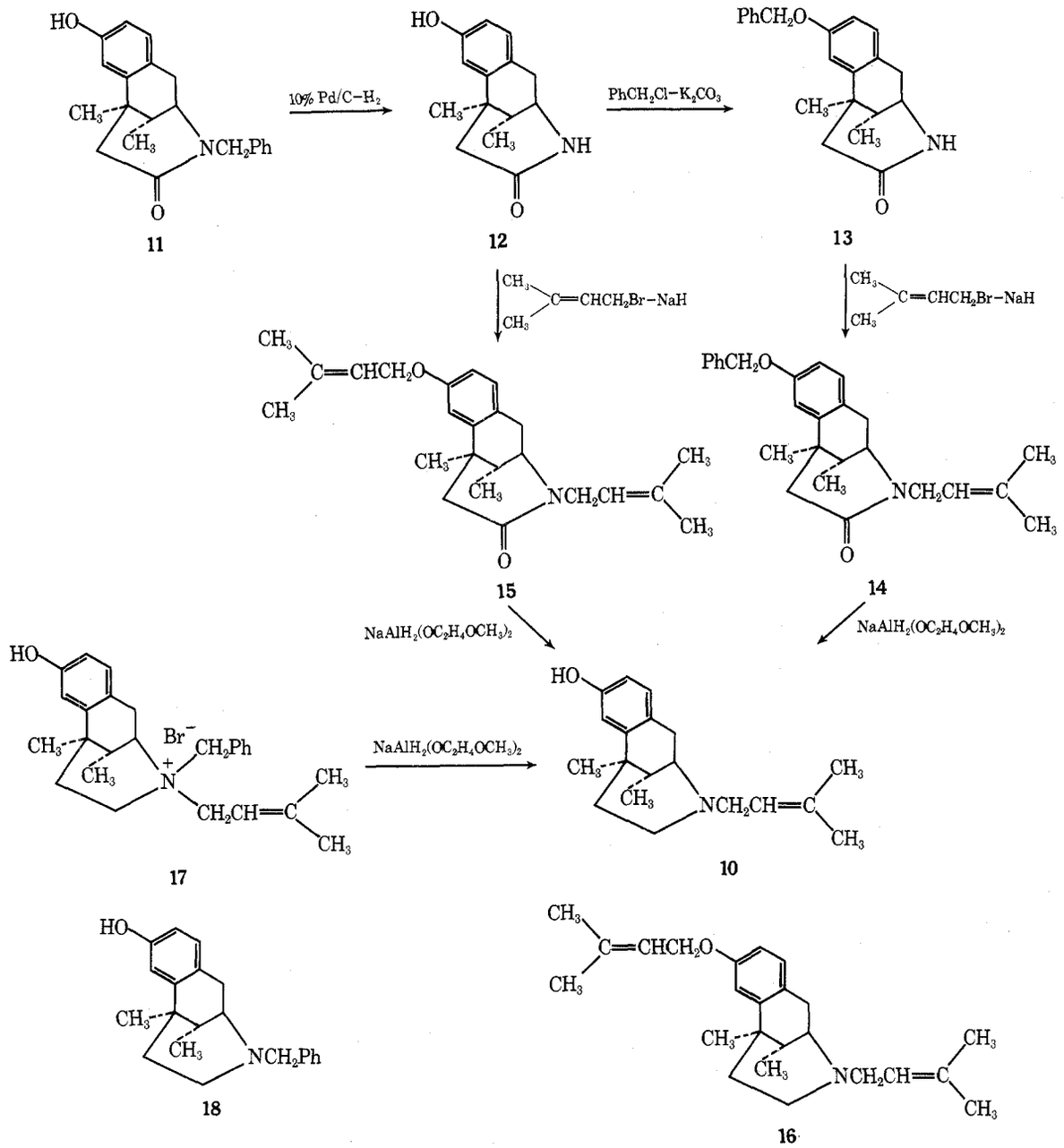
***p*-Cresol (3).** A mixture of 212 mg of 4-benzyloxybenzaldehyde (**1**) and 1.5 g of 70% sodium bis(2-methoxyethoxy)aluminum hydride in 5 ml of dry xylene was refluxed for 60 h under stirring and protection from moisture. After an addition of an excess of 10% aqueous sodium hydroxide solution, the separated organic layer was extracted with water. The combined aqueous layers were acidified with 10% hydrochloric acid and extracted with chloroform. The extract was washed with saturated sodium chloride solution, dried over Na_2SO_4, and evaporated to give 75 mg of *p*-cresol (**3**) as an oil, bp 76 °C (5 mmHg), which was identical with an authentic sample.

