TABLE I

PHYSICAL CONSTANTS AND ANALYTICAL DATA

Compound	Source	Yield, %	B. p., °C.	B. p., Mm.	n^{20}D	d^{20}
4-Hexen-1-yn-3-ol[a]	Crotonaldehyde	46	66	20	1.4650	0.9155
3-Methyl-4-penten-1-yn-3-ol	Methyl vinyl ketone[b]	21	58–59	60	1.4444	.8895
3-Methyl-4-hexen-1-yn-3-ol	Ethylidene acetone[c]	27	61–62	25	1.4530	.8886
3,5-Dimethyl-4-hexen-1-yn-3-ol	Mesityl oxide	24	65–66	17	1.4629	.8939
3-Methyl-5-phenyl-4-penten-1-yn-3-ol	Benzalacetone	20	114–116	4	M. p., 50–51	
2,5-Dimethoxy-2,5-dimethyl-3,6-dipropenyl-1,4-dioxane		22	M. p., 119–120			

Formula	Mol. wt. Calcd.	Mol. wt. obsd.	Carbon, % Calcd.	Carbon, % Obsd.[d]	Hydrogen, % Calcd.	Hydrogen, % Obsd.[d]	MR Calcd.	MR Obsd.
C_6H_8O							28.96	29.00
C_6H_8O	96	97	75.00	75.20	8.33	8.4	28.96	28.69
$C_7H_{10}O$	110	108	76.36	76.80	9.09	9.3	33.58	33.45
$C_8H_{12}O$	124	125	77.42	77.41	9.68	9.4	38.20	38.24
$C_{12}H_{12}O$	172	174	83.72	83.12	6.98	6.91		
$C_{14}H_{24}O_4$[e]	256	258	65.62	65.67	9.37	9.43		

[a] Previously reported by Lespieau and Lombard, *Compt. rend.*, **198**, 2179 (1934), and by Jones and McCombie, ref. 8. [b] Supplied by the Jackson Laboratory, du Pont Company. [c] Prepared according to Grignard and Fluchaire, *Ann. chim.*, [10] **9**, 10 (1928). [d] Analyses (except last line) by Arlington Laboratories, Fairfax, Va. [e] Analysis for methoxyl, %, calcd., 24.2; obsd., 23.8.

yield of carbinol. The distillate was put through a small Fenske–Whitmore column, yielding 112 g. of 4-hexen-1-yn-3-ol, a colorless liquid, b. p. 66° at 20 mm.

Other Reactions with Sodium Acetylide.—The above procedure was used. One and four-tenths moles of methyl vinyl ketone yielded 30 g. of the carbinol and 5 g. of residue. Two moles of ethylidene acetone gave the expected carbinol and 26 g. of residue, most of which could be distilled with decomposition at 65–127° at 4 mm. Mesityl oxide (3 moles) returned 132 g. unreacted, 44 g. of the carbinol, and 29 g. of higher boiling residue. One mole of benzalacetone gave only 35 g. of carbinol and 83 g. of higher boiling material. One and one-half moles (198 g.) of cinnamaldehyde formed 211 g. of brown amorphous solid, soluble in benzene and ligroin.

Addition of Methanol to 4-Hexen-1-yn-3-ol.—The previously described procedure[11] with 96 g. of 4-hexen-1-yn-3-ol gave 28 g. of solid after distillation of the excess methanol. Several crystallizations from aqueous methanol afforded a white crystalline solid, m. p. 119–120°.

Summary

1. The 1,2 addition of sodium acetylide to a number of α,β-unsaturated carbonyl compounds is reported and five products are described.

2. The addition of methanol to 4-hexen-1-yn-3-ol gave a cyclic addition product identified as 2,5-dimethoxy-2,5-dimethyl-3,6-dipropenyl-1,4-dioxane.

