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ALKYNATION OF CHLORINATED COTARNINE BY SILVER PROPARGYLAMINES

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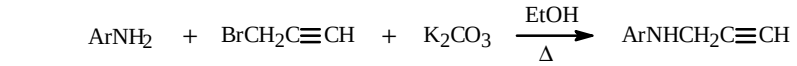
Chlorinated cotarnine was alkynated in the 1-position upon brief heating in acetonitrile with silver acetylenides of propargylamines to form the corresponding propargylamine derivatives.

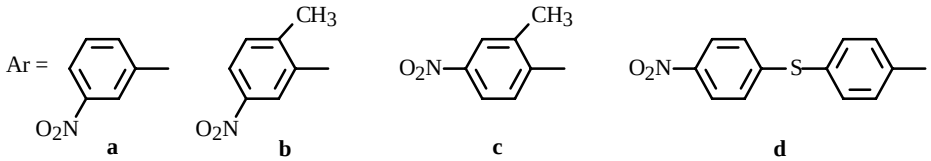
Key words: cotarnine, propargylamines, silver organoacetylenides, alkynation.

Cotarnine is obtained by oxidative cleavage of one of the principal opium alkaloids narcotine, which has a broad spectrum of physiological activity. It acts as a tonic and stimulant for smooth muscle, constricts vessels, exhibits local hemostatic activity, and possesses sedative and analgesic effects [1]. Its modification can produce new compounds that exhibit various types of physiological activity.

We previously reported [2, 3] the synthesis of acetylenic derivatives of cotarnine using acetylenides of Group 11 metals. In this manner, alkyl- and arylacetylenes and propargyl alcohols and ethers were introduced into cotarnine. Dialkylaminoalkyl groups are used widely in medicinal chemistry as pharmacophores [4]. Therefore, we developed a method of synthesizing propargylamine derivatives of cotarnine. Of interest on their own, they are also considered convenient precursors for conversion to aminopropyl derivatives. Propargylanilines and tertiary aliphatic propargylamines are used in alkynation reactions. Propargylanilines were prepared from the corresponding anilines and propargyl bromide:



1 **2**



a **b** **c** **d**

Silver derivatives of propargylanilines **2** form readily upon mixing their alcohol solutions with alcohol-ammonia solutions of silver nitrate. However, standard methods were unsuitable for synthesizing acetylenides of tertiary aliphatic propargylamines **4e-g** owing to their higher solubility. A separate isolation procedure was developed for each of these acetylenides.

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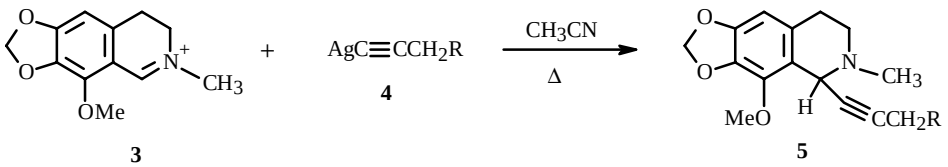
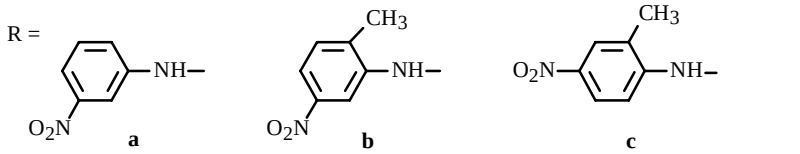
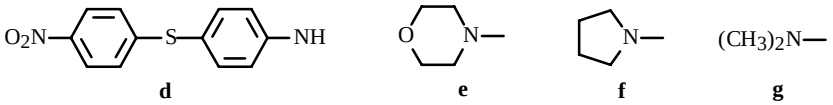
TABLE 1. PMR Spectra of Propargylamine Derivatives of Cotarnine

Compound	Solvent, δ, ppm, J/Hz
5a HCl	(DMSO-d_6 + CCl_4): 2.76-3.38 (m, 4H, C(4)H_2+C(3)H_2), 2.82 (s, 3H, NCH_3), 3.92 (s, 3H, OCH_3), 4.04 (s, 2H, CH_2N), 5.29 (s, 1H, C(1)H), 5.96 (split s, 2H, OCH_2O), 6.39 (s, 1H, C(5)H), 6.74 (br.s, 1H, NH), 7.00-7.55 (m, 4H, CH_{arom}), 12.17 (s, 1H, $^+$NH)
5b	($CDCl_3$): 2.18 (s, 3H, C(2′)CH_3), 2.40 (s, 3H, NCH_3), 2.50-2.63 (m, 2H, C(4)H_2), 2.71-2.94 (m, 2H, C(3)H_2), 3.92 (s, 3H, OCH_3), 3.98 (t, 1H, NH, J = 6), 4.07 (d, 2H, CH_2N, J = 6), 4.65 (s, 1H, C(1)H), 5.85 (s, 2H, OCH_2O), 6.27 (s, 1H, C(5)H), 7.14 (d, 1H, C(3′)H, J = 8.1), 7.49 (d, 1H, C(6′)H, J = 2.2), 7.54 (dd, 1H, C(4′)H, ^{3}J = 8.1, ^{4}J = 2.2)
5c	($CDCl_3$): 2.16 (s, 3H, C(2′)CH_3), 2.43 (s, 3H, NCH_3), 2.53-2.97 (m, 4H, C(4)H_2+C(3)H_2), 3.92 (s, 3H, OCH_3), 4.07 (dd, 2H, CH_2N, ^{3}J = 5.75, ^{4}J = 1.75), 4.44 (t, 1H, NH, J = 5.75), 4.67 (s, 1H, C(1)H), 5.86 (split s, 2H, OCH_2O), 6.29 (s, 1H, C(5)H), 6.63 (d, 1H, C(6′)H, J = 9), 7.96 (d, 1H, C(3′)H, J = 2.6), 8.02 (dd, 1H, (C(5′)H, ^{3}J = 9.0, ^{4}J = 2.6)
5d HCl	(DMSO-d_6): 2.79-3.40 (m, 4H,C(3)H_2+C(4)H_2), 2.83 (s, 3H, NCH_3), 3.95 (s, 3H, OCH_3), 4.00 (unresolv. d, CH_2N), 5.31 (s, 1H, C(1)H), 5.97 (split s , 2H, OCH_2O), 6.42 (s, 1H, C(5)H), 6.60 (br.s, 1H, NH), 6.74 (d, 2H, CH_{arom}, J = 8.6), 7.08 (d, 2H, CH_{arom}, J = 9), 7.27 (d, 2H, CH_{arom}, J = 8.6), 8.04 (d, 2H, CH_{arom}, J = 9.0), 12.11 (s, 1H, $^+$NH)
5e	($CDCl_3$): 2.50 (s, 3H, NCH_3), 2.53 (t, 4H, NCH_2, J = 4.7), 2.60-2.70 (m, 2H, C(4)H), 2.80-2.95 (m, 2H, C(3)H_2), 3.33 (d, 2H, ≡CCH_2, J = 1.7), 3.71 (t, 4H, OCH_2, J = 4.7), 3.99 (s, 3H, OCH_3), 4.72 (s, 1H, C(1)H), 5.85 (s, 2H, OCH_2O), 6.29 (s, 1H, C(5)H)
5f	($CDCl_3$): 1.76 (m, 4H, CH_2), 2.49 (s, 3H, NCH_3), 2.52-2.71 (m, 6H, CH_2), 2.80-2.98 (m, 2H, C(3)H_2), 3.43 (s, 2H, CH_2N), 3.98 (s, 3H, OCH_3), 4.71 (s, 1H, C(1)H), 5.85 (s, 2H, OCH_2O), 6.28 (s, 1H, C(5)H)
5g	($CDCl_3$): 2.26 (s, 6H, N(CH_3)$_2$), 2.51 (s, 3H, NCH_3), 2.57-2.71 (m, 2H, C(4)H_2), 2.82-2.98 (m, 2H, C(3)H_2), 3.27 (s, 2H, CH_2N), 3.99 (s, 3H, OCH_3), 4.73 (s, 1H, C(1)H), 5.83 (s, 2H, OCH_2O), 6.29 (s, 1H, C(5)H)

Brief heating of cotarnine chloride **3** with silver acetylenides of propargylamines **4** in acetonitrile formed the propargylamine derivatives of cotarnine **5**:







Acetylenides **4e-g** were prepared from commercially available starting compounds.

