Synthesis and Antiviral Activity of 11-Azapentacyclo[6.2.1.0.^{2,7}0.^{4,10}0^{5,9}]decane

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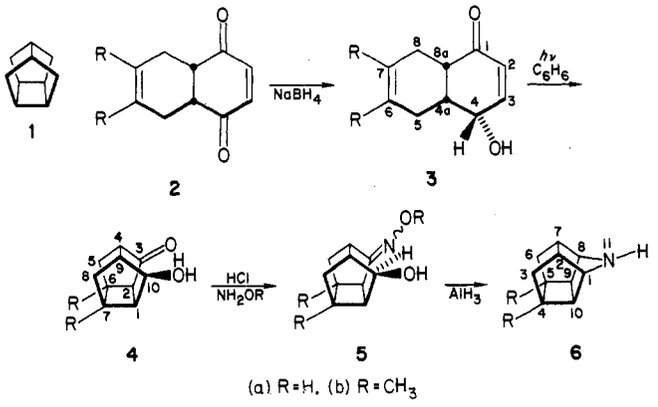
11-Azapentacyclo[6.2.1.0.^{2,7}0.^{4,10}0^{5,9}]decane (**6a**) as well as its 6,7-dimethyl derivative **6b** was synthesized by a novel, four-step sequence that holds promise for the construction of a variety of cage compounds with bridging nitrogen atoms. The hydrochloride salt of **6a** was shown to possess no antiviral activity against either the influenza virus A/Victoria/3/75 or the herpes simplex viruses HSV-1 and HSV-2.

Alicyclic cage compounds continue to fascinate chemists in three main ways: (1) as synthetic challenges, (2) as



molecules possessing unusual physical and chemical properties, and (3) as biologically active substances, particularly as antiviral agents. Since the discovery in the early 1960s of 1-aminoadamantane's potent inhibitory properties against several viruses, especially influenza viruses, a large number of nitrogen-containing polycyclic cage compounds have been synthesized in order to assess their antiviral activity.[1] Our own interest in this area was stimulated by our discovery[2] of a short, general synthetic entry into the tetracyclo[5.3.0.0.^{2,6}0^{4,9}]decane ring system 1. In this paper we report the preparation of a nitrogen bridged derivative of 1, viz., the title compound 11-azapentacyclo[6.2.1.0.^{2,7}0.^{4,10}0^{5,9}]decane (**6a**) as well as its dimethyl derivative **6b**. We also report a comparison of the antiviral activity of compound **6a** with that of 1-aminoadamantane and 5-ethyl-2′-deoxyuridine.

The synthesis proceeded from the readily available Diels–Alder adducts **2a**[3] and **2b**.[4] In what appears to be a general sequence, monoreduction of these enediones with sodium borohydride afforded the corresponding α-hydroxycyclohexenones **3a** and **3b**, which photocyclized (benzene, uranium glass filter) in good yield to give the ketols **4a** and **4b**. These compounds were oximated (syn/anti mixtures), and the synthesis was completed by treatment of the oxime mixtures with aluminum hydride; the yield of **6a** in this final step was 30%. In the case of **6b**, solubility problems dictated the use of the oxime methyl ether rather than the oxime itself. The yield of **6b** in the final step was 21%. Although the yields are modest, this novel aluminum hydride cyclization reaction holds promise as an attractive method for the construction of a variety of bridged nitrogen systems.

Cage amine **6a**, like its bridged oxygen analogue,[2] is a volatile white solid. Both **6a** and **6b** are best isolated via salt formation following alumina column chromatography of the crude reaction mixtures. The cage amines were characterized both as their picrate and/or hydrochloride salts, the proton and ^{13}C NMR spectra of which clearly indicated their C_s symmetry.

Cage amine **6a** was tested for antiviral activity as its hydrochloride salt and compared with 1-aminoadamantane hydrochloride. The method employed was a plaque reduction assay using the influenza virus A/Victoria/3/75. The assay was carried out as described by Tobita et al.,[5] using established cell monolayers prepared from canine kidney cells (MDCK) in the presence of trypsin. The results showed that, under conditions where 1-aminoadamantane hydrochloride (25 μg/mL) caused a two- to three-fold reduction in plaque formation, no significant reduction in plaque formation was observed in preparations containing similar concentrations of the hydrochloride salt of compound **6a**.