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[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY OF THE NATIONAL RESEARCH COUNCIL]

The Synthesis of *l*-Roemerine[1]

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Roemerine was discovered in the papaveraceous plant *Roemeria refracta*, D.C., by Konowalowa, Yunussov and Orekhov[2] who assigned to it the formula $C_{18}H_{17}O_2N$. Subsequently, with the aid of degradative experiments, they demonstrated that roemerine is a methylenedioxy-aporphine,[3] possessing the structure VII. This alkaloid being the first example of a naturally occurring aporphine carrying no substituents except in the tetrahydroisoquinoline moiety, it was of interest to attempt its synthesis which, furthermore, was desirable to confirm the proof of the structure VII assigned to it.

For this synthesis it was necessary to prepare β-3,4-methylenedioxy-phenylethylamine and 2-nitrophenylacetic acid required as starting materials.

From the amine I and the acid chloride II, 6′-nitrophenylaceto-β-3,4-methylenedioxyphenylethyl amide III was obtained which, by a modified Bischler–Napieralsky reaction, was converted to 6′-nitro-1-benzyl-6,7-methylenedioxy-3,4-dihydroisoquinoline IV. The methiodide V of this base was reduced with zinc and hydrochloric acid to 6′-amino-1-benzyl-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline VI isolated as the dihydrochloride. In the Pschorr ring-closure reaction this dihydrochloride gave rise to *dl*-roemerine VII and an unidentified by-product. The racemic base was resolved into its optical isomers by treatment first with *d*-tartaric acid and then with *l*-tartaric acid. Synthetic *l*-roemerine was found to exhibit dimorphism. For

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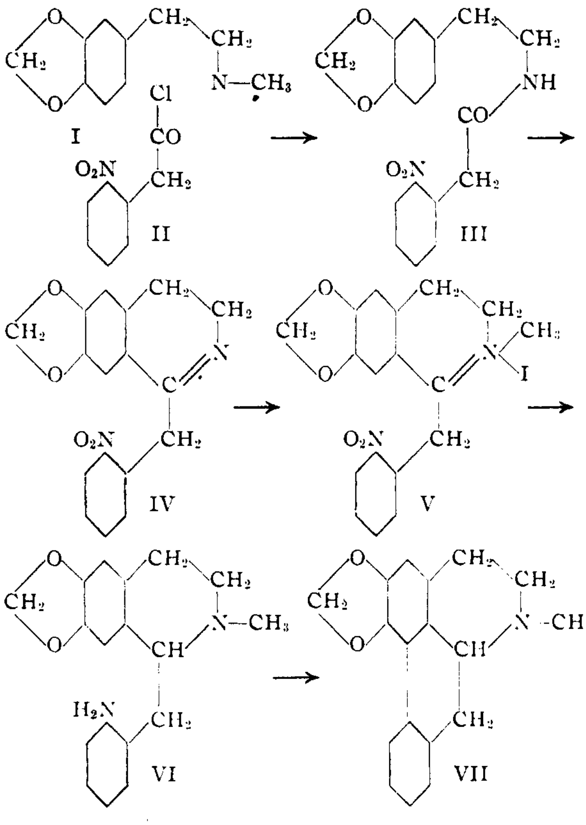
[1] Published as N. R. C. No. 1184.

[2] Konowalowa, Yunussov and Orekhov, *Bull. soc. chim.*, [5] **6**, 811 (1939).

[3] *Ibid.*, [5] **6**, 1479 (1939); [5] **7**, 70 (1940).



a long time it could be obtained only in a form melting at 87°. However, when *d*-roemerine was obtained subsequently it melted at 102° and when afterward *l*-roemerine was recrystallized it was always the high melting form which separated from the solution. The melting point 102° is in agreement with that recorded by Konowalowa, Yunussov and Orekhov.[2] The melting points of the derivatives prepared are also in fair agreement with those recorded by these authors.

