

ALKYNYLATION OF COTARNINE HYDROCHLORIDE BY Ag(I) ACETYLENIDES

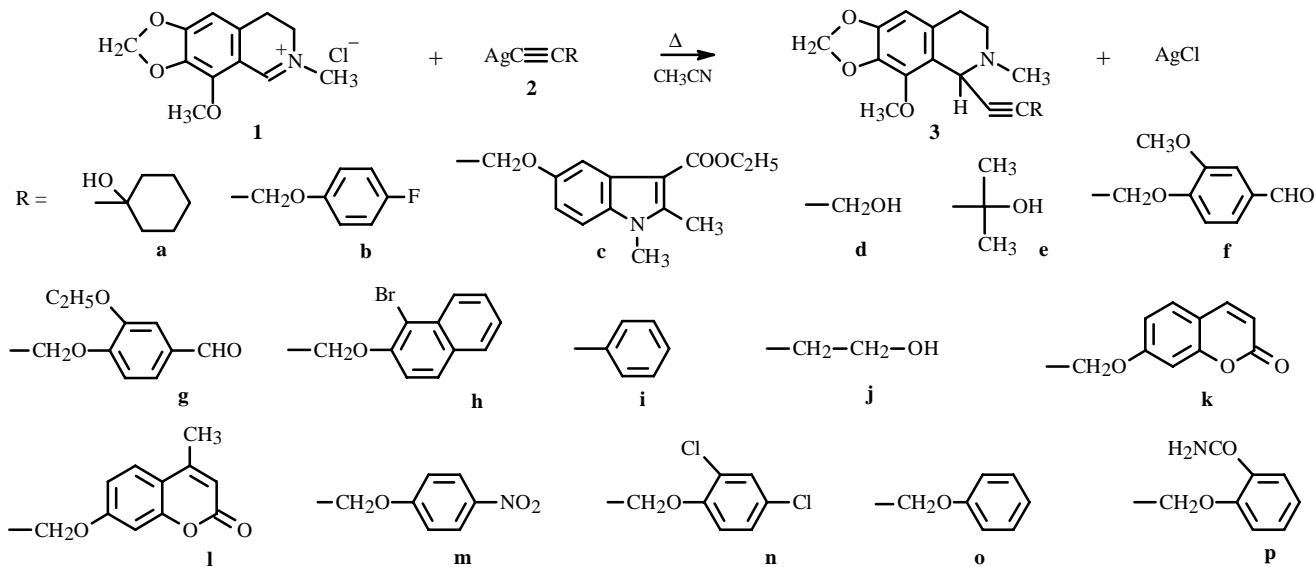
L. Yu. Ukhin,¹ K. Yu. Suponitskii,² and V. G. Kartsev³

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1-Organoacetylene derivatives were prepared by reaction of cotarnine hydrochloride with silver organoacetylenides with brief heating in acetonitrile. The structure of one of these, 1-(3'-hydroxypropyn-1-yl)-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline, was proved by an X-ray structure analysis.

Key words: cotarnine hydrochloride, silver organoacetylenides, alkylation, X-ray structure analysis.

Organoacetylenides of Cu(I) and Ag(I) are extensively used in organic synthesis [1, 2] because of their peculiarities that are not typical of analogous compounds of active metals, i.e., their hydrolytic stability and the ability to use them in the presence of most functional groups. In addition to the reaction with covalent halides, the most famous of which is the Castro—Sladkov reaction [3, 4], these compounds are used for alkylation of organic cations. Acylpyridinium and acylquinolinium salts react with silver phenylacetylenide to form α -phenylethynyl derivatives of N-acyl-1,2-dihydropyridines and N-acyl-1,2-dihydroquinolines [5]. Reaction of diazonium salts with silver organoacetylenides produces azoethynyl compounds [6-9]. 1-Aminobenzimidazolium salts are alkylation by Cu(I) and Ag(I) phenylacetylenides at the 2-position with subsequent cyclization and rearrangement into pyrazole derivatives [10]. Iminium salts react smoothly with Cu(I) and Ag(I) phenylacetylenides to form the corresponding propargylamines [11]. Analogous behavior can be expected from cotarnine hydrochloride, which possesses a wide spectrum of biological activity and has the structure of a cyclic iminium salt. Such modification of cotarnine promises to produce new physiologically active compounds.