Cage amine **6a** was also found to be ineffective against the herpes simplex viruses HSV-1 and HSV-2. In these studies, compound **6a** (as its hydrochloride salt) was compared with 5-ethyl-2′-deoxyuridine.[6] The assay consisted of determining the inhibitory effect that the test compounds have on BHK-21 (baby hamster kidney) cell cultures infected with virus. Under conditions where ethyldeoxyuridine exhibited a 50% inhibitory dose (ID_{50}) of approximately 0.5 μg/mL, the hydrochloride salt of **6a** was found to be totally without inhibitory effect, even at concentrations at high as 25 μg/mL.

The functional groups present in ketols **4a** and **4b** should permit ready synthesis of unbridged amine derivatives of 1, and this aspect of the work is being pursued.[7]

Experimental Section

4α-Hydroxy-4aβ,5,8,8aβ-tetrahydronaphthalen-1(4*H*)-one (3a). Diels–Alder adduct **2a**[3] (500 mg, 3.05 mmol) was dissolved in 10 mL of methanol and the mixture was cooled in an ice bath.

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(7) The synthesis of several unbridged amine derivatives of 1 has been described in the patent literature: R. J. Stedman, *Chem. Abstr.*, **71**, 300 (1969) and **76**, 348 (1972). No antiviral activity data was reported for these compounds.

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Sodium borohydride (46.2 mg, 1.22 mmol) suspended in 2 mL of cold methanol was added slowly over a period of 10 min with stirring. After stirring of the reaction mixture at the temperature of the ice bath for 35 min, about 15 mL of water was added and the resulting pale yellow solution extracted with six 20-mL portions of chloroform. The combined extracts were washed with brine and dried over anhydrous sodium sulfate. Removal of the solvent and recrystallization of the residue from cyclohexane–benzene afforded 350 mg (70%) of hydroxynaphthalenone **3a**, mp 130–131 °C. Compound **3a** displayed the following spectral characteristics: IR (KBr) 3300 (OH), 1680 cm^{-1} (C=O); MS (parent), m/e 164; ^1H NMR ($CDCl_3$) δ 6.70 (m, 1 H, C(3) vinyl), 5.95 (dd, 1 H, J_1 = 10 Hz, J_2 = 2.5 Hz, C(2) vinyl), 5.70 (m, 2 H), 4.85–4.95 (m, 1 H), 2.60–2.95 (m, 3 H), 2.30 (s, 1 H, exchange with D_2O), 1.90–2.30 (m, 3 H).

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 72.90; H, 7.49.

10-*exo*-Hydroxytetracyclo[5.3.0.0.^{2,6}0^{4,9}]decan-3-one (4a). Naphthoquinonol **3a** (400 mg, 2.44 mmol) was dissolved in 350 mL of benzene and the resulting solution purged with nitrogen for 90 min. Internal irradiation (450-W Hanovia lamp, uranium glass filter, Pyrex immersion well) of **3a** was monitored by gas chromatography and stopped after 16 h, at which time less than 1% of **3a** remained. Benzene was removed under reduced pressure to afford a yellow oil, which was purified by silica gel column chromatography using ethyl acetate–petroleum ether (7:3) as eluent. In this way 356 mg (89%) of solid **4a** was isolated, which was recrystallized from petroleum ether–benzene to give colorless crystals: sealed tube mp 231–233 °C; IR (KBr) 3400 (OH), 1730 cm^{-1} (C=O); MS (parent), m/e 164; ^1H NMR δ 4.14 (br s, 1 H, C*H*OH), 3.16–3.05 (m, 1 H), 2.86–2.70 (m, 2 H), 2.60–2.50 (m, 2 H), 2.40–2.30 (m, 1 H), 2.14 (m, 2 H), 1.83–1.95 (m, 1 H), 1.58 (s, 1 H, exchange with D_2O), 1.40–1.30 (m, 1 H).

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 72.85; H, 7.42.