Creosol (6). A mixture of 242 mg of 4-benzyloxy-3-methoxybenzaldehyde (**4**) and 1.5 g of 70% sodium bis(2-methoxyethoxy)aluminum hydride in 5 ml of dry xylene was refluxed for 10 h under the same conditions as above. The same workup as above gave 92 mg of creosol (**6**) as an oil, bp 79 °C (4 mmHg), which was identical with the authentic sample.

5,6,13,13a-Tetrahydro-10-hydroxy-2,3,11-trimethoxy-8*H*-dibenzo[*a,g*]quinolizine (8). A mixture of 80 mg of 10-benzyloxy-5,6,13,13a-tetrahydro-2,3,11-trimethoxy-8*H*-dibenzo[*a,g*]quinolizine (**7**) and 550 mg of 70% sodium bis(2-methoxyethoxy)aluminum hydride in 3 ml of dry xylene was heated under reflux and stirring in an oil bath for 6 h under a current of nitrogen gas. After the reaction mixture had been decomposed with 10% sodium hydroxide, the separated aqueous layer was washed with benzene, neutralized with crystalline ammonium chloride, and extracted with chloroform. After drying over Na_2SO_4, evaporation of the solvent gave a pale yellow solid, which was recrystallized from methanol to afford 58 mg of **8** as crystals, mp 193–195 °C (lit.[4] mp 193–195 °C).

1,2,3,4,5,6-Hexahydro-8-hydroxy-2,6-methano-6,11-dimethyl-3-benzazocin-4-one (12). A mixture of 500 mg of 3-benzyl-1,2,3,4,5,6-hexahydro-2,6-methano-6,11-dimethyl-3-benzazocin-4-one (**11**)[7] and 300 mg of 10% Pd/C in 20 ml of acetic acid was stirred at 80 °C for 21 h under a current of hydrogen. After filtration through Celite and washing with ethanol, evaporation of the combined filtrate and washings gave a pale brown caramel, which was solidified by addition of *n*-hexane. The resulting solid was collected by filtration and washed with chloroform to give a pale brown solid, whose recrystallization from ethanol afforded 354 mg of **12** as colorless crystals: mp 275–277 °C dec; ir ν_{max} ($CHCl_3$) 3600 (OH), 3400 (NH), and 1650 cm^{-1} (C=O); NMR (CF_3CO_2H) δ 1.16 (3 H, d, J = 7 Hz, C_{11} Me), 1.56 (3 H, s, C_6 Me), 2.82 (2 H, broad s, C_5 CH_2), and 6.76–7.20 (3 H, m, $C_{7,9}$ and C_{10} CH); mass spectrum *m/e* 231 (M^+).

Scheme II



Anal. Calcd for $C_{14}H_{17}NO_2 \cdot \frac{1}{4}H_2O$: C, 71.31; H, 7.48; N, 5.94. Found: C, 71.24; H, 7.24; N, 5.65.

1,2,3,4,5,6-Hexahydro-2,6-methano-6,11-dimethyl-3-(3-methyl-2-butenyl)-8-(3-methyl-2-butenyloxy)-3-benzazocin-4-one (15). A mixture of 475 mg of the above amide (**12**) and 495 mg of 50% sodium hydride in 200 ml of dry dioxane was refluxed for 2.5 h. After cooling, 1.55 ml of dimethylallyl bromide was added to the above mixture and the resulting mixture was further refluxed for 5 h under protection from moisture. The excess of sodium hydride was decomposed with crystalline ammonium chloride. After evaporation of the solvent, the resulting residue was dissolved in chloroform, washed with water and saturated aqueous sodium chloride solution, dried over Na_2SO_4, and evaporated to afford a solid, which was washed with *n*-haxane to give a colorless solid. Recrystallization from benzene–*n*-hexane gave 589 mg of **15** as colorless crystals: mp 129–131 °C; ir ν_{max} ($CHCl_3$) 1672 (C=C) and 1620 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.0 (3 H, d, J = 7 Hz, C_{11} Me), 1.34 (3 H, s, C_6 Me), 1.73 [12 H, s, 2 =C(Me)$_2$], 2.43 (2 H, s, C_5 CH_2), 2.87 (2 H, d, J = 7 Hz, C_1 CH_2), 5.17 (1 H, m, >C=C**H**CH_2N<), 5.49 (1 H, m, >C=C**H**CH_2O–), and 6.53–7.06 (3 H, m, $C_{7,9}$ and C_{10} CH); mass spectrum *m/e* 367 (M^+).

Anal. Calcd for $C_{24}H_{33}NO_2$: C, 78.43; H, 9.05; N, 3.81. Found: C, 78.31; H, 9.19; N, 3.65.

8-Benzyloxy-1,2,3,4,5,6-hexahydro-2,6-methano-6,11-dimethyl-3-benzazocin-4-one (13). A mixture of 140 mg of the amide (**12**), 91 mg of benzyl chloride, and 51 mg of potassium carbonate in 15 ml of dry methanol was refluxed for 3 days. The inorganic materials were filtered off and washed with methanol. Evaporation of the combined filtrate and washing gave a pale yellow solid, which was dissolved in chloroform. The chloroform layer was washed with water and saturated aqueous sodium chloride solution, dried over Na_2SO_4, and evaporated. The residue was triturated with *n*-hexane to give a colorless powder, which was recrystallized from benzene to afford 150 mg of **13** as colorless crystals: mp 194 °C; ir ν_{max} ($CHCl_3$) 3400 (NH) and 1645 cm^{-1} (C=O); NMR (CF_3CO_2H) δ 1.13 (3 H, d, J = 7 Hz, C_{11} Me), 1.50 (3 H, s, C_6 Me), 2.25 (1 H, m, C_{11} CH), 2.76 (2 H, broad s, C_5 CH_2), 5.23 (2 H, s, PhC**H**$_2$O), 7.06 (3 H, s, $C_{7,9}$ and C_{10} CH), and 7.36 (5 H, s, Ph).

Anal. Calcd for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.13; H, 7.21; N, 4.18.

8-Benzyloxy-1,2,3,4,5,6-hexahydro-2,6-methano-6,11-dimethyl-3-(3-methyl-2-butenyl)-3-benzazocin-4-one (14). A mixture of 90 mg of **13** and 90 mg of 50% sodium hydride in 6 ml of anhydrous dioxane was refluxed for 2.5 h, and then treated with 0.09 ml of dimethylallyl bromide as the case of **15**. The same workup as before gave a solid, which was washed with *n*-hexane to give a colorless

solid. Recrystallization from benzene–*n*-hexane gave 98 mg of **14** as colorless crystals: mp 151–152 °C; ir ν_{max} ($CHCl_3$) 1620 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.98 (3 H, d, J = 7 Hz, C_{11} Me), 1.33 (3 H, s, C_6 Me), 1.70 [6 H, s, $=C(Me)_2$], 2.43 (2 H, s, C_5CH_2), 2.87 (2 H, m, C_1CH_2), 3.53 (2 H, m, $NCH_2OCH=$), 4.43 (1 H, , C_2 CH), 5.02 (2 H, s, $PhCH_2O$), 6.83 (3 H, m, $C_{7,9}$ and C_{10} CH), and 7.35 (5 H, s, Ph).

Anal. Calcd for $C_{26}H_{31}NO_2$: C, 80.17; H, 8.02; N, 3.60. Found: C, 80.08; H, 8.09; N, 3.62.

1,2,3,4,5,6-Hexahydro-8-hydroxy-2,6-methano-6,11-dimethyl-3-(3-methyl-2-butenyl)-3-benzazocine (Pentazocine, 10). A. A mixture of 450 mg of the amide (**15**) and 3.6 g of 70% sodium bis(2-methoxyethoxy)aluminum hydride in 20 ml of dry xylene was heated under reflux and stirring in an oil bath for 42 h under a current of nitrogen. After the reaction mixture had been acidified with 10% hydrochloric acid while cooling, the organic layer separated was extracted with water. Both aqueous layers were combined and neutralized with 10% ammonia, and the separated free base was extracted with chloroform. The extract was dried over Na_2SO_4 and evaporated to give a caramel-like substance, which was purified on silica gel chromatography using benzene–methanol (98.5:1.5 v/v) to afford a caramel. Recrystallization from acetone gave 216 mg of pentazocine (**10**) as colorless crystals, mp 146–148 °C (lit.[8] mp 146–148 °C), which was identical with the authentic sample[8] from the ir and NMR spectra and TLC comparisons and mixture melting point test.

B. A mixture of 45 mg of the amide (**14**) and 350 mg of 70% sodium bis(2-methoxyethoxy)aluminum hydride in 3 ml of dry xylene was refluxed for 60 h with stirring under a current of nitrogen. The same workup as above gave a pale brown caramel, which was purified by preparative TLC on silica gel with methanol–ethyl acetate–benzene (1:5:4 v/v) to afford 18 mg of pentazocine (**10**).