A characteristic feature of **5** is the lack of stretching vibrations for the triple bond in their IR spectra recorded in mineral oil. This is applicable to all previously described [2, 3] acetylenic derivatives of cotarnine. In view of the paucity of information, we did not include these spectra in the present article. Table 1 lists the PMR spectra of **5a-g**.

EXPERIMENTAL

IR spectra of propargylanilines **2a-d** were recorded on a UR-20 instrument in KBr disks. PMR spectra were recorded on a Varian UNITY-300 spectrometer. Elemental analyses of all compounds corresponded with those calculated.

General Method for Synthesizing N-Propargylanilines (2a-d). A mixture of arylamine (0.1 mol), freshly distilled propargyl bromide (0.1 mol), and finely ground freshly calcined K_2CO_3 (0.11 mol) in EtOH (95%, 250 mL) was boiled for 14 h. The precipitate was separated. The filtrate was evaporated in vacuum. The solid was chromatographed over a silica-gel column (eluent benzene:acetone, 11:1). The product was crystallized from benzene to afford yellowish-orange compounds, yield 55-65%. IR spectra of **2a-d** contain strong absorptions ν_{NO_2} (1320-1350, 1530-1540 cm^{-1}), $\nu_{=CH}$ (3290-3310 cm^{-1}), and ν_{NH} (3390-3410 cm^{-1}).

N-(2′-Propynyl)-3-nitroaniline (2a): mp 92-93°C.

N-(2′-Propynyl)-2-methyl-5-nitroaniline (2b): mp 121-123°C.

N-(2′-Propynyl)-2-methyl-4-nitroaniline (2c): mp 126-127°C (lit. [5] mp 121-123°C).

4-(N-Propargylamino)-4′-nitrodiphenylsulfide (2d): mp 88-90°C.

General Method of Synthesizing Silver Derivatives of N-Propargylanilines (4a-d). A solution of $AgNO_3$ (1 g, 5.8 mmol) in EtOH (5 mL) and conc. NH_4OH (5 mL) was poured into a hot solution of the appropriate propargylaniline (**2a-d**, 5.5 mmol) in EtOH (40 mL). The reaction mixture was cooled with ice, transferred to a filter (Buchner funnel), separated, washed with EtOH, and dried at 70-80°C. Yellowish-orange compounds, quantitative yields.

3-Morpholinoprop-1-yne Acetylenide (4e). Finely ground $AgNO_3$ (1 g, 6 mmol) was dissolved in MeOH (1 mL) and conc. NH_4OH (2 mL), stirred, treated with morpholinoprop-1-yne (1 mL, 7 mmol) and acetone (5 mL), poured into a Petri dish, and evaporated with gentle heating almost to dryness. Distilled water was added. The solid was ground with a rod with cooling on an ice bath. The solid was transferred to a filter, separated, washed with distilled water, and dried. Colorless compound, yield 1.1 g (80%).

3-Pyrrolidinoprop-1-yne Acetylenide (4f). Finely ground $AgNO_3$ (1 g, 6 mmol) was dissolved in MeOH (1 mL) and conc. NH_4OH (2 mL), treated with 3-pyrrolidinoprop-1-yne (0.9 mL, 8 mmol) and acetone (3 mL), and left for 30 min. The resulting precipitate was filtered off, washed with acetone, and dried. Yield 1.2 g (94%).

3-Dimethylaminoprop-1-yne Acetylenide (4g). Finely ground $AgNO_3$ (1.5 g, 9 mmol) was dissolved in MeOH (2 mL) and conc. NH_4OH (2 mL), treated with 3-dimethylaminoprop-1-yne (1 mL, 9 mmol), and left for 30 min. Acetone (20 mL) was added. The mixture was cooled with ice. The solid was transferred to a filter, separated, washed with acetone, and dried in vacuum at room temperature. Yield 1.6 g (95%).

1-[3′-(3″-Nitrophenylamino)propyn-1-yl]-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (5a). Cotarnine chloride (1.2 g, 4.7 mmol) and **2a** (1.5 g, 5.3 mmol) in CH_3CN (10 mL) were stirred for 10 min at room temperature and 5 min at boiling and filtered. The solid was washed with hot CH_3CN. Addition of water to the filtrate precipitated an orange oil that was cooled with ice and ground to solidify it. The solid was filtered off, washed with water, dried, dissolved in $CHCl_3$, and passed over an Al_2O_3 column, discarding the colorless lead fraction. Solvent was evaporated. The orange oil was dissolved with heating in a small amount of *i*-PrOH, treated with conc. HCl (1 mL), cooled with ice, and ground with a rod. The solid was filtered off and recrystallized from CH_3CN (100 mL). Orange compound, mp 220-225°C (dec.). Yield 0.8 g (39%).