10-*exo*-Hydroxytetracyclo[5.3.0.0.^{2,6}0^{4,9}]decane 3-Ketoxime (5a). The tetracyclic keto alcohol **4a** (1.31 g, 8.0 mmol) was dissolved in 25 mL of methanol with stirring in a 100-mL round-bottomed flask. Hydroxylamine hydrochloride (2.63 g, 37.9 mmol) and potassium acetate (1.87 g, 19.1 mmol) were added to the solution with stirring, whereupon a white suspension was formed. The flask was then equipped with a reflux condenser and the suspension heated in an oil bath with stirring while water was introduced slowly until a clear colorless solution was obtained. After refluxing overnight, methanol was removed under reduced pressure and the oxime precipitated as a white solid, which was collected by filtration and washed thoroughly with water. The solid was dried in vacuo to give 972 mg of the desired oxime. The aqueous residue was extracted with four 20-mL portions of ethyl acetate, and the combined extracts were washed successively with dilute hydrochloric acid, saturated sodium bicarbonate solution, water, and brine and dried over anhydrous sodium sulfate. Removal of solvent under reduced pressure provided another 95 mg of oxime. The total yield was 1.07 g (75%). The crude oxime was recrystallized from a mixture of ethyl acetate and a small amount of ethanol, mp 209.5–211 °C. Oxime **5a** displayed the following spectral properties: IR (KBr) 3300 (OH), 1675 cm^{-1} (C=N); MS (parent), m/e 179; ^1H NMR (Me_2SO-d_6) δ 4.53 (br s, 1 H, exchange with D_2O), 3.67 (br s, 1 H), 3.46–3.33 (m, 1 H), 3.32 (s, superimposed on the multiplet, 1 H, exchange with D_2O), 2.84–2.48 (m, 4 H), 2.30 (d, 0.6 H, J = 10 Hz), 2.23 (d, 0.4 H, J = 10 Hz), 1.92 (two superimposed doublets, 1 H, J = 12 Hz), 1.74 (two superimposed doublets, 1 H, J = 12 Hz), 1.55 (m, 1 H), 0.90–0.80 (m, 1 H).

Anal. Calcd for $C_{10}H_{13}O_2N$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.20; H, 7.34; N, 7.76.

11-Azapentacyclo[6.2.1.0.^{2,7}0.^{4,10}0^{5,9}]decane (6a). Aluminum hydride was generated by the procedure of Yoon and Brown.[8] An oven-dried, two-necked, 50-mL, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and a reflux condenser attached to a dry nitrogen source was charged with 7.5 mL (2.52 M, 19 mmol) of lithium aluminum hydride solution in THF via a syringe. Sulfuric acid (100%; 503 μL, 9.5 mmol) was added dropwise over a period of 20 min while the solution was vigorously stirred in a cold water bath (5–10 °C) by means of a magnetic stirrer. Hydrogen was evolved with the precipitation of lithium sulfate. The resulting grey suspension was allowed to stir for another hour at room temperature. To this suspension at room temperature was added slowly 450 mg (2.5 mmol) of oxime **5a** dissolved in 20 mL of THF. Hydrogen was again evolved vigorously, and when it ceased, the reaction mixture was refluxed for 7 h. The excess hydride was quenched with 4 mL of 1:1 aqueous THF while the reaction mixture was cooled in a cold water bath (5–10 °C). This was followed by the addition of 10 mL of aqueous sodium hydroxide solution (3.75 M) at room temperature. The original voluminous precipitate coagulated to a smaller gelatinous mass. The THF layer was decanted and the aqueous phase extracted with three 15-mL portions of ether. The combined organic extracts were dried over anhydrous potassium carbonate and then filtered. Slow removal of solvent under reduced pressure gave a white solid, which was chromatographed on an alumina column (activity grade III) using methanol–chloroform (7:93) as eluent. The desired cage amine (110 mg, 30%) was isolated and proved to be homogeneous by gas chromatography. Compound **6a** displayed the following spectral characteristics: MS (parent), m/e 147; ^1H NMR (CD_3OD) δ 3.74 (br s, 2 H, C(1) and C(8) methines), 2.65 (br s, 4 H, C(2), C(7), C(9), and C(10) methines), 2.35 (br s, 2 H, C(4) and C(5) methines), 1.53 (d, 2 H, J = 12 Hz, C(3) and C(6) inner H's), 1.18 (br d, 2 H, J = 12 Hz, C(3) and C(6) outer H's).