1) Scientific-Research Institute of Physical and Organic Chemistry, Rostov State University, 344090, Rostov-on-Don, pr. Stachki, 194/2, fax (8632) 43 46 67, e-mail: may@ipoc.rsu.ru; 2) A. N. Nesmeyanov Institute of Elementorganic Compounds, Russian Academy of Sciences, 117813, Moscow, ul. Vavilova, 28, e-mail: kira@xrlab.ineos.ac.ru; 3) OOO "Interbioscreen," 142432, Chernogolovka, Moscow District, Institutskii pr., 8, fax (095) 788 06 52, e-mail: screen@nsp.chg.ru. Translated from *Khimiya Prirodnikh Soedinenii*, No. 5, pp. 395-400, September-October, 2003. Original article submitted September 5, 2003.

TABLE 1. PMR Spectra of **3**

Compounds	Solvent, δ , ppm, J/Hz
3a	(CDCl ₃): 1.1-1.9 (11H, m, CH ₂ , OH), 2.48 (3H, s, NCH ₃), 2.60 (2H, m, 2H-4), 2.85 (2H, m, 2H-3), 3.98 (3H, s, OCH ₃), 4.73 (1H, s, H-1), 5.86 (2H, s (split), OCH ₂ O), 6.28 (1H, s, H-5)
3b	(CDCl ₃): 2.41 (3H, s, NCH ₃), 2.5-3.0 (4H, m, 2H-3+2H-4), 3.92 (3H, s, OCH ₃), 4.66 (2H, d, J = 1.8, CH ₂ O), 4.69 (1H, s, H-1), 5.86 (2H, s, OCH ₂ O), 6.28 (1H, s, H-5), 6.90 (4H, m, Ar-H)
3c	(CDCl ₃): 1.39 (3H, t, J = 7.1, CH ₃), 2.41 (3H, s, NCH ₃), 2.55 (2H, m, 2H-4), 2.73 (3H, s, CH ₃), 2.85 (2H, m, 2H-3), 3.65 (3H, s, CH ₃), 3.90 (3H, s, OCH ₃), 4.33 (2H, q, J = 7.1, CH ₂), 4.71 (1H, s, H-1), 4.76 (2H, d, J = 1.5, CH ₂ O), 5.84 (2H, s, OCH ₂ O), 6.25 (1H, s, H-5), 6.87 (1H, dd, ³ J = 8.8, ⁴ J = 2.5, H-6'), 7.14 (1H, d, J = 8.8, H-7'), 7.66 (1H, d, J = 2.5, H-4')
3d	(DMSO-d ₆): 2.38 (3H, s, NCH ₃), 2.54 (2H, m, 2H-4), 2.77 (2H, m, 2H-3), 3.96 (3H, s, OCH ₃), 4.03 (2H, dd, J = 6.0, J = 1.7, CH ₂ O), 4.52 (1H, s, H-1), 4.87 (1H, t, J = 6.0, OH), 5.89 (2H, s, OCH ₂ O), 6.29 (1H, s, H-5)
3e	(CDCl ₃): 1.48 (6H, s, 2CH ₃), 2.48 (3H, s, NCH ₃), 2.60 (2H, m, 2H-3), 3.85 (2H, s (), 2H-3), 3.99 (3H, s, OCH ₃), 4.71 (1H, s, H-1), 5.87 (2H, m, OCH ₂ O), 6.30 (1H, s, H-5)
3f	(DMSO+CCl ₄): 2.84 (3H, s, NCH ₃), 3.20-3.45 (4H, m, 2H-3+2H-4), 3.84 (3H, s, OCH ₃), 3.96 (3H, s, OCH ₃), 4.89 (2H, s, CH ₂ O), 5.39 (1H, s, H-1), 5.97 (2H, s, OCH ₂ O), 6.42 (1H, s, H-5), 7.17 (1H, d, J = 8.0, H-6'), 7.37 (1H, d, J = 1.7, H-3'), 7.47 (1H, dd, ³ J = 8.0, ⁴ J = 1.7, H-5'), 9.81 (1H, s, CHO), 12.30 (1H, s, NH)
3g	(CDCl ₃): 1.45 (3H, t, J = 7.0, CH ₃), 2.40 (3H, s, NCH ₃), 2.50-2.90 (4H, m, 2H-4+2H-3), 3.91 (3H, s, OCH ₃), 4.10 (2H, q, J = 7.0, CH ₂), 4.68 (1H, s, H-1), 4.87 (2H, d, J = 1.5, CH ₂ O), 5.85 (2H, s, OCH ₂ O), 6.27 (1H, s, H-5), 7.13 (1H, d, J = 8.0, H-6'), 7.36 (2H, m, H-3'+H-5'), 9.82 (1H, s, CHO)