C. A solution of 100 mg of the amide (**15**) and 900 mg of 70% sodium bis(2-methoxyethoxy)aluminum hydride in 5 ml of dry benzene was refluxed for 5 h with stirring under a current of nitrogen. The same workup as before gave 6 mg of pentazocine (**10**). The organic layer was washed with saturated aqueous sodium chloride solution, dried over Na_2SO_4, and evaporated to give a colorless caramel, which was solidified by triturating with ether. The resulting solid was recrystallized from methanol–ether to afford 70 mg of 1,2,3,4,5,6-hexahydro-2,6-methano-6,11-dimethyl-3-(3-methyl-2-butenyl)-8-(3-methyl-2-butenyloxy)-3-benzazocine (**16**) hydrochloride as colorless crystals: mp 117 °C; ir ν_{max} ($CHCl_3$) 1670 cm^{-1} (C=C); NMR ($CDCl_3$) δ 0.83 (3 H, d, J = 7 Hz, C_{11} Me), 1.34 (3 H, s, C_6 Me), 1.73 [12 H, s, 2 $=C(Me)_2$], 4.5 (2 H, d, J = 7 Hz, $ArOCH_2CH=$), and 6.78 (3 H, m, $C_{7,9}$ and C_{10} CH).

Anal. Calcd for $C_{24}H_{35}NO{\cdot}HCl{\cdot}\frac{1}{3}H_2O$: C, 72.79; H, 9.08; N, 3.54. Found: C, 72.65; H, 9.11; N, 3.29.

A mixture of 32 mg of the above amine (**16**) and 300 mg of 70% sodium bis(2-methoxyethoxy)aluminum hydride in 2 ml of dry xylene was refluxed for 42 h. The same workup as above gave 19 mg of pentazocine (**10**).

D. To a solution of 91 mg of the quaternary ammonium salt (**17**) in 0.5 ml of hexamethylphosphoric triamide, 48 mg of 50% sodium hydride, and 76 mg of *n*-propyl mercaptan were added at 0 °C under a current of nitrogen. The reaction mixture was stirred for 15 min at 0 °C and then poured into ice–water, a mixture of which was washed with ether. The aqueous layer was neutralized with crystalline ammonium chloride and then extracted with chloroform. The extract was dried over Na_2SO_4 and evaporated. Purification of a pale brown caramel by preparative TLC on silica gel with methanol–ethyl acetate–benzene (1:5:4 v/v) gave 5 mg of pentazocine (**10**) and 12 mg of the amine (**18**), whose ir and NMR spectra and TLC behaviors were identical with those of **18**.

E. A mixture of 91 mg of the quaternary ammonium salt (**17**) and 58 mg of triphenylphosphine in 2 ml of acetonitrile was heated at 130–140 °C in a sealed tube for 12 h. After evaporation of the solvent, the residue was acidified with 10% hydrochloric acid and washed with ether. The aqueous layer was neutralized with 10% ammonia and extracted with chloroform. The extract was dried over Na_2SO_4 and evaporated to give a colorless caramel, which was purified by preparative TLC as above to give 10 mg of pentazocine (**10**) and 35 mg of the amine (**18**).

F. A mixture of 91 mg of the quaternary ammonium salt (**17**) and 576 mg of 70% sodium bis(2-methoxyethoxy)aluminum hydride in 4 ml of dry xylene was refluxed for 17 h with stirring under a current of nitrogen. The same workup as method A, followed by purification by preparative TLC, gave 6 mg of pentazocine (**10**) and 26 mg of the amine (**18**).

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Registry No.—**1**, 4397-53-9; **3**, 106-44-5; **4**, 2426-87-1; **6**, 93-51-6; **7**, 59069-55-5; **8**, 39595-83-0; **10**, 359-83-1; **11**, 59122-20-2; **12**, 59069-56-6; **13**, 59069-57-7; **14**, 59069-58-8; **15**, 59069-59-9; **16**, 59069-60-2; **17**, 59122-21-3; **18**, 57573-46-3; sodium bis(2-methoxyethoxy)aluminum hydride, 21608-56-0; dimethylallyl bromide, 870-63-3; benzyl chloride, 100-44-7.

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Microbial Transformations of Natural Antitumor Agents. 2. Studies with *d*-Tetrandrine and Laudanosine

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Microbial transformation studies have been conducted on benzyltetrahydroisoquinoline and bisbenzyltetrahydroisoquinoline alkaloids. The 4′-methyl ether of laudanosine (**2**) was cleaved in high yield by *Cunninghamella blakesleeana* (ATCC 8688a) to give pseudocodamine (**2b**) as the sole product. *Streptomyces griseus* (UI 1158) was used to chemically transform the natural antitumor alkaloid, *d*-tetrandrine (**1**). The metabolite was identified as *N*(2′)-nor-*d*-tetrandrine (**1a**) on the basis of NMR and mass spectral correlations, and was obtained in 50% yield. Both reactions represent highly selective dealkylations of polyfunctional molecules.

The successful application of microorganisms in the preparation of difficult-to-synthesize steroids has been well documented.[1] The use of microbial systems as tools for achieving chemical transformations of other classes of natural products has not been systematically exploited. Advantages of such microbial systems include mild reaction conditions, their se-