Experimental

A. Preparation of the Starting Materials

β-3,4-Methylenedioxy-phenylethylamine.—This amine was prepared as described prevously[4] except that the intermediate 3,4-methylenedioxycinnamic acid was reduced to the corresponding dihydro-acid catalytically. The cinnamic acid (50 g.) dissolved in water (340 cc.) and 32% sodium hydroxide (60 cc.) was hydrogenated in the presence of Raney nickel (*ca.* 10 g.) at 50° and 375 lb. for two hours. The yield of reduced acid was 80%.

2-Nitrophenylacetic Acid.—2-Nitrophenylpyruvic acid was obtained in 50% yield by gently refluxing for eighteen hours a mixture of *o*-nitrotoluene (137 g.), sodium ethylate (powdered sodium, 25 g.; absolute ethanol, 47 g.), ethyl oxalate (156 g.) and absolute ether (1000 cc.). The substituted pyruvic acid (72 g.) was dissolved in 2 *N* sodium hydroxide (800 cc.) and oxidized by the addition of 30% hydrogen peroxide (60 cc.) which was sufficient to change the color of a test portion when added to 2 *N* sodium hydroxide from a reddish brown to a reddish-yellow. The solution was kept at 50° for thirty minutes, cooled and saturated with sulfur dioxide. After several hours, the crystalline 2-nitrophenylacetic acid was filtered off, washed with water and recrystallized from boiling water from which it separated as long, pale yellow needles melting at 139–140°;[4a] yield, 23.5 g. (38.6%).

B. Synthesis of *l*-Roemerine

6′-Nitro-phenylaceto-β-3,4-methylenedioxy-phenylethyl Amide (III).—The amide was prepared from methylenedioxy-phenylethylamine and 2-nitrophenylacetyl chloride according to the procedure described by Douglas and Gulland,[5] which was followed exactly. The crystalline product was recrystallized from chloroform–methanol, from which it separated as soft colorless needles melting at 120°; yield, 74.4% calculated on weight of acid used. Calcd. for $C_{17}H_{16}O_5N_2$: C, 62.19; H, 4.88; N, 8.54. Found: C, 62.05, 62.16; H, 4.97, 4.97; N, 8.48, 8.32.

6′-Nitro-1-benzyl-6,7-methylenedioxy-3,4-dihydroisoquinoline (IV).—This substance was produced from the amide III by the Bischler–Napieralsky reaction as modified by Gulland and Haworth.[6]

The amide (2 g.) was added to a suspension of phosphorus pentachloride (2 g.) in chloroform (12 cc.) and shaken until it had all dissolved. The reaction mixture was protected from moisture with a calcium chloride tube and allowed to stand at room temperature for twenty-four hours. Ice was then added and the chloroform distilled off at 35° under reduced pressure. The residue was repeatedly digested with small volumes of dilute (1:1) hydrochloric acid and the combined acid solution filtered through charcoal and basified with strong aqueous sodium hydroxide. The precipitated base was collected in chloroform, the extract washed with water and the solvent distilled off. The residual gum was dissolved in boiling methanol from which it crystallized on cooling. After one recrystallization, the base was obtained in clusters of small, yellowish, prismatic needles melting at 164.5°; wt. 0.7 g. Calcd. for $C_{17}H_{14}O_4N_2$: C, 65.80; H, 4.52; N, 9.03. Found: C, 65.28; H, 4.41; N, 9.03.

6′-Nitro-1-benzyl-6,7-methylenedioxy-3,4-dihydroisoquinoline methiodide (V).—A mixture of the substituted dihydroisoquinoline IV (10 g.) and methyl iodide (25 cc.) was refluxed gently on the steam-bath for six hours. After cooling, absolute ether was added, the methiodide filtered with suction and washed with absolute ether. It was dissolved in boiling methanol from which it separated on cooling as glistening yellow prisms melting at 262°; wt. 13.7 g.; yield, 94%. Calcd. for $C_{18}H_{17}O_4N_2I$: C, 47.79; H, 3.76; N, 6.20. Found: C, 47.89, 47.89; H, 3.69, 3.81; N, 6.04.

6′-Amino-1-benzyl-2-methyl-6,7-methylenedioxy-1,2,3,-4-tetrahydroisoquinoline (VI).—The methiodide V (8 g.) was dissolved in water (80 cc.) and concentrated hydrochloric acid (160 cc.) with the aid of heat. In the course of thirty minutes, zinc dust (24 g.) was added to the hot solution with vigorous stirring. The combined filtered solutions from several runs were basified with strong ammonia and the base extracted with ether (3 portions). The combined extract was dried over potassium hydroxide pellets and the ether distilled off on the steam-bath. An oily base was thus obtained which was dissolved in a mixture of methanol and dry ether and the solution saturated with dry hydrogen chloride. The dihydrochloride which separated was recrystallized from methanol from which it separated as colorless needles melting at 283–284°; yield, 55.4%. Calcd. for $C_{18}H_{22}O_2N_2Cl_2$: Cl, 19.24. Found: Cl, 18.73, 19.18.

dl-**Roemerine (VII).**—The dihydrochloride of VI (5 g.) was dissolved in 2 *N* sulfuric acid (50 cc.) and methanol (50 cc.), the solution cooled and diazotized with a solution of sodium nitrite (0.97 g.) in water (3 cc.). The diazotized solution was allowed to stand in the cold for fifteen minutes and kept on the steam-bath for thirty minutes, during which a strong evolution of nitrogen took place. Concentrated hydrochloric acid (7.2 cc.) and zinc dust (2.8 g.) were then added and the mixture kept on the steam-bath a further twenty minutes to complete the reaction

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(4) L. Marion, THIS JOURNAL, **66**, 1125 (1944).

(4a) All melting points are corrected.

(5) R. L. Douglas and J. M. Gulland, *J. Chem. Soc.*, 2893 (1931).

(6) J. M. Gulland and R. D. Haworth, *ibid.*, 581 (1928).

and remove the methanol. The hot solution was decanted from the unused zinc which was washed by decantation with a little hot water. The decantate was basified with ammonia, cooled and the precipitated base extracted with ether. After removal of the solvent the residual base was triturated with a slight excess of 10% hydrochloric acid and the hydrochloride filtered and washed with a little water. It was recrystallized from hot water, from which it separated as colorless needles melting at 274°; yield, 24.3%. Calcd. for $C_{18}H_{17}O_2N \cdot HCl$: Cl, 11.25. Found: Cl, 11.21, 11.01. The *dl*-roemerine recovered from the hydrochloride crystallized from a concentrated solution in absolute ether as small colorless prisms melting at 85–87°. Calcd. for $C_{18}H_{17}O_2N$: C, 77.43; H, 6.09; N, 5.02. Found: C, 77.63; H, 6.11; N, 4.90. It formed a picrate which separated as light yellow needles from methanol, m. p. 197°. When refluxed with methyl iodide for two hours *dl*-roemerine was converted to the methiodide which after recrystallization from methanol consisted of colorless prismatic needles melting at 221°. Calcd. for $C_{19}H_{20}O_2NI$: C, 54.16; H, 4.75. Found: C, 54.12, 54.15; H, 4.78, 4.73.

The aqueous mother liquor from *dl*-roemerine hydrochloride when basified with ammonia yielded a basic by-product which is less soluble in ether than roemerine and separated from that solvent as colorless prisms melting at 133.5°. Found: C, 72.61, 72.91; H, 6.44, 6.62; N, 4.64, 4.60. Calcd. for $C_{18}H_{19}O_2N$: C, 72.73; H, 6.40; N, 4.71.

Roemerine Methine.—*dl*-Roemerine methiodide (0.7 g.) was refluxed for six hours with a solution of potassium hydroxide (2.4 g.) in methanol (12 cc.). The methine obtained from the ether extract of the cooled mixture was recrystallized from absolute ether from which it separated as clusters of small colorless prisms melting at 81°. Calcd. for $C_{19}H_{19}O_2N$: C, 77.81; H, 6.48. Found: C, 77.96; H, 6.26. When refluxed with methyl iodide the methine base was converted to a methiodide which after recrystallization from 50% methanol consisted of clusters of colorless needles melting at 280°. Calcd. for $C_{20}H_{22}O_2NI$:' C, 55.17; H, 5.06; N, 3.22. Found: C, 55.00; H, 5.15; N, 3.12, 3.21.