3h	(CDCl ₃): 2.37 (3H, s, NCH ₃), 2.40-2.60 (2H, m, 2H-4), 2.65-2.90 (2H, m, 2H-3), 3.88 (3H, s, OCH ₃), 4.67 (1H, s, H-1), 4.92 (2H, d, J = 1.7, CH ₂ O), 5.82 (2H, m, OCH ₂ O), 6.20 (1H, s, H-5), 7.38 (2H, m, Ar-H), 7.54 (1H, m, Ar-H), 7.90 (2H, m, Ar-H), 8.19 (1H, d, J = 8.5, Ar-H)
3i	(CDCl ₃): 2.57 (3H, s, NCH ₃), 2.64 (2H, m, 2H-4), 2.94 (2H, m, 2H-3), 4.03 (3H, s, OCH ₃), 4.92 (1H, H-1), 5.87 (2H, s, OCH ₂ O), 6.32 (1H, s, H-5), 7.24 (3H, m, Ar-H), 7.39 (2H, m, Ar-H)
3j	(DMSO-d ₆): 2.36 (2H, t, J = 6.4, CH ₂), 2.89 (3H, s, N+CH ₃), 2.80-3.50 (6H, m, 2H-4+2H-3+CH ₂), 4.02 (3H, s, OCH ₃), 4.65 (1H, m, OH), 5.26 (1H, s, H-1), 5.98 (2H, d, J = 2.4, OCH ₂ O), 6.43 (1H, s, H-5), 12.14 (1H, s, N+H)
3k	(CDCl ₃): 2.43 (3H, s, NCH ₃), 2.50-2.96 (4H, m, 2H-3+2H-4), 3.93 (3H, s, OCH ₃), 4.70 (1H, s, H-1), 4.96 (2H, d, J = 1.7, CH ₂ O), 5.85 (2H, s, OCH ₂ O), 6.25 (1H, d, J = 8.5, H-3'), 6.27 (1H, s, H-5), 6.86 (1H, dd, ³ J = 8.5, ⁴ J = 2.4, H-6'), 6.89 (1H, d, J = 2.4, H-8'), 7.34 (1H, d, J = 8.5, H-4'), 7.62 (1H, d, J = 8.5, H-5')
3l	(DMSO-d ₆): 2.38 (3H, s, CH ₃), 2.43 (3H, s, NCH ₃), 2.5-3.0 (4H, m, 2H-3+2H-4), 3.94 (3H, s, OCH ₃), 4.70 (1H, s, H-1), 4.76 (2H, d, J = 1.7, CH ₂ O), 5.85 (2H, s, OCH ₂ O), 6.14 (1H, s, H-3'), 6.26 (1H, s, H-5), 6.88 (1H, dd, ³ J = 8.5, ⁴ J = 2.4, H-6'), 6.89 (1H, d, J = 2.4, H-8'), 7.46 (1H, d, J = 8.4, H-5')
3m	(CDCl ₃): 2.41 (3H, s, NCH ₃), 2.5-3.0 (4H, m, 2H-3+2H-4), 3.92 (3H, s, OCH ₃), 4.68 (1H, s, H-1), 4.79 (2H, d, J = 1.8, CH ₂ O), 5.85 (2H, s (split), OCH ₂ O), 6.27 (1H, s, H-5), 7.00 (2H, d, J = 9.2, H-2'+H-6'), 8.15 (2H, d, J = 9.2, H-3'+H-5')
3n	(CDCl ₃): 2.65-3.65 (4H, m, 2H-3+2H-4), 2.88 (3H, s, NCH ₃), 3.98 (3H, s, OCH ₃), 4.79 (2H, d, J = 1.6, CH ₂ O), 5.21 (1H, s, H-1), 5.88, 5.93 (2H, dd, J = 1.2, OCH ₂ O), 6.30 (1H, s, H-5), 6.86 (1H, d, J = 8.8, H-6'), 7.13 (1H, dd, ³ J = 8.8, ⁴ J = 2.4, H-5'), 7.35 (1H, d, J = 2.4, H-3'), 13.31 (1H, s, N+H)
3o	(CDCl ₃): 2.44 (3H, s, NCH ₃), 2.5-3.0 (4H, m, 2H-3+2H-4), 3.93 (3H, s, OCH ₃), 4.70 (2H, d, J = 1.7, CH ₂ O), 4.72 (1H, s, H-1), 5.36 (2H, s, OCH ₂ O), 6.28 (1H, s, H-5), 6.93 (3H, m, Ar-H), 7.24 (2H, m, Ar-H)
3p	(DMSO-d ₆): 2.33 (3H, s, NCH ₃), 2.5-2.9 (4H, m, 2H-3+2H-4), 3.89 (3H, s, OCH ₃), 4.55 (1H, m, H-1), 4.92 (2H, d, J = 1.5, CH ₂ O), 5.89 (2H, d, J = 1.0, OCH ₂ O), 6.27 (1H, s, H-5), 7.0-7.9 (6H, m, 4Ar-H+NH ₂)

In fact, it has been noted [12] that cotarnine hydrochloride (**1**) reacts readily with silver organoacetylenides **2** (prepared from the corresponding acetylenes **4**) upon brief heating in CH₃CN to form acetylene derivatives **3**.

The free bases of **3** cannot always be isolated as crystalline solids. As a rule, oils formed in such instances give hydrochlorides that crystallize well (**3f**, **h**, **j**, **n**).

The structure of **3** was proved using PMR spectra (Table 1) and confirmed by an X-ray structure analysis of 1-(3'-hydroxypropyn-1-yl)-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline (**3d**) (Tables 2 and 3, Figs. 1 and 2).

TABLE 2. Bond Lengths (d) in **3d**

Bond	d/Å	Bond	d/Å
O1-C4	1.382(7)	C1-C2	1.539(7)
O1-C5	1.419(6)	C2-C8	1.378(7)
O2-C6	1.405(7)	C2-C3	1.408(8)
O2-C5	1.409(7)	C3-C4	1.377(8)
O3-C14	1.412(6)	C4-C6	1.372(9)
O4-C3	1.375(6)	C6-C7	1.337(9)
O4-C15	1.401(7)	C7-C8	1.398(8)
N1-C1	1.458(6)	C8-C9	1.485(7)
N1-C10	1.461(7)	C9-C10	1.508(7)
N1-C11	1.484(6)	C12-C13	1.163(8)
C1-C12	1.487(8)	C13-C14	1.461(8)

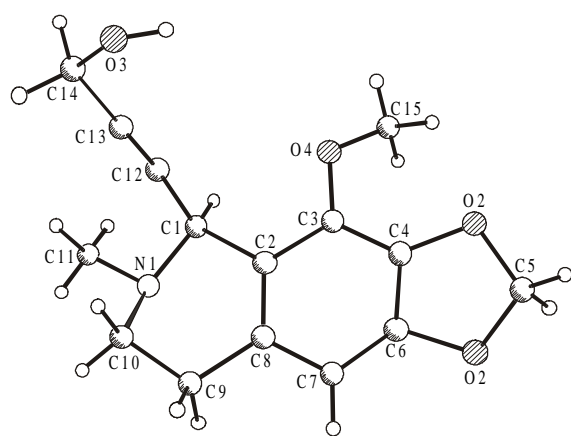


Fig. 1

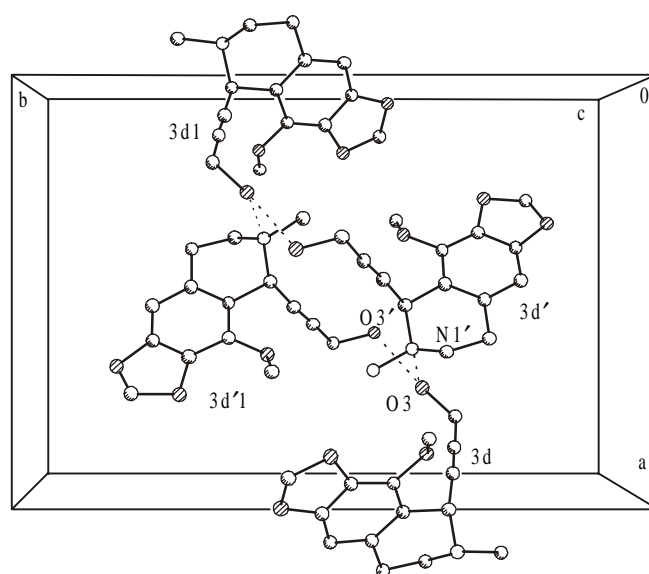


Fig. 2

Fig. 1. General view of **3d**.

