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NOVEL QUININE, LUPININE, AND ANABASINE DERIVATIVES CONTAINING DITHIOPHOSPHINATE GROUPS

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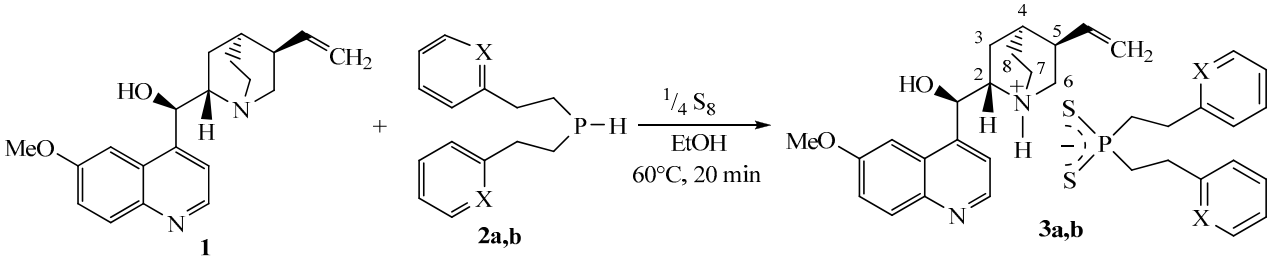
A three-component, atom-economic reaction between natural quinine, lupinine, or anabasine, secondary phosphines, and elemental sulfur occurs under mild conditions to yield previously unknown optically active dithiophosphinates.

Keywords: anabasine, bis(2-arylethyl)phosphines, dithiophosphinates, elemental sulfur, lupinine, quinine, synthesis, three-component reaction.

The alkaloids quinine, lupinine, and anabasine are readily isolated from natural sources and possess a broad spectrum of biological activity [1-4]. They are used in the design of pharmacological preparations and pesticides. Derivatives of these alkaloids are also being actively studied including analgesic compounds with markedly greater activity than cocaine and procaine (lupinine derivatives [5]), agents lowering the desire to smoke (anabasine hydrochloride [6]), antimalarial medications (quinine sulfate and hydrochloride [7]), and substances possessing antitumor, antituberculous, hepatoprotective, antiviral, antibacterial, anticholinesterase and antifungal activity (phosphorylated derivatives of lupinine and anabasine [8]). Anabasine sulfate is an efficient insecticide used in agriculture [9, 10].

The search for novel synthetic intermediates in the design of biologically active alkaloid-based preparations is also continuing to develop. In this regard, modification of alkaloids *via* the introduction of pharmacophoric functional groups into these molecules is particularly promising.



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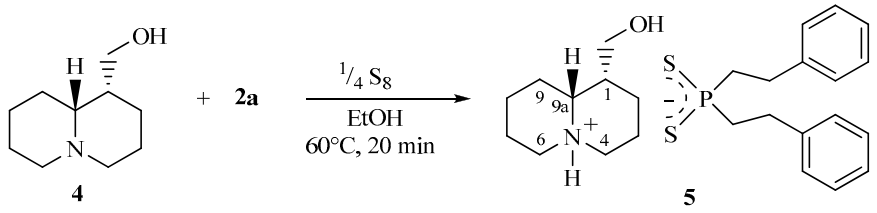
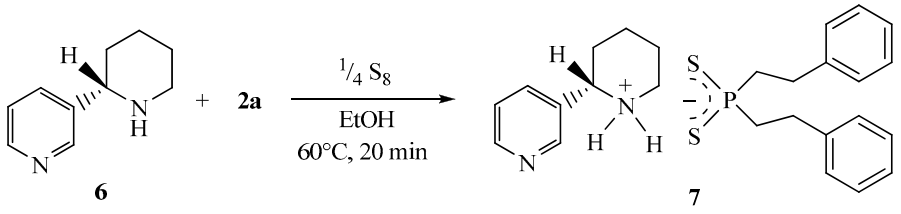
Investigating the modification of alkaloids, we have carried out a targeted synthesis of the previously unknown dithiophosphinates of quinine, lupinine, and anabasine *via* a three-component, atom-economic reaction between the indicated alkaloids, secondary phosphines, and elemental sulfur. It is known that compounds containing the dithiophosphinate group (PS_2^-) show marked biological activity [11, 12].