1-[3′-(2″Methyl-4″-nitrophenylamino)-propyn-1-yl]-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline (5b). Cotarnine chloride (1.2 g, 4.7 mmol) and **2b** (1.75 g, 5.9 mmol) in CH_3CN (10 mL) were stirred for 10 min at room temperature and 5 min at boiling and filtered hot. The filtrate was cooled with ice. The resulting precipitate was filtered off, washed with cold CH_3OH, and dried. Orange compound, mp 185-190°C. Yield 0.6 g (31%).

1-[3′-(2″-Methyl-5″-nitrophenylamino)propyn-1-yl]-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline (5c). Cotarnine chloride (1.2 g, 4.7 mmol) and **2c** (1.45 g, 4.9 mmol) in CH_3CN (10 mL) were stirred for 10 min at room temperature and 5 min at boiling and filtered. The solid was washed with hot CH_3CN. Water precipitated an oil from the filtrate that crystallized upon cooling with ice and grinding. The solid was filtered off, washed with water, and dried. Bright yellow crystals, mp 90-95°C (CH_3OH). Yield 1.25 g (66%).

1-{3′-[4″-(4‴-Nitrophenylmercapto)phenylamino]propyn-1-yl}-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (5d). Cotarnine chloride (1.3 g, 5.1 mmol) and **2d** (2.6 g, 6 mmol) in CH_3CN (15 mL) were stirred for 10 min at room temperature and 10 min at boiling and filtered. The solid was washed with hot CH_3CN. Water

precipitated an oil from the filtrate that was separated, dissolved in *i*-PrOH (4 mL), treated with conc. HCl (1.5 mL), cooled with ice, and ground with a rod. The solid was filtered off, washed with *i*-PrOH, dried, dissolved with heating in CH_3OH (100 mL), and left for 12 h in a refrigerator. The resulting precipitate was filtered off, washed with cold CH_3OH, and dried. Yellow compound, mp 170-175°C (dec.). Yield 0.68 g (26.5%).

1-(3′-Morpholinopropyn-1-yl)-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline (5e). Cotarnine chloride (1 g, 3.9 mmol) and **2e** (1.1 g, 4.7 mmol) in CH_3CN (10 mL) were stirred for 10 min at room temperature and 5 min at boiling and filtered hot. The solvent was evaporated. The resulting oil was solidified by cooling with ice and ground. The solid was dissolved in $CHCl_3$ and chromatographed over a column of Al_2O_3. The solvent was evaporated. The colorless oil crystallized on cooling with ice and grinding with petroleum ether. The solid was filtered off, washed with petroleum ether, and dried. Colorless crystals, mp 77-80°C. Yield 0.6 g (45%).

1-(3′-Pyrrolidinopropyn-1-yl)-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline (5f). Cotarnine chloride (1 g, 3.9 mmol) and **2f** (1.2 g, 5.5 mmol) in CH_3CN (10 mL) were stirred for 10 min at room temperature and 5 min at boiling and filtered hot. The solvent was evaporated. The resulting oil solidified on cooling with ice and grinding. The solid was chromatographed over a column of Al_2O_3 with $CHCl_3$ eluent. The solvent was evaporated. The resulting oil crystallized on cooling and grinding with petroleum ether. The solid was filtered off, washed with petroleum ether, and dried in vacuum. Colorless crystals, mp 70-75°C. Yield 0.61 g (45.5%).

1-(3′-Dimethylaminopropyn-1-yl)-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline (5g). Cotarnine chloride (1 g, 3.9 mmol) and **2g** (1.6 g, 8.4 mmol) in CH_3CN (10 mL) were stirred for 10 min at room temperature and 5 min at boiling and filtered hot. The solvent was evaporated. The resulting oil solidified on grinding. The solid was dissolved in $CHCl_3$ and passed over a column of Al_2O_3. The solvent was evaporated. The colorless oil crystallized on cooling with ice and grinding with petroleum ether. The solid was filtered off, washed with cold petroleum ether, and dried in vacuum. Colorless crystals, mp 65-67°C. Yield 0.3 g (25%).

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