Fig. 2. Section of crystal packing of **3d**. H-Bonded clusters formed by two molecules are shown.

The crystal of **3d** contains two symmetrically independent molecules **3d** and **3d'**, the structures of which differ mainly in the orientation of the CH₂OH group relative to the C(13)–C(14) bond. In **3d**, the torsion angle C(12)–C(13)–C(14)–O(3) is 1.1° whereas it is -140.9° in **3d'** (Fig. 1). The five-membered ring in both molecules has the envelope conformation [C(5) and C(5') deviate from the ring plane by 0.191 (**3d**) and 0.350 Å (**3d'**), respectively]. The isoquinoline fragment has the half-chair conformation [atoms N(1) and C(10) deviate from the C(1)–C(2)–C(8)–C(9) plane by -0.538 and 0.233 Å, respectively, in **3d** and by -0.514 and -0.272 Å, respectively, in **3d'**]. The methoxyl group is twisted by 31.9 and 42.1° relative to the benzene ring in **3d** and **3d'**, respectively.

The difference in the orientation of the hydroxyls is apparently caused by the formation of a system of H-bonds. The bond O(3)–H(3)...N(1') [O...N 2.747(8) Å, H...O 1.92 Å, OHN 164°] forms between **3d** and **3d'**; O(3')–H(3')...O(3) (-x+1, -y+1, -z) [O...O 2.844(8) Å, H...O 2.01 Å, OHO 169°], between **3d'** and **3d1** (Fig. 2). Thus, the crystal is constructed of H-bonded clusters formed by four molecules.

TABLE 3. Bond Angles (ω) in **3d**

Angle	w/deg	Angle	w/deg
C4-O1-C5	103.3(5)	C6-C4-O1	111.9(6)
C6-O2-C5	105.0(6)	C3-C4-O1	131.2(8)
C3-O4-C15	119.3(5)	O2-C5-O1	110.1(6)
C1-N1-C10	112.0(5)	C7-C6-C4	127.0(7)
C1-N1-C11	109.6(5)	C7-C6-O2	125.2(8)
C10-N1-C11	112.5(5)	C4-C6-O2	107.8(8)
N1-C1-C12	113.2(5)	C6-C7-C8	115.6(6)
N1-C1-C2	106.9(5)	C2-C8-C7	121.1(6)
C12-C1-C2	110.2(5)	C2-C8-C9	119.4(6)
C8-C2-C3	120.0(6)	C7-C8-C9	119.4(6)
C8-C2-C1	123.1(6)	C8-C9-C10	114.6(5)
C3-C2-C1	116.8(6)	N1-C10-C9	108.5(5)
O4-C3-C4	123.4(8)	C13-C12-C1	174.8(7)
O4-C3-C2	117.2(7)	C12-C13-C14	179.0(7)
C4-C3-C2	119.4(6)	O3-C14-C13	114.1(5)
C6-C4-C3	116.9(7)		

TABLE 4. Propargyl Ethers of Phenols **4**: HC≡CCH₂OR

Compound	Amount		Reaction time, h	Yield, %	mp, °C	IR spectrum (mineral oil), ν , cm ⁻¹
	phenol, mole	acetone, mL				
4b	0.2	7.510e+17	44.573665	5.05366e+15	Liquid	2120 (C≡C), \ 3300 (=CH) (film)
4f	0.1	100	4.5	53	92-93° (from CCl ₄ —petrol.ether, 1:2)	2114 (C≡C), 3240 (=CH)
4h	0.1	75	7	65	82° (from petrol.ether)	2120 (C≡C), 3287 (=CH)
4k	0.025	35	3	49	117-120° (from toluene—petrol.ether, 1:2)	2114 (C≡C), 3267 (=CH)
4l	0.07	75	6	62	130-135° (from <i>i</i> -PrOH)	2127 (C≡C), 3300 (=CH)
4m	0.2	150	6	64	115-117° (from toluene—petrol.ether, 1:1)	2127 (C≡C), 3260 (=CH)
4n	0.05	50	5	64	50° (from petrol.ether)	2114 (C≡C), 3267 (=CH)
4p	0.1	50	4	55	148-152° (from EtOH)	2100 (C≡C), 3200 (=CH)

EXPERIMENTAL

IR spectra were recorded on a Specord IR-75 instrument in mineral oil. PMR spectra were recorded on a UNITY-300 (Varian) spectrometer. Analytical data of all compounds corresponded to those calculated.

Syntheses of Starting Compounds.

1. Syntheses of Propargyl Ethers of Phenols. Propargyl ethers **4(b,f,h,k,l,m,n,p)** were synthesized by Claisen condensation [13] by boiling equimolar amounts of phenol and K₂CO₃ with a 10% excess of propargyl bromide in acetone for 3-7 h with TLC monitoring. The reaction mixture was filtered while hot. The precipitate was washed with hot acetone. The filtrate was cooled. The propargyl ether was precipitated by water. The solid ethers were filtered off. The precipitate on the filter was treated with hot water. The insoluble part was combined with the precipitated ether and recrystallized. The liquid ether obtained from *p*-fluorophenol (**b**) was separated in a separatory funnel, washed with water, dried over Na₂SO₄, and distilled at reduced pressure using a water aspirator. The fraction distilling at 114-118° at 20 mm Hg was collected.

Characteristic C≡C and C=H stretching-vibration bands in the IR spectra showed the presence in the compounds of the propargyl group. The final proof of structure in all instances was the synthesis of the corresponding cotarnine derivatives. Table 4 summarizes the synthesis data and properties of these ethers.

Propargyl Ether of Dimecarbaine (4c). Dimecarbaine was alkynylated by a variation of the literature method [14]. A suspension of 1,2-dimethyl-3-ethoxycarbonyl-5-hydroxyindole (1.5 g, 6.4 mmole) was treated with NaOH (0.52 g, 13 mmole) in H₂O (1 mL) and propargyl bromide (0.6 mL, 8 mmole), boiled for 2 min, and cooled. A crystalline solid was precipitated with water, filtered off, dried, and chromatographed over an Al₂O₃ column using CHCl₃. The solvent was evaporated. The solid was ground with CH₃OH, filtered off, and washed with cold CH₃OH to afford a colorless substance, mp 123-125°C. Yield 1.1 g (63%).

PMR spectrum (CDCl₃, δ, ppm, J/Hz): 1.43 (3H, t, J = 7.1, CH₃), 2.50 (1H, t, J = 2.2, ≡CH), 2.72 (3H, s, CH₃), 3.64 (3H, s, NCH₃), 4.36 (2H, q, J = 7.1, CH₂), 4.74 (2H, d, J = 2.2, CH₂), 6.90 (1H, dd, ³J = 8.8, ⁴J = 2.4, H-6), 7.16 (1H, d, J = 8.8, H-7), 7.73 (1H, d, J = 2.4, H-4). IR spectrum (ν, cm⁻¹): 2127 (C≡C), 3233 (≡CH), 1694 (CO).

Propargyl Ether of 4-Hydroxy-3-ethoxybenzaldehyde (4g). NaOH (0.8 g, 0.02 mole) was treated with DMSO (5 mL), ground with a glass rod into a fine powder, treated with 4-hydroxy-3-ethoxybenzaldehyde (1.66 g, 0.01 mole), ground with a glass rod for 10 min, treated with a toluene solution of propargyl bromide (1.35 mL, 0.01 mole, 80%), and left for 12 h. Water was added. The mixture was kept on ice for 2 h. The precipitate was filtered off and recrystallized from petroleum ether to afford colorless crystals (1.4 g, 68%), mp 75-77°C. IR spectrum (ν, cm⁻¹): 2114 (C≡C), 3247, 3267 (≡CH), 1687 (CO).