Experiments have shown that natural quinine (**1**) reacts with the secondary phosphines **2a,b** and elemental sulfur (molar ratio of reagents 1.0:1.1:0.25) under mild conditions (60ºC, 20 min, EtOH) to give the quinine dithiophosphinates **3a,b** in 90% and 84% yield, respectively.

A three-component reaction of natural lupinine (**4**), the secondary phosphine **2a**, and elemental sulfur proceeds under analogous conditions to give the lupinine dithiophosphinate **5** in 95% yield.



The anabasine dithiophosphinate **7** was prepared by the same scheme from natural anabasine (**6**), the secondary phosphine **2a**, and elemental sulfur in 87% yield.



The choice of the secondary phosphines **2a,b** was not accidental: they are readily prepared from red phosphorus and styrene or 2-vinylpyridine [13-15].

Assignment of the ^1H and ^{13}C NMR signals in the synthesized quinine, lupinine, and anabasine derivatives was based on the known spectroscopic data for the previously studied salts of these alkaloids (sulfates, halides, perchlorates etc.). Analysis of the spectroscopic data for the latter showed that exchange of the counter-ion has practically no effect on the NMR parameters of the cations of the protonated alkaloids. Hence the ^1H and ^{13}C NMR spectroscopic parameters for the cationic part of the obtained quinine dithiophosphinates **3a,b** agree well with the NMR data for quinine hydrochloride. The ^1H-^1H and ^1H-^{13}C 2D NMR spectra of the quinine dithiophosphinates **3a,b** also confirm the correctness of the assignments given. The HSQC and HMBC correlation results for the quinine bis(2-phenylethyl)dithiophosphinate **3a** are given in Table 1.

Thus based on a three-component, atom-economic reaction between natural lupinine, anabasine, or quinine, available secondary phosphines, and elemental sulfur we have developed an efficient one-pot method of synthesis of the previously unknown pharmacophoric dithiophosphinates which are of promise for creating pharmacologically active preparations and pesticides.

EXPERIMENTAL

IR spectra were recorded on a Bruker Vertex 70 spectrometer using KBr pellets. ^1H, ^{13}C, and ^{31}P NMR spectra were obtained on a Bruker DPX-400 spectrometer (400, 102, and 162 MHz, respectively) for $CDCl_3$ solutions with HMDS (0.05 ppm) as internal standard and 85% H_3PO_4 as external standard for the ^{31}P NMR

TABLE 1. Results of the HSQC and HMBC Experiments for Salt **3a**

Atom or group	δ, ppm	HSQC	HMBC
H-2	3.39-3.56	59.9	37.2; 45.1; 65.7
3-CH_2	2.08-2.15	19.1	26.7; 143.8
H-4	1.95-2.00	26.7	—
H-5	2.66-2.77	37.2	—
6-CH_2	3.39-3.56	54.7	37.2; 45.1; 65.7; 137.2
7-CH_2	4.61-4.68	45.1	—
8-CH_2	2.08-2.15	24.5	—
CH_3O	4.01	57.2	100.5; 131.4; 158.5
CH_2=	5.01; 5.05	117.1	37.2; 137.2
CH_2=$\underline{CH}$	5.53	137.2	27.6; 37.2; 54.7
CHOH	6.85	65.7	119.1; 125.6
H-2'	8.72	147.1	119.1; 125.6
H-3'	7.66	122.5	65.7; 125.6; 143.7; 147.1; 158.5
H-5'	7.47	100.5	131.4; 143.7; 143.8; 158.5
H-7'	7.33	119.1	100.5; 125.6; 143.7; 158.5
H-8'	7.98	131.4	119.1; 125.6; 143.7; 158.5
NH, OH	10.98	—	—
CH_2P	2.34-2.41	43.7	29.8; 141.8
CH_2Ph	3.04-3.11	29.8	128.3
C_6H_5	7.11-7.25	141.8 (*i*-C); 128.3 (*m*-C); 125.8 (*p*-C); 128.2 (*o*-C)	29.8; 125.8; 128.2; 141.8

spectra. Assignment of the signals in the ^{1}H and ^{13}C NMR spectra was made using COSY, NOESY, HSQC, and HMBC homo- and heteronuclear experiments. Specific optical rotations were determined on a Polamat A polarimeter using EtOH. Elemental analysis was performed on a Flash EA 1112 instrument. The secondary phosphines **2a,b** were synthesized from red phosphorus and styrene [14] or 2-vinylpyridine [15], respectively. Technical grade ethanol (96%) was used as solvent. All of the experiment stages were carried out under an inert argon atmosphere.