Picrate of Compound 6a. To 77 mg (0.52 mmol) of **6a** in 2 mL of chloroform was added 4 mL of picric acid solution (prepared by dissolving 1 g of picric acid in 15 mL of benzene followed by drying over anhydrous calcium chloride). After the mixture stood at room temperature for 1–2 min, bright yellow needles precipitated. The mixture was kept in the refrigerator overnight, after which 158 mg (80%) of picrate, mp 228.5–230 °C, was obtained by filtration. The picrate of **6a** displayed the following spectral characteristics: IR (KBr) 2900 (secondary amine salt), 1320 cm^{-1} (NO_2); ^1H NMR (Me_2SO-d_6) δ 8.80–8.60 (m, 2 H, NH_2), 8.56 (s, 2 H, aromatics), 4.09 (s, 2 H, C(1) and C(8) methines), 2.82 (s, 2 H, C(2) and C(7) or C(9) and C(10) methines), 2.68 (s, 2 H, C(2) and C(7) or C(9) and C(10) methines), 2.58 (s, 2 H, C(4) and C(5) methines), 1.56 (d, 2 H, J = 13.5 Hz, inner C(3) and C(6) H's), 1.19 (br d, 2 H, J = 13.5 Hz, outer C(3) and C(6) H's); ^{13}C NMR (Me_2SO-d_6) δ 24.1 (C(3) and C(6)), 33.8 (C(4) and C(5)), 39.7 (C(2) and C(7) or C(9) and C(10)), 40.7 (C(2) and C(7) or C(9) and C(10)), 64.0 (C(1) and C(8)).

Anal. Calcd for $C_{16}H_{16}N_4O_7$: C, 51.07; H, 4.29; N, 14.89. Found: C, 50.99; H, 4.35; N, 15.00.

Hydrochloride Salt of Compound 6a. The picrate of cage amine **6a** (890 mg, 2.37 mmol) was suspended in 7 mL of chloroform in a 60-mL separatory funnel, 2 g (83.3 mmol) of lithium hydroxide and 15 mL of water were added, and the contents were mixed thoroughly. The organic phase was removed and the aqueous phase was extracted with three 15-mL portions of chloroform. The organic extracts were combined and dried over anhydrous sodium sulfate and filtered. Dry hydrogen chloride gas was bubbled through the solution until the pH was less than 2 as indicated by pH paper. Chloroform was removed under reduced pressure, whereupon a pale yellow solid was obtained, which was redissolved in 10 mL of methanol and treated with a small amount of Norit. Removal of Norit and solvent gave 376 mg (87%) of the hydrochloride as a white solid. Recrystallization from cyclohexane–ethanol afforded white needles: mp 250 °C dec; IR (KBr) 2900 cm^{-1} (secondary amine salt); MS (parent), m/e 147; ^1H NMR ($CDCl_3$) δ9.69 (m, 2 H, NH_2), 4.12 (s, 2 H, C(1) and C(8) methines), 3.10 (s, 2 H, C(2) and C(7) or C(9) and C(10) methines), 2.91 (s, 2 H, C(2) and C(7) or C(9) and C(10) methines), 2.77 (s, 2 H, C(4) and C(5) methines), 1.62 (d, 2 H, J = 13 Hz, inner C(3) and C(6) H's), 1.25 (d, 2 H, J = 13 Hz, outer C(3) and C(6) H's); ^{13}C NMR ($CDCl_3$) δ 64.6 C(1) and C(8)), 41.2 (C(2) and C(7) or C(9) and C(10)), 40.2 (C(2) and C(7) or C(9) and C(10)), 34.4 (C(4) and C(5)), 24.7 (C(3) and C(6)).

Anal. Calcd for $C_{10}H_{14}NCl$: C, 65.39; H, 7.68; N, 7.63. Found: C, 65.51; H, 7.59; N, 7.57.