2. Method for Synthesizing Acetylenides (see also [15]). A solution of AgNO₃ (1.7 g, 0.01 mole) in a mixture of EtOH (10 mL) and conc. NH₄OH (10 mL) was added to a solution of an acetylene derivative (0.01 mole) in EtOH. Liquid acetylene derivatives were dissolved in EtOH (10 mL); solid, in EtOH (40-50 mL), as a rule, with heating. The alcohol can be replaced with acetone or dioxane if the solubility in EtOH is poor (for example, **2o**). The resulting white precipitate was filtered off in a Buchner funnel; washed with EtOH, ether, and petroleum ether; and dried in the dark in air or a vacuum desiccator.*

3. Method for Synthesizing Cotarnine Acetylene Derivatives (3).** Cotarnine hydrochloride (1 g, 4 mmole) and acetylenide (**2**, 5 mmole) in CH₃CN (10 mL) were stirred for 10 min at room temperature, refluxed for 5 min, and filtered while hot. The precipitate on the filter was washed with hot CH₃CN.

1-Ethynylcyclohexan-1'-ol-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline (3a). The filtrate was cooled with ice. The precipitate was filtered off, washed with cold CH₃CN, and dried. Colorless crystals, mp 135°C, yield 0.66 g (49%).

1[(4'-Fluorophenoxy)propyn-1-yl]-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline (3b) was prepared analogously. It was additionally purified by chromatography over an Al₂O₃ column (CHCl₃). The CHCl₃ was evaporated. The resulting oil was recrystallized by grinding with petroleum ether. Colorless compound, mp 100°C, yield 1.08 g (75%).

1-[(1'',2''-Dimethyl-3''-ethoxycarbonyl-5''-indolyloxy)propyn-1'-yl]-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline (3c) was prepared analogously. The oil from the Al₂O₃ column was ground with EtOH, from which the resulting precipitate was recrystallized. Colorless compound, mp 175-180°C, yield 0.79 g (42%).

1-(3'-Hydroxypropyn-1-yl)-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline (3d). Solvent (CH₃CN) was evaporated. The oily remainder was dissolved in CHCl₃ and chromatographed over an Al₂O₃ column, discarding a small initial fraction. The CHCl₃ was evaporated. The oil that solidified upon grinding was recrystallized from toluene. Colorless crystals, mp 154-156°C, yield 0.47 g (44%).

*Some silver organoacetylenides can decompose on storage to form explosive products. According to our observations, such unstable acetylenides include silver derivatives of phenylethynylcarbinol and diphenylethynylcarbinol. Therefore, acetylenides should be prepared immediately before the synthesis in quantities required for the reaction. Schott filters should not be used (decomposition can occur upon scraping the dry acetylenide with a spatula). Remaining compounds should be destroyed by decomposing them with acid after work is completed.

Commercial acetylene derivatives were used to synthesize **3(a,d,e,i,j,o).

1-(3'-Hydroxy-3'-methyl)butyn-1-yl-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline (3e) was prepared analogously to **3d** without discarding the initial fraction. The oil that solidified upon grinding with petroleum ether was recrystallized from hexane. Colorless crystals, mp 110°C, yield 0.68 g (57%).

1-[3'-(2''-Methoxy-4''-formylphenoxy)propyn-1-yl]-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (3f) was prepared analogously to **3e**. The oil from the column was dissolved in *i*-PrOH (20 mL), treated with conc. HCl (0.4 mL), cooled with ice, and ground with a rod. The precipitate was filtered off, washed with ether, and dried. Colorless crystals, mp 155°C (*i*-PrOH), yield 1 g (57%).

1-[3'-(2''-Ethoxy-4''-formylphenoxy)propyn-1-yl]-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline (3g) was prepared analogously to **3e**. The oil from the column was ground with petroleum ether and cooled with ice until solidified. The solid was filtered off, washed with petroleum ether, and dried in vacuum. Colorless compound, mp 110-115°C (*i*-PrOH), yield 1.42 g (68%).

1-[3'-(α -Bromo- β -naphthoxy)propyn-1-yl]-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (3h). The filtrate was cooled and filtered through a dense filter. The solvent was evaporated. The oil was ground with acetone and conc. HCl (0.5 mL). The resulting solid was filtered off, washed with acetone, and dried. Colorless crystals, mp 195-200°C (*i*-PrOH), yield 0.9 g (45%).

