cooled to room temperature, and poured into 300 ml. of *n*-hexane. The crude product (49.9 g.; 93% yield; m.p. 85–89°) was removed by filtration and air dried. Recrystallization from a benzene-*n*-hexane mixture gave 45 g. (83% yield) of product (m.p. 92–93.5°).

Method B

Preparation of 4-chloro-2-butynyl N-(2,5-dimethoxyphenyl)-carbamate. A mixture of 2,5-dimethoxyaniline (7.66 g., 0.05 mol.), pyridine (3.96 g., 0.05 mol.) and 50 ml. of benzene was cooled to 10°. 4-Chloro-2-butynyl chloroformate (8.5 g., 0.05 mol.) was added dropwise at 10–15°. The mixture was stirred for 3 hr. at ambient temperature then diluted with an equal volume of water. The benzene layer was separated, dried over anhydrous calcium chloride, diluted with 2 volumes of *n*-hexane and chilled to 0°. The crude product (12.2 g.; 85% yield; m.p. 42–45°) was collected by filtration. Recrystallization from benzene-*n*-hexane gave 11.4 g. (m.p. 45–46°, 80% yield).

Method C

Chlorination of 4-hydroxy-2-butynyl N-(3-chlorophenyl)-carbamate. A mixture of 4-hydroxy-2-butynyl *N*-(3-chlorophenyl)carbamate (0.25 mol., 60.0 g.), ethylene dichloride (120 ml.) and 0.5 ml. pyridine was heated to 60°. Thionyl chloride (31.2 g., 0.262 mol.) was added dropwise at 60–65° (20 min.) and held at 60–65° for 2 hr. after addition was complete. The reaction mixture was cooled to 25°, poured into 300 ml. of *n*-hexane, and chilled to 0°. The product (60.3 g.; 93.4% yield; m.p. 70–72°) was collected by filtration and air dried.

Method D

Metathesis with 4-chloro-2-butynyl N-(3-chlorophenyl)-carbamate and potassium iodide. To a solution of 7.0 g. of potassium iodide and 1.5 l. of absolute acetone was added 4-chloro-2-butynyl *N*-(3-chlorophenyl)carbamate (10.0 g., 0.039 mol.). The solution was heated to reflux for 2 hr. and filtered. The solvent was removed under reduced pressure, the residue was dissolved in 15 ml. of benzene, filtered, diluted with 50 ml. of *n*-hexane, and allowed to cool. The product was collected by filtration (13.0 g., 96% yield). A small portion was recrystallized from benzene-hexane several times to give a colorless product melting at 87–88°.

4-Hydroxy-2-butynyl N-(3-chlorophenyl)carbamate. The following example is representative of the method of preparing this compound regardless of the mole ratios employed. Actual ratios studied were 1.25/1, 2.5/1, 5/1, 10/1, and 20/1. Yields obtained were, respectively, 67%, 82%, 87%, 91%, and 93%.

3-Chlorophenyl isocyanate (30.7 g., 0.2 mol.) was added dropwise, with stirring, to molten 2-butyn-1,4-diol (86.0 g., 1.0 mol.). The temperature was maintained at 60 ± 5° during the addition and stirring was continued for an additional 30 min. The reaction mixture was poured into 500 ml. of water at 85°, the slurry cooled to 0°, and filtered. The residue was washed with 250 ml. of water at 85°, cooled to 0°, and filtered. The crude carbamate was dried to give 47.0 g. of product melting at 80–98°. An infrared analysis determined the material to be 87% pure. The crude carbamate was recrystallized two times from ethylene dichloride and once from toluene to give 28.1 g. (57% yield) melting at 87–88°.

Anal. Calcd. for $C_{11}H_{10}ClNO_3$: C, 55.2; H, 4.2. Found: C, 55.4; H, 4.5.

Isolation of 2-butynylene-1,4-bis[N-(3-chlorophenyl)carbamate]. The reaction product from a reaction using a 5/1 mole ratio of 2-butyn-1,4-diol to 3-chlorophenyl isocyanate was washed free of diol with water as described above. Forty-six and seven-tenths grams of the residual solid was recrystallized 3 times from 5 parts of ethylene dichloride to yield 33.0 g. of 4-hydroxy-2-butynyl *N*-(3-chlorophenyl)-carbamate, m.p. 85–86° analyzing 96% pure by infrared. The filtrates were combined and evaporated and the residual solid, 13.1 g., was extracted nine times with 200-ml. portions of boiling water leaving 7.0 g. of tan solid, m.p. 90–125°. This residue was recrystallized twice from ethanol-water and then from chloroform to yield 1.6 g. of white solid, m.p. 143–143.5°. A small sample was recrystallized from absolute alcohol to yield white needles, m.p. 146.5–147°.

Anal. Calcd. for $C_{18}H_{14}Cl_2N_2O_4$: C, 55.0; H, 3.6; N, 7.1. Found: C, 55.2; H, 3.8; N, 7.2.