4α-Hydroxy-6,7-dimethyl-4aβ,5,8,8aβ-tetrahydronaphthalen-1(4*H*)-one (3b). A 50-mL, round-bottomed flask

(8) N. M. Yoon and H. C. Brown, *J. Am. Chem. Soc.*, **90**, 2927 (1968).

was charged with 2.17 g (11.4 mmol) of Diels–Alder adduct **2b**[4] and 30 mL of methanol. The mixture was stirred magnetically, and a pale yellow suspension was formed. To the stirred mixture cooled in an ice bath was added slowly sodium borohydride (173 mg, 4.55 mmol) suspended in 4 mL of ice-cold methanol over a period of 5 min with vigorous stirring. After the mixture was stirred for 1 h at ice bath temperature, 2 mL of saturated ammonium chloride solution was added, and the reaction mixture was allowed to warm to room temperature; a light brown solution was obtained. The methanol was removed under reduced pressure and the residue transferred to a separatory funnel with the aid of about 30 mL of water and a small amount of chloroform. Extraction was carried out with seven 30-mL portions of chloroform, and the combined extracts were washed successively with water and dried over anhydrous sodium sulfate. Filtration and removal of solvent in vacuo afforded a pale yellow solid, which was recrystallized from cyclohexane–ethyl acetate. This provided the hydroxynaphthalenone **3b** as white needles (1.56 g, 71%): mp 122–122.5 °C; IR (KBr) 3300 (OH), 1685 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.59 (s, 3 H, C(6) or C(7) methyl), 1.66 (s, 3 H, C(6) or C(7) methyl), 1.91 (s, 1 H, exchange with D_2O), 1.88–2.28 (m, 3 H), 2.50–2.90 (m, 3 H), 4.82–5.02 (m, 1 H, C*H*OH), 5.99 (dd, 1 H, J_1 = 10 Hz, J_2 = 2 Hz, C(2) vinyl), 6.71 (m, 1 H, C(3) vinyl).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.14; H, 8.44.

6,7-Dimethyl-10-*exo*-hydroxytetracyclo[5.3.0.0.^{2,6}0^{4,9}]decan-3-one (4b). A solution of naphthoquinonol **3b** (1.16 g, 6.04 mmol) in 500 mL of benzene was purged with nitrogen for 90 min and irradiated as before. After 3.5 h, less than 1% of starting material **3b** remained as shown by gas chromatography. Removal of benzene under reduced pressure afforded a yellow oil, which was purified by silica gel column chromatography (1:1 ethyl acetate–petroleum ether). This afforded a white solid (0.83 g, 71%), which upon recrystallization from petroleum ether and a small amount of ethyl acetate, gave colorless cubes: sealed tube mp 194–196 °C; IR (KBr) 3400 (OH), 1730 cm^{-1} (C=O); MS (parent), *m/e* 192; ^1H NMR ($CDCl_3$) δ 1.05 (dd, 1 H, J_1 = 12.5 Hz, J_2 = Hz), 1.14 (s, 3 H, C(6) or C(7) methyl), 1.29 (s, 3 H, C(6) or C(7) methyl), 1.59 (s, 1 H, exchange with D_2O), 1.73 (dd, 1 H, J_1 = 12.5 Hz, J_2 = 3 Hz), 2.05 (d, 1 H, J = 13 Hz), 2.17 (d, 1 H, J = 13 Hz), 2.18 (dd, 1 H, J_1 = 9 Hz, J_2 = 2.5 Hz), 2.30 (dd, 1 H, J_1 = 9 Hz, J_2 = 2.5 Hz), 2.38 (m, 1 H), 2.50 (m, 1 H), 4.06 (br s, 1 H, C*H*OH).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.07; H, 8.50.