Synthesis of Dithiophosphinates 3a,b, 5, 7 (General Method). Orthorhombic sulfur (0.064 g, 0.25 mmol) was added to a solution of the secondary phosphine **2a,b** (1.10 mmol) and quinine, lupinine, or anabasine (1.0 mmol) in EtOH (10 ml) at 23-25ºC. The suspension obtained was stirred at 60ºC to dissolution of the sulfur precipitate (about 20 min) to form a colorless, transparent solution. The solvent was evaporated, and the residue was washed with hexane (2×15 ml) and ether (5 ml) and dried *in vacuo* at 40-45ºC (1 mm Hg).

(2*S*,4*S*,5*R*)-2-[(*R*)- Hydroxy(6-methoxyquinolin-4-yl)methyl]-2-methyl-5-vinylquinuclidinium Bis-(2-phenylethyl)dithiophosphinate (3a). Yield 0.57 g (90%) Colorless powder, mp 138-140ºC (Et_2O), α_D^{23} -228º (c = 2.0). IR spectrum, ν, cm^{-1}: 3422, 3278, 3082, 3060, 3024, 2999, 2929, 2905, 2831, 2750, 2576, 2541, 2492, 2376, 2346, 1947, 1638, 1620, 1602, 1590, 1509, 1495, 1473, 1453, 1431, 1400, 1364, 1339, 1320, 1301, 1258, 1241, 1228, 1206, 1173, 1131, 1094, 1082, 1028, 1000, 947, 919, 879, 855, 831, 801, 751, 718, 698, 670, 639, 613, 574, 553, 529, 511, 488, 467. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.18-1.26 (1H, m, H-3-*e*); 1.77-1.85 (1H, s, H-8-*e*); 1.95-2.00 (1H, m, H-4); 2.08-2.15 (2H, m, H-3-*a*, 8-*a*); 2.34-2.41 (4H, m, 2CH_2P); 2.66-2.77 (1H, m, H-5); 3.04-3.11 (4H, m, 2CH_2Ph); 3.26-3.32 (1H, m, H-6-*e*); 3.39-3.56 (3H, m, H-2,6-*a*,7-*e*); 4.01 (3H, s, CH_3O); 4.61-4.68 (1H, m, H-7-*a*); 5.01 (1H, d, ^3J = 11.6) and 5.05 (1H, d, ^3J = 17.1, H_2C=); 5.53 (1H, dd, ^3J = 10.6, ^3J = 17.1, $\underline{H}C$=CH_2); 6.85 (1H, s, C$\underline{H}$OH); 7.11-7.25 (10H, m, H Ph); 7.33 (1H, dd, ^3J = 2.3, ^3J = 9.1, H-7'); 7.47 (1H, d, ^3J = 2.2, H-5'); 7.66 (1H, d, ^3J = 4.4, H-3'); 7.98 (1H, d, ^3J = 9.1, H-8'); 8.72 (1H, d, ^3J = 4.4, H-2'); 10.98 (2H, br. s, NH, OH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 19.1 (C-3); 24.5 (C-8); 26.7 (C-4); 29.8 (CH_2Ph); 37.2 (C-5); 43.7 (d, $^1J_{C–P}$ = 50.5, CH_2P); 45.1 (C-7); 54.7 (C-6); 57.2 (CH_3O); 59.9 (C-2); 65.7 (CHOH); 100.5 (C-5'); 117.1 (=CH_2); 119.1 (C-7'); 122.5 (C-3'); 125.6 (C-9'); 125.8 (C-*p*); 128.2 (C-*o*); 128.3 (C-*m*); 131.4 (C-8'); 137.2 ($\underline{C}$H=CH_2); 141.8 (d, $^3J_{C–P}$ = 17, C-*i*); 143.7 (C-10'); 143.8 (C-4'); 147.1 (C-2');

158.5 (C-6'). ^{31}P NMR spectrum, δ, ppm (*J*, Hz): 69.2 (satellite d, $^{1}J_{C–P}$ = 49.3). Found, %: C 68.50; H 6.68; N 4.37; P 4.98; S 9.98, $C_{36}H_{43}N_2O_2PS_2$. Calculated, %: C 68.54; H 6.87; N 4.44; P 4.91; S 10.17.

(2*S*,4*S*,5*R*) 2-[(*R*)-Hydroxy(6-methoxyquinolin-4-yl)methyl]-2-methyl-5-vinylquinuclidinium Bis-[2-(2-pyridyl)ethyl]dithiophosphinate (3b). Yield 0.53 g (84%). Colorless, viscous liquid, α_D^{23} = -225º (c = 2.1). IR spectrum, ν, cm^{-1}: 3439, 1641, 1622, 1600, 1569, 1510, 1475, 1434, 1367, 1344, 1241, 1228, 1131, 1051, 1028, 1003, 948, 855, 832, 763, 718, 668, 616, 520, 468. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.33-1.40 (1H, m, H-3-*e*); 1.91-1.98 (1H, m, H-8-*e*); 2.15-2.25 (3H, m, H-3-*a*,4,8-*a*); 2.57-2.70 (4H, m, 2CH$_2$P); 2.76-2.84 (1H, m, H-5); 3.32-3.56 (5H, m, 2C<u>H</u>$_2$Py, H-6-*e*); 3.65-3.71 (2H, m, H-2,7-*e*,); 3.88-3.94 (1H, m, H-6-*a*); 4.09 (3H, s, CH$_3$O); 4.75-4.82 (1H, m, H-7-*a*); 5.10 (1H, d, ^3J = 10.4) and 5.15 (1H, d, ^3J = 17.1, H$_2$C=); 5.61-5.69 (1H, dd, ^3J = 10.4, ^3J = 17.1, <u>H</u>C=CH$_2$); 7.08 (1H, s, C<u>H</u>OH); 7.15 (1H, dd, ^3J = 2.3, ^3J = 9.1, H-7'); 7.25 (2H, d, ^3J = 7.6, H-3 Py); 7.41-7.43 (2H, m, H-5 Py); 7.52 (1H, s, H-5'); 7.64 (2H, dd, ^3J = 7.6 and ^3J = 7.6, H-4 Py); 7.88 (1H, d, ^3J = 4.4, H-3'); 8.07 (1H, d, ^3J = 9.1, H-8'); 8.48 (2H, d, ^3J = 4.2, H-6 Py); 8.87 (1H, d, ^3J = 4.4, H-2'). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 19.4 (C-3); 24.7 (C-8); 27.0 (C-4); 32.7 (CH$_2$Py); 37.2 (C-5); 41.6 (d, $^{1}J_{C–P}$ = 51.3, CH$_2$P); 45.3 (C-7); 54.7 (C-6); 57.2 (CH$_3$O); 59.7 (C-2); 66.1 (CHOH); 100.6 (C-5'); 116.9 (=CH$_2$), 119.0 (C-7'); 121.1(C-3 Py); 122.6 (C-3'); 123.0 (C-5 Py); 125.9 (C-9'); 131.7 (C-8'); 136.6 (C-4 Py); 137.6 (<u>C</u>H=CH$_2$); 144.3 (C-10'); 144.5 (C-4'); 147.3 (C-2'); 148.7 (C-6 Py); 158.5 (C-6'); 161.5 (d, $^{3}J_{C–P}$ = 17.3, C-2 Py). ^{31}P NMR spectrum, δ, ppm (*J*, Hz): 70.0 (satellite d, $^{1}J_{C–P}$ = 50.0). Found, %: C 64.41; H 6.28; N 8.60; P 4.78; S 10.22. $C_{34}H_{41}N_4O_2PS_2$. Calculated, %: C 64.53; H 6.53; N 8.85; P 4.89; S 10.13.

(1*R*,9a*R*)-1-(Hydroxymethyl)octahydro-2*H*-quinolizinium Bis(2-phenylethyl)dithiophosphinate (5). Yield 0.454 g (95%). Needle crystals, mp 186-188ºC (EtOH), α_D^{23} = -19.0º (c = 2.0). IR spectrum, ν, cm^{-1}: 3348, 3311, 3106, 3084, 3061, 3023, 3000, 2941, 2865, 2766, 2719, 2594, 2512, 1957, 1939, 1885, 1868, 1709, 1656, 1601, 1583, 1495, 1452, 1426, 1401, 1378, 1364, 1349, 1335, 1314, 1270, 1262, 1240, 1214, 1191, 1159, 1124, 1107, 1077, 1057, 1050, 1030, 1015, 996, 988, 948, 931, 905, 878, 859, 837, 766, 754, 739, 695, 609, 569, 537, 517, 509, 472. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.15-1.25 (1H, m, H-8-*a*); 1.38–2.05 (11H, m, H-2,3,7,9-CH$_2$, H-4-*a*,6-*a*,8-*e*); 2.31-2.38 (4H, m, 2CH$_2$P); 2.48-2.61 (1H, m, H-1); 2.67-2.75 (1H, m, H-9a); 3.06–3.13 (4H, m, 2C<u>H</u>$_2$Ph); 3.57-3.62 (1H, m, H-6-*e*); 3.77-3.83 (1H, m, H-4-*e*); 3.94-3.97 (1H, m) and 4.10-4.14 (1H, m, C<u>H</u>$_2$OH); 7.23-7.37 (10H, m, H Ph); 10.02 (2H, br. s, NH, OH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 17.4; 18.3 (C-3); 19.6 (C-8); 22.1 (C-7); 22.2; 23.0 (C-9); 27.7; 28.0 (C-2); 30.0 (CH$_2$Ph); 39.7 (C-1); 43.9 (d, $^{1}J_{C–P}$ = 50.0, CH$_2$P); 45.1; 53.3 (C-6); 56.3; 57.1 (C-4); 58.9 (C-10); 61.4 (C-9a); 62.7 (C-10); 67.1 (C-9a); 125.7 (C-*p*); 128.2 (C-*o*); 128.3 (C-*m*); 142.4 (d, $^{3}J_{C–P}$ = 16.9, C-*i*). ^{31}P NMR spectrum, δ, ppm (*J*, Hz): 68.6 (satellite d, $^{1}J_{C–P}$ = 49.3). Found, %: C 65.70; H 8.08; N 2.85; P 6.40; S 13.44. $C_{26}H_{38}NOPS_2$. Calculated, %: C 65.65; H 8.05; N 2.94; P 6.51; S 13.48.

(*S*)-2-(3-Pyridyl)piperidinium Bis(2-phenylethyl)dithiophosphinate (7). Yield 0.41 g (87%). Colorless powder, mp 159-161ºC (EtOH–hexane), α_D^{23} = -4.5º (c = 2.0). IR spectrum, ν, cm^{-1}: 3484, 3055, 3023, 2999, 2943, 2928, 2861, 2753, 2677, 2542, 2446, 1986, 1958, 1873, 1813, 1756, 1600, 1578, 1547, 1495, 1482, 1452, 1424, 1403, 1360, 1339, 1223, 1204, 1278, 1267, 1258, 1240, 1222, 1205, 1192, 1155, 1122, 1103, 1076, 1048, 1029, 1019, 1005, 948, 904, 870, 852, 838, 808, 799, 766, 743, 712, 699, 583, 571, 517, 490, 443. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.66-2.10 (6H, m, 3,4,5-CH$_2$); 2.19–2.24 (4H, m, 2CH$_2$P); 2.89-2.96 (4H, m, 2CH$_2$Ph); 3.06 (1H, ddd, ^2J = 12.3, ^3J = 9.1, ^3J = 3.4, H-6-*a*); 3.88 (1H, d, ^2J = 12.3, H-6-*e*); 4.19 (1H, dd, ^3J = 11.2, ^3J = 4.6, H-2); 7.13-7.29 (11H, m, H Ph, H-5 Py); 8.24 (1H, d, ^3J = 7.8, H-4 Py); 8.47 (1H, d, ^3J = 4.0, H-6 Py); 8.74 (1H, s, H-2 Py); 9.20 (2H, br. s, NH$_2^+$). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 22.2 (C-4); 22.9 (C-5); 29.7 (CH$_2$Ph); 30.7 (C-3); 43.5 (d, $^{1}J_{C–P}$ = 49.8, CH$_2$P); 45.5 (C-6); 58.8 (C-2); 124.0 (C-5 Py); 125.8 (C-*p*); 128.3 (C-*o*); 128.3 (C-*m*); 132.1 (C-3 Py); 136.2 (C-4 Py); 142.1 (d, $^{3}J_{C–P}$ = 17.0, C-*i*); 148.9 (C-2 Py); 150.3 (C-6 Py). ^{31}P NMR spectrum, δ, ppm (*J*, Hz): 68.0 (satellite d, $^{1}J_{C–P}$ = 49.9). Found, %: C 66.51; H 7.18; N 5.78; P 6.47; S 13.54. $C_{26}H_{33}N_2PS_2$. Calculated, %: C 66.63; H 7.10; N 5.98; P 6.61; S 13.68.

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