Five grams of the above carbamate mixture containing 87% 4-hydroxy-2-butynyl *N*-(3-chlorophenyl)carbamate (0.018 mol.) was dissolved in acetone and refluxed with 2.8 g. (0.18 mol.) of 3-chlorophenyl isocyanate for 4 hr. The volatile materials were removed under reduced pressure (final conditions 100° at 5 mm.) leaving 7.6 g. of tan solid (97% crude) melting at 130–138°. Recrystallization from benzene-hexane gave 5.6 g. (72%) melting at 140–141°. A mixed melting point with an authentic sample of 2-butynylene-1,4-bis[*N*-(3-chlorophenyl)carbamate] gave no depression.

Preparation of 4-chloro-2-butynyl chlorocarbonate. Phosgene (50 ml., 0.7 mol.) was condensed in a 200-ml. flask. 4-Chloro-2-butyn-1-ol (44 g., 0.42 mol.) was added dropwise at a rate which maintained the reaction temperature at approximately 0°. After the chlorohydrin addition the mixture was allowed to rise to room temperature whereupon the excess phosgene was removed under reduced pressure. The product was distilled. There was obtained 48.8. g. (70%) of the desired chlorocarbonate boiling at 100–103°/16 mm.; n_D^{20} 1.4830.

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Synthesis of 2-Oxo-3-ethyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11bH-benzo[*a*]-quinolizine

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Synthesis of 2-oxo-3-ethyl-9,10-dimethoxy-1,2,-3,4,6,7-hexahydro-11bH-benzo [a] quinolizine (IV), a key intermediate in the synthesis of emetine and allied compounds, has been described by two different groups of authors.[2a,b] In this paper we are reporting a third synthesis of this compound.

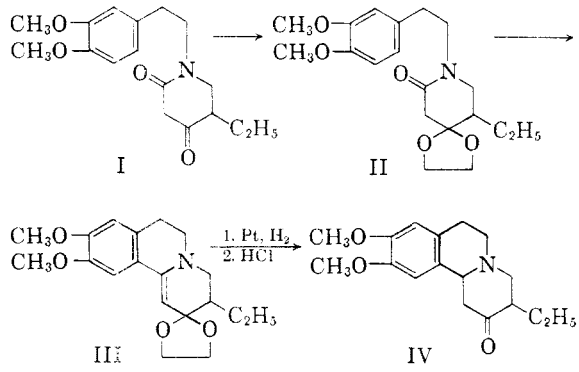
N-3,4-Dimethoxyphenylethyl-2,4-dioxo-5-ethylpiperidine (I) was converted to the corresponding ethyleneketal derivative, *N*-3,4-dimethoxyphenylethyl - 2 - oxo - 4,4 - ethylenedioxy - 5 - ethylpiperidine (II), by the standard method, and the ketal underwent a cyclization when treated with a mixture of phosphorus pentoxide and sea sand in boiling pyridine.[3] $\Delta^{1,11b}$-2,2-Ethylenedioxy-3-ethyl - 9,10 - dimethoxy - 3,4,6,7 - tetrahydro - 2H-benzo[a]quinolizine (III) thus obtained was reduced catalytically followed by acid hydrolysis to furnish 2-oxo-3-ethyl-9,10-dimethoxy-1,2,3,4,6,7-

(1) Present address: No. 40, 3-chome, Iogi, Suginami-ku, Tokyo.

(2) (a) A. R. Battersby, H. T. Openshaw, and H. C. S. Wood, *J. Chem. Soc.*, 2436 (1953). (b) A. Brossi, H. Lindlar, M. Walter, and O. Schnider, *Helv. Chim. Acta*, **41**, 119 (1958).

(3) N. Itoh and S. Sugasawa, *Tetrahedron*, **6**, 16 (1959).

hexahydro-11bH-benzo[a]quinolizine (IV) in a fair yield.



EXPERIMENTAL

1-(3,4-Dimethoxyphenylethyl)-4,4-ethylenedioxy-5-ethyl-2-piperidone (II). A mixture of 5 g. of 1-(3,4-dimethoxyphenylethyl)-5-ethyl-2,4-dioxopiperidine (I)[4] in 150 ml. of benzene, 2 g. of ethylene glycol and 0.2 g. of *p*-toluenesulfonic acid was boiled for 3 hr. surmounted with a constant water separator. On cooling the reaction mixture was shaken with 10% sodium hydroxide solution to remove the starting ketone and toluenesulfonic acid, washed with water, and dried. Benzene was then removed to leave a colorless clear sirup, yield 5 g. (85%), in which the absence of the original ketone was proved by inspection of the infrared spectrum. This was directly used in the next step.

$\Delta^{1:11}$-2,2-Ethylenedioxy-9,10-dimethoxy-3,4,6,7-tetrahydro-2H-benzo[a]quinolizine (III). To a boiling solution of 1 g. of the foregoing compound in 50 ml. of pyridine was added an intimate mixture of 5 g. of phosphorus pentoxide and 50 g. of purified sea sand in 4 portions with stirring.[5] After being refluxed for 6 hr. altogether the pyridine solution was decanted while still hot and the resultant residue was extracted with 3 × 10 ml. portions of hot pyridine. Pyridine was distilled from the combined pyridine solution. The residue was mixed with 10 ml. of benzene, which was distilled off to remove the residual pyridine. This manipulation was repeated twice more, thus leaving 0.7 g. of a reddish brown sirup, which was characterized as the picrate, yellow prisms from ethanol, m.p. 109–110°.

Anal. Calcd. for $C_{25}H_{28}O_{11}N_4$: C, 53.6; H, 5.0; N, 10.0. Found: C, 53.6; H, 5.2; N, 10.3.

2-Oxo-3-ethyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11bH-benzo[a]quinolizine (IV). A solution of 0.5 g. of aforementioned crude base in 20 ml. of ethanol, acidified with a few drops of 10% hydrochloric acid, was hydrogenated over platinum catalyst, 53 ml. of hydrogen being absorbed. One-half g. of a colorless sirup thus obtained was dissolved in a few ml. of 10% hydrochloric acid and warmed on a steam bath for 1 hr. The solution was filtered through a wet filter paper and the filtrate was made alkaline with potassium carbonate with cooling. The base that separated was taken up in benzene and dried, and the solvent was removed to leave 0.43 g. of a colorless glass, which solidified on standing. This formed colorless needles from *n*-hexane, m.p. 109°, which was not depressed on admixture with an authentic sample prepared according to the method of Battersby *et al.*,[2a] yield 0.2 g. The total yield from II was 31%.

The picrate formed yellow prisms from ethanol, m.p. 182–183° (decomp.).

Anal. Calcd. for $C_{25}H_{26}O_{10}N_4$: C, 53.3; H, 5.0; N, 10.8. Found: C, 53.65; H, 5.3; N, 10.7.

(4) Y. Ban, *Pharm. Bull. (Japan)*, **3**, 53 (1955).

(5) After some time stirring became impossible through caking.

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Synthesis of 1-*p*-Methoxybenzyl-1,2,3,4,5,6,7,8-octahydroisoquinoline

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1-Substituted 3,4,5,8-tetrahydroisoquinolines are precursors of 1,2,3,4,5,6,7,8-octahydroisoquinolines, which, when suitably substituted in the 1-position, form key intermediates for the synthesis of morphinans. Bischler-Napieralski cyclization of *N*-acyl-2-(1,4-cyclohexadienyl)ethylamine to yield 1-substituted 3,4,5,8-tetrahydroisoquinolines has been described by the present authors.[2]

We now report the acylation of 2-(1,4-cyclohexadienyl)ethylamine with *p*-methoxyphenylacetyl chloride to form the corresponding amide which was then cyclized to give 1-*p*-methoxybenzyl-3,4,5,8-tetrahydroisoquinoline. Since the latter is unstable in air it was catalytically reduced without purification to yield 1-*p*-methoxybenzyl-1,2,3,4,5,6,7,8-octahydroisoquinoline. The identity of the latter was confirmed by a mixed melting point with an authentic sample prepared according to the procedure of Schnider and Hellerbach.[3] It was converted to 3-hydroxy-*N*-methylmorphinan by the method of these authors.

EXPERIMENTAL

N-2-(1,4-Cyclohexadienyl)ethyl-p-methoxyphenylacetamide. 2-(1,4-Cyclohexadienyl)ethylamine (6.2 g.) in 80 ml. of benzene was treated with *p*-methoxyphenylacetyl chloride (9.4 g. in benzene) in the presence of sodium bicarbonate (5%, 200 ml.) with cooling and stirring. An oily amide was obtained, which solidified on scratching and was purified from a mixture of *n*-hexane and benzene, colorless scales, m.p. 86–86.5°, yield 12.5 g. or 92%.

Anal. Calcd. for $C_{17}H_{21}O_2N$: C, 75.3; H, 7.75; N, 5.2. Found: C, 75.5; H, 7.7; N, 5.1.

1-p-Methoxybenzyl-1,2,3,4,5,6,7,8-octahydroisoquinoline. A mixture of *N*-2-(1,4-cyclohexadienyl)ethyl-*p*-methoxyphenylacetamide (3 g.), phosphoryl chloride (3 ml.) and benzene (50 ml.) was refluxed for 30 min., giving a reddish yellow solution, a copious evolution of hydrogen chloride being observed. On cooling enough petroleum ether was added to the reaction solution to produce a reddish precipitate, which

(1) Present address: No. 40, 3-chome, Iogi, Suginami-ku, Tokyo, Japan.

(2) S. Sugasawa and R. Tachikawa, *Tetrahedron*, **4**, 205 (1958).

(3) O. Schnider and J. Hellerbach, *Helv. Chim. Acta*, **33**, 1437 (1950).