1-(2'-Phenylethynyl)-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline (3i). The CH₃CN was evaporated. The oil was dissolved in CHCl₃ and chromatographed over an Al₂O₃ column. The solvent was evaporated. The resulting oil crystallized after 1 d. The compound is very soluble in most organic solvents and crystallizes poorly. mp 80°C (aqueous CH₃OH), yield 1 g (79%).

1-(4'-Hydroxybutyn-1-yl)-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline (3j). The CH₃CN was evaporated. The oil was dissolved in acetone (10 mL) and treated with conc. HCl (1 mL) in acetone (3 mL). The resulting precipitate was filtered off and recrystallized from CH₃CN. Colorless compound, mp 225-230°C (dec.), yield 0.58 g (46%).

1-[3'-(7''-Coumaroxy)propyn-1-yl]-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline (3k). An oil precipitated from the filtrate and crystallized upon grinding with CH₃OH. Colorless crystals, mp 143-145°C (CH₃OH), yield 0.68 g (41%).

1-[3'-(4''-Methyl-7''-coumaroxy)propyn-1-yl]-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline (3l) was prepared analogously to **3k**. Colorless crystals, mp 160-163°C (CH₃OH), yield 0.8 g (47%).

1-[3'-(4''-Nitrophenoxy)propyn-1-yl]-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline (3m). An oil was precipitated from the filtrate by water and solidified upon grinding. The solid was filtered off and chromatographed over Al₂O₃ with CHCl₃. The solvent was evaporated. The solid was ground with CCl₄ and filtered off. Colorless compound, mp 140°C (CH₃CN), yield 1.2 g (78%).

1-[3'-(2'',4''-Dichlorophenoxy)propyn-1-yl]-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline (3n) was prepared analogously to **3m**. The oil from the Al₂O₃ column was dissolved in acetone, treated with conc. HCl (0.5 mL), and cooled with ice. The solid was filtered off, washed with cold acetone, and dried. Colorless compound, mp 185-190°C, yield 0.75 g (40%).

1-(3'-Phenoxypropyn-1-yl)-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline (3o). The filtrate was treated with conc. NH₄OH (10 mL). The oil crystallized upon cooling with ice and grinding. The solid was filtered off and chromatographed over an Al₂O₃ column with CHCl₃. The solvent was evaporated. The colorless oil crystallized upon grinding and was recrystallized from CH₃OH (5 mL). Colorless crystals, mp 75-80°C, yield 0.83 g (60%).

1-(3'-O-Salicylamidopropyn-1-yl)-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline (3p). The filtrate was treated with icewater (40 mL). The separated oil crystallized upon grinding. The solid was filtered off, dried, recrystallized from toluene (40 mL), washed on the filter with petroleum ether, and dried. Colorless crystals, mp 156-158°C, yield 0.68 g (44%).*

*IR spectra of **3** (mineral oil) were not very informative because the triple-bond stretching vibrations did not appear in them. Therefore, they are not reported.

X-ray Structure Analysis of 3d. Crystals of **3d** ($C_{15}H_{17}NO_4$) are monoclinic at room temperature: $a = 13.807(6)$, $b = 20.415(8)$, $c = 9.604(5)$ Å, $\beta = 92.23(4)^\circ$, $V = 2705(2)$ Å³, $Z = 8$, space group $P2_1/c$, $M = 275.30$, μ (Mo-K α) = 0.098 mm⁻¹, $d_{\text{calc}} = 1.325$ g·cm⁻³. Intensities of 5109 reflections were measured on an automated four-circle Siemens P3/PC diffractometer [λ (Mo-K α) = 0.71073 Å, graphite monochromator, $\theta/2\theta$ -scanning, $2\theta < 50^\circ$]. The structure was solved by direct methods and refined by full-matrix anisotropic least-squares methods over F^2_{hkl} . Hydrogen atoms were placed geometrically at calculated positions with the exception of the two hydroxyls (H3 and H3'), which were located in a difference electron-density synthesis and refined isotropically using the rider method. A total of 4799 independent reflections were used in the refinement ($R_{\text{int}} = 0.1152$). The agreement was refined over all independent reflections to $wR_2 = 0.2014$ calculated over F^2_{hkl} [$R_1 = 0.0907$ calculated over F_{hkl} for 1175 reflections with $I > 2\sigma(I)$]. Calculations were performed on an IBM PC AT using the SHELXTL-97 program set [16].

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