6,7-Dimethyl-10-*exo*-hydroxytetracyclo[5.3.0.0.^{2,6}0.^{4,9}]decane 3-(*O*-Methylketoxime) (5b). The tetracyclic keto alcohol **4b** (318 mg, 1.66 mmol) was dissolved in 5 mL of methanol in a 50-mL, round-bottomed flask. Methoxyamine hydrochloride (1.11 g, 13.25 mmol) and potassium acetate (650 mg, 6.63 mmol) were added to the above solution with stirring, whereupon a heavy suspension was formed. The flask was then equipped with a reflux condenser and the suspension heated with stirring with slow addition of water until a clear, colorless solution was formed. This solution was refluxed for 20 h. After cooling of the reaction mixture to room temperature, the methanol was removed under reduced pressure and the residue was diluted with water and extracted with four 20-mL portions of ethyl acetate. The combined extracts were washed with water and brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to afford a yellow oil. Purification by distillation using a Kugelrohr oven (140 °C (0.1 mmHg)) gave 337 mg (92%) of the oxime ether **5b** as a colorless oil: IR (film) 1650 (C=N), 3375 cm^{-1} (OH); MS (parent), *m/e* 221; ^1H NMR ($CDCl_3$) δ 0.84 (dd, 0.5 H, J_1 = 6 Hz, J_2 = 3 Hz), 0.87 (dd, 0.5 H, J_1 = 6 Hz, J_2 = 3 Hz), 1.02 (s, 3 H, C(6) or C(7) methyl), 1.23 (s, 3 H, C(6) or C(7) methyl), 1.40–1.60 (m, 1 H, exchange with D_2O), 1.54 (dd, 1 H, J_1 = 13 Hz, J_2 = 3 Hz), 1.82 (dd, 1 H, J_1 = 13 Hz, J_2 = 3 Hz), 1.95–2.04 (m, 1 H), 2.23 (m, 1 H), 2.41 (m, 0.5 H), 2.47 (m, 0.5 H), 2.53 (dd, 0.5 H, J_1 = 9 Hz, J_2 = 2.5 Hz), 2.73 (m, 0.5 H), 3.12 (dd, 0.5 H, J_1 = 9 Hz, J_2 = 2.5 Hz), 3.45 (m, 0.5 H), 3.77–3.82 (2 sharp s, ratio = 1:1, total 3 H, 2 nonequivalent O-methyls), 3.97 (2 s, 1 H, C*H*OH).

4,5-Dimethyl-11-azapentacyclo[6.2.1.0.^{2,7}0.^{4,10}0^{5,9}]decane (6b) Picrate. The procedure followed was exactly the same as that used in the preparation of cage amine **6a**. The crude reaction mixture was purified by alumina column chromatography (activity grade III) using methanol–chloroform (8:92) as eluent to afford 30 mg (21%) of **6b** as a white solid. This was immediately dissolved in 2 mL of chloroform and a solution of 60 mg (0.26 mmol) of dry picric acid in 1 mL of benzene was added. The picrate precipitated as yellow needles: mp 262–265 °C; IR (KBr) 2950 (secondary amine salt), 1320–1360 cm^{-1} (NO_2); ^1H NMR (Me_2SO-d_6) δ 1.05 (d, 2 H, J = 12 Hz, outer C(3) and C(6) H's), 1.16 (s, 6 H, C(4) and C(5) methyls), 1.57 (d, 2 H, J = 12 Hz, inner C(3) and C(6) H's), 2.40 (s, 2 H, C(2) and C(7) or C(9) and C(10) methines), 2.56 (s, 2 H, C(2) and C(7) or C(9) and C(10) methines), 4.16 (br s, 2 H, C(1) and C(8) methines), 8.57 (s, 2 H, aromatics), 8.55–8.75 (br m, 2 H, exchange with D_2O, NH_2).

Anal. Calcd for $C_{18}H_{20}N_4O_7$: C, 53.46; H, 4.99; N, 13.85. Found: C, 53.26; H, 4.79; H, 13.63.

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Registry No. **2a**, 35043-92-6; **2b**, 35774-01-7; **3a**, 74069-53-7; **3b**, 74069-54-8; **4a**, 74069-58-2; **4b**, 74069-63-9; *syn*-**5a**, 95617-28-0; *anti*-**5a**, 95721-13-4; *syn*-**5b**, 95617-29-1; *anti*-**5b**, 95721-14-5; **6a**, 95617-30-4; **6a**·picrate, 95617-31-5; **6a**·HCl, 95617-32-6; **6b**, 95617-33-7; **6b**·picrate, 95617-34-8.