***l*-Roemerine.**—*dl*-Roemerine (5.10 g.) was dissolved in hot absolute ethanol (115 cc.) and added to a hot solution of *d*-tartaric acid (3.06 g.) in absolute ethanol (46 cc.). While still warm, *l*-roemerine *d*-tartrate crystallized out. It was filtered, refluxed with 95% ethanol (1.5 liters), filtered again and washed with ethanol. The base was liberated from an aqueous suspension of the salt by means of ammonia and extracted with ether. After removal of the solvent, the oily residue was dissolved in absolute ethanol and again treated with *d*-tartaric acid. The salt crystallized as small colorless needles melting at 264.5° (dec.). *l*-Roemerine was recovered from the salt as before and allowed to crystallize from a concentrated solution in absolute ether from which it separated as colorless prisms melting at 87°; yield, 49.2% of the racemic base. Several recrystallizations from ether failed to alter the melting point. *d*-Roemerine when eventually obtained melted at 102° and afterward, *l*-roemerine when recrystallized from ether always melted at 102°. *l*-Roemerine, therefore, affords a definite example of dimorphism. Calcd. for $C_{18}H_{17}O_2N$: C, 77.43; H, 6.09; N, 5.02. Found: C, 77.38, 77.59; H, 5.99, 6.13; N, 4.93, 5.02; α_D (abs. ethanol) = $-2.113°$, $C = 0.2643$, $l = 1$, $[\alpha]_D$ $-79.9°$. The methiodide (m. p. 224.5°) was prepared by refluxing with methyl iodide.

***d*-Roemerine.**—The combined alcoholic mother-liquors from which *l*-roemerine *d*-tartrate had crystallized were evaporated to dryness under reduced pressure. The residue was dissolved in water, the solution basified with ammonium hydroxide and the base extracted with ether. The crude *d*-base crystallized from the concentrated extract; wt. 2.34 g. (45.9% of the weight of racemic base). A portion of the crude *d*-roemerine (1.1 g.) was dissolved in hot absolute ethanol (60 cc.) and added to a hot solution of *l*-tartaric acid (0.6 g.) in absolute ethanol (40 cc.). *d*-Roemerine *l*-tartrate separated on cooling and was recrystallized from boiling ethanol from which it was obtained as small colorless needles melting at 264.5° (dec.). In admixture with *l*-roemerine *d*-tartrate it melted at 245° (dec.). The *d*-roemerine recovered from the salt crystallized from ether as colorless prisms melting at 102°; α_D (abs. ethanol) $+1.467°$, $c = 0.1829$, $l = 1$, $[\alpha]_D$ $+80.2°$. In admixture with *l*-roemerine it melted at 84–89°. *d*-Roemerine methiodide, prepared by refluxing the base with methyl iodide, melted at 224.5°, and in admixture with *l*-roemerine methiodide it melted at 220.5°.

The sample of *l*-tartaric acid used in this resolution was supplied by Professor E. G. D. Murray, McGill University, to whom our indebtedness is now acknowledged.

Summary

1. The methylenedioxy-aporphine structure assigned to *l*-roemerine has been confirmed by synthesis of the alkaloid and its known derivatives.

2. β-3,4-Methylenedioxy-phenylethylamine and 2-nitro-phenylacetyl chloride were combined to form an amide which was converted to the corresponding dihydroisoquinoline by an improved Bischler–Napieralsky reaction. The methiodide of the dihydroisoquinoline was reduced and the product transformed by the Pschorr ring closure reaction to *dl*-roemerine.

3. Racemic roemerine was converted to the methiodide from which the methine base was prepared.

4. The synthetic racemic roemerine was resolved into its optical isomers by means of its salts with the optically active tartaric acids.

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