58.3%), which was identical with the sample obtained from 11 by mixed melting points, IR, and ^1H NMR comparisons. The second fraction gave 2-*exo*-hydroxy-4-*endo*-(methylbenzylamino)protoadamantane (**15**) as crystals (14 mg, 13.6%), mp 126–127 °C (MeOH–ether).

***endo*-Bicyclo[3.3.1]non-6-ene-3-carboxaldehyde (16).** This aldehyde **16** was previously reported by us.[18] The following improved procedure raised the yield to 82% from 53%. To a cooled (−10 to −15 °C) and stirred solution of $NaBH_4$ (110 mg, 2.91 mmol) in methanol (20 mL) and water (5 mL) was added 4(e)-(methylsulfonoxy)adamantan-2-one[27] (1.00 g, 4.00 mmol). After the stirring was continued for 2 h (the reaction was monitored by TLC, silica gel–$CHCl_3$), the remaining $NaBH_4$ was decomposed by addition of acetic acid (0.5 mL). The reaction temperature was allowed to come up to room temperature, and the mixture was concentrated to ca. 10 mL under reduced pressure. After addition of 1% aqueous $NaHCO_3$ (30 mL) and ether (20 mL), the two-phase mixture was heated under reflux for 2 h. After cooling, the organic layer was separated, and the aqueous layer was extracted with ether (10 mL × 2). The combined organic layer and extracts were dried (Na_2SO_4) and evaporated to give crude aldehyde, which was chromatographed on a silica gel column (CH_2Cl_2) to afford the aldehyde **16** as a colorless solid (495 mg, 82.4%), mp 185–188 °C (lit.[18] oil).

General Procedure for Generation and Cycloaddition of *endo*-Bicyclo[3.3.1]non-6-en-3-ylnitrones (17a–e). A mixture of the aldehyde **16** (150 mg, 1.00 mmol), an appropriate hydroxylamine (**2a–e**, 1.10 mmol; for **2c** and **2d**, the hydrochlorides were freed with Et_3N before use) and a molecular sieve (type 4A or 3A, 0.5 g) was stirred in a selected solvent (3 mL). The intramolecular cycloaddition of thus generated nitrones **17a–e** proceeded at 25–80 °C. The molecular sieve was filtered and washed with the solvent used. The combined filtrate and washings were evaporated to dryness to give a crude product, which was purified by chromatography on a silica gel and/or an alumina column (*n*-hexane–CH_2Cl_2–MeOH system). The reaction conditions and results are summarized in Table I. The products had the following melting points: **18a**, 84–85 °C (*n*-hexane); **19a**, 57–58 °C (*n*-hexane); **20a**, 97–98 °C (*n*-hexane–CH_2Cl_2); **18b**, oil; 19b, oil; **20b**, 111–112 °C (*n*-hexane-CH_2Cl_2); **18c**, oil; **19c**, oil; **18d**, 155–156 °C (*n*-hexane–CH_2Cl_2); **19d**, 179–180 °C (*n*-hexane–CH_2Cl_2); **18e**, 72–74 °C (ether); **19e**, 46–48 °C (sublimed at 100–120 °C (15 mmHg)). The spectral and analytical data are given in Tables II and III.

General Procedures for Reductive Cleavage of 4-Aza-5-oxatetracyclo[6.3.1.$0^{2,6}$.$0^{3,10}$]dodecane (18a-e) and 3-Aza-4-oxatetracyclo[6.3.1.$0^{2,6}$.$0^{5,10}$]dodecane (19a-e). (A) With H_2–Pd–C. The adduct **18a** (40 mg, 0.17 mmol) was hydrogenated in methanol (5 mL) with 10% Pd–C (90 mg) under an atmosphere of hydrogen for 3 h at room temperature. The usual workup after removal of the catalyst through Celite and chromatography (alumina, CH_2Cl_2) gave the amino alcohol **21a** as a colorless oil (24 mg, 58%). Similarly **19a** gave **20a** (26 mg, 62%).

(B) With Zinc–AcOH. The adduct **18b** (28 mg, 0.11 mmol) was stirred with zinc dust (30 mg) in 58% (v/v) aqueous AcOH (1.2 mL) at 50–60 °C for 2 h. The usual workup with 20% aqueous KOH and extraction with $CHCl_3$ gave the amino alcohol **21b** after chromatography (silica gel–CH_2Cl_2) as a colorless oil (18 mg, 64%).

(C) With H_2–PtO_2. The adduct (**18c–e** and **19c–e**, 0.20 mmol) was hydrogenated in ethanol (2 mL) and AcOH (0.5 mL) under an atmosphere of hydrogen for 3–24 h at room temperature by using PtO_2 (10–20 mg) as the catalyst. After removal of the catalyst by filtration through Celite, the filtrate was evaporated to dryness to give a residue which was applied to chromatography (alumina, CH_2Cl_2–AcOEt) to afford the corresponding amino alcohols: **21c** as an oil (75.0%), HCl salt, mp 277–278 °C; **20c** as an oil (79.3%), HCl salt, mp 272–275 °C; **21d** (91.4%), mp 133–135 °C (*n*-hexane–ether); **20d** (87.3%), mp 181–183 °C (*n*-hexane–ether); **21e** (69.5%), mp 81–82 °C (*n*-hexane–CH_2Cl_2); **20e** (72.2%), mp 79–81 °C (*n*-hexane–CH_2Cl_2).

(D) Thermal Reductive Cleavage. A solution of **19b** (8 mg) in toluene (2 mL) was heated at 120 °C for 10 h in a sealed tube under an atmosphere of argon. Removal of the solvent and chromatography (alumina, $CHCl_3$) gave the amino alcohol **20b** (6 mg, 75%). The spectral and analytical data of these amino alcohols are given in Tables II and III.

2(a)-Hydroxy-4(a)-(phenylamino)adamantane (20a) from 2(a)-Hydroxyadamantan-2-one (22). A mixture of **22**[19] (84 mg, 0.50 mmol), aniline (465 mg, 5.00 mmol), and $NaBH_3CN$ (32 mg, 0.50 mmol) in methanol (5 mL) was stirred at room temperature for 3 days at pH ca. 3 (the pH was controlled by addition of MeOH–concentrated HCl (1:1).[28] The basified mixture by addition of 20% aqueous KOH was extracted with CH_2Cl_2 (8 mL × 5). The combined extracts were dried ($MgSO_4$) and evaporated to afford a solid residue, which was chromatographed (silica gel, CH_2Cl_2–MeOH) to afford the amino alcohol **20a** (61 mg, 50.2%). This sample was identical with those obtained from the cycloaddition of **17a** and the reductive cleavage of **19a** by IR and ^1H NMR comparisons.

Supplementary Material Available: IR, ^1H NMR, and mass spectral and analytical data of the nitrone cycloadducts **3**, **9**, and **17** and related amino alcohols (Table III) (4 pages). Ordering information is given on any current masthead page.

Sulfurization of 2-Aminobenzotrifluoride with Sodium Sulfide

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Sodium sulfide in dimethyl sulfoxide reacts with 2-aminobenzotrifluoride to form 2-(2-aminophenyl)-4*H*-3,1-benzothiazine-4-thione and 2,1-benzisothiazoline-3-thione. The addition of CS_2 gave 2*H*-3,1-benzothiazine-2,4(1*H*)-dithione. N-Substituted 2-aminobenzotrifluorides gave the corresponding substituted 2,1-benzisothiazoline-3-thiones. The reaction conditions and possible mechanism are discussed.

Aromatic trifluoromethyl groups, activated by electron-donating moieties such as amino or hydroxyl, have been shown to undergo hydrolysis with aqueous sodium hydroxide to form the corresponding carboxylic acids.[1] More recently,[2] there have been reports of reactions of aromatic trifluoromethyl groups with oxygen and nitrogen nucleophiles. These reports have prompted us to describe the reactions we have observed involving 2-aminobenzotrifluorides with sodium sulfide.

When 2-aminobenzotrifluoride (**1a**), was treated with sodium sulfide in refluxing Me_2SO, a red solution was formed with the disappearance of **1a** (Scheme I). Upon acidification, a red, highly crystalline solid, mp 153–154 °C, was obtained. Spectral data suggested that instead

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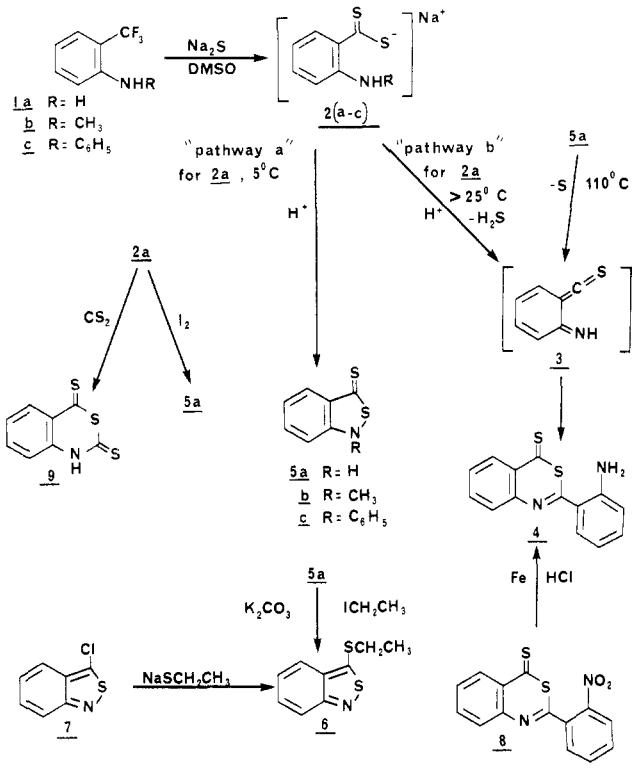
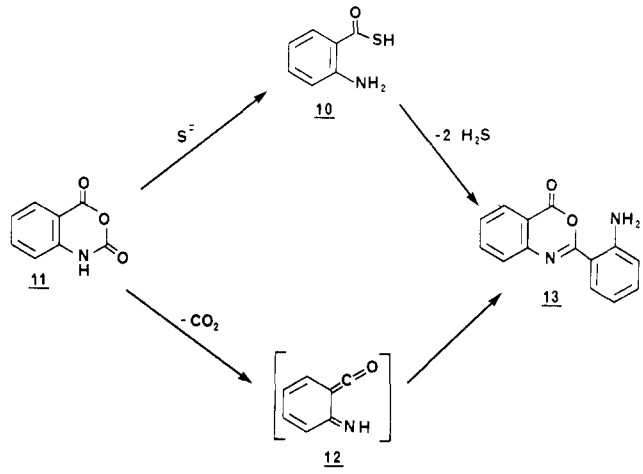
0022-3263/82/1947-5255$01.25/0

Scheme I



Scheme II



of the expected dithiocarboxylic acid, 2-(2-aminophenyl)-4*H*-3,1-benzothiazine-4-thione (**4**), had been isolated. The structure of **4** was identical with the material obtained by the iron–hydrochloric acid reduction[3] of **8**, which was prepared according to Legrand's procedure.[4]

When the acidification of the reaction mixture was carried out at lower temperatures (5 °C), a new material, 2,1-benzisothiazoline-3-thione (**5a**), was isolated in addition to **4**. The structure of **5a** was determined by spectral methods and by conversion to **6** with ethyl iodide. Compound **6** was identical with the product from the reaction of 3-chloro-2,1-benzisothiazole (**7**) and ethanethiol.[5] The NMR, IR, and UV spectra of **5a** support this tautomeric form. During the melting point determination of **5a** it was observed that the yellow-orange crystals formed a red melt and that H_2S could be detected at the melting point of 106–107 °C. Examination of the capillary contents by TLC (CH_2Cl_2) revealed that **5a** had been converted to **4** plus elemental sulfur. Compound **5a** was also synthesized directly from **2a** by cyclization with I_2.

The sodium salts of enamino dithiocarboxylates similar to **2a** are reported to react with carbon disulfide to give thiazine dithiones.[6] The addition of carbon disulfide to **2a** gave 2*H*-3,1-benzothiazine-2,4(1*H*)-dithione (**9**)[7] as the product.

Having substantiated, by the preparation of known derivatives, that the sulfurization of the trifluoromethyl groups resulted in the formation of a dithiocarboxylate entity, we extended the reaction to N-substituted 2-aminobenzotrifluorides **1b,c**. Under identical reaction conditions, the products isolated upon acidification were **5b**, having spectral properties and melting point identical with literature values,[5,8] and **5c**, having a melting point 10 °C higher than the reported value,[8] but the spectral measurements supported the proposed structure.

Table I. Yields of 4 and 5a as a Function of Temperature during Acidification of 2a

run	temp, °C	yield of 4, %	yield of 5a, %
a	85	82	3
b	25	74	11
c	5	59	33

Discussion of Mechanism

The reactions of **1a–c** with sodium sulfide appear to initially follow a mechanism similar to that proposed for the hydrolysis of 2-aminobenzotrifluoride[2] (e.g., the displacement of fluoride by sulfide ion to form the sodium 2-aminodithiocarboxylates **2a–c**).

Upon acidification of **2a–c**, the resulting dithiocarboxylic acid is converted to a more stable form either by cyclization (Scheme I, pathway a) or, in the case of **2a**, by decomposition (pathway b). The cyclization to the corresponding 2,1-benzisothiazoline-3-thiones is spontaneous and does not require the deliberate addition of an oxidizing agent, although ambient oxygen and/or Me_2SO from the reaction may be contributing to this reaction.

Thioanthranilic acid (**10**), prepared by the reaction of isotoic anhydride (**11**) and potassium sulfide (Scheme II), has been shown to convert to **13** upon standing via the loss of hydrogen sulfide and subsequent self acylation.[9] The formation of **4** (Scheme I, pathway b) can likewise be explained by this mechanism. The elimination of H_2S gives the imino thioketene **3**, which through self-condensation gives **4**. Analogous iminoketenes **12** have also been postulated as intermediates in the thermal decomposition of isotoic anhydride (**11**) to the benzoxazine (**13**)[10] and in the flash thermolysis of methyl anthranilate.[11]

The isolation of increasing amounts of **5a** at lower temperatures during the acidification of **2a** (Table I) reflects the increased stability of the dithiocarboxylic acid, apparently permitting cyclization to compete with decomposition. The decomposition of **5a**, by the extrusion of sulfur at its melting point to give **4**, can also be explained

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through the imino thioketene pathway.

In summary, the reactions of 2-aminobenzotrifluorides with sodium sulfide constitute a novel synthetic approach to derivatives of dithiocarboxylates. The product distribution obtained from these reactions is dependent upon the stability of the resulting dithio acid as determined either by the temperature of the reaction at workup or by substituents on the amino function.

Experimental Section

Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. NMR spectra were taken on a Bruker Model WM 250 spectrometer, and IR spectra were obtained with a Pye Unicam Model SP3-200A spectrometer. Mass spectra were obtained with a Hewlett-Packard 5985 GC/MS, and UV spectra were recorded with a Cary Model 118 spectrophometer.

Low-pressure chromatographic separations were achieved by utilizing Michel-Miller columns (Ace Glass) packed with Silica Woelm DCC. Solvent delivery to the columns was with a Fluid Metering Inc. Lab Pump.

Reagent grade $Na_2S·9H_2O$ (Baker) was recrystallized from ethanol, and Me_2SO (Fisher) and 2-aminobenzotrifluoride (Aldrich) were used as purchased. Whatmann IPS disposable phase separators were used to separate and dry organic solutions.

Procedure for Reaction of 2-Aminobenzotrifluoride (1a) with $Na_2S·9H_2O$ To Give 2a as a Me_2SO Solution. To a stirring solution of **1a** (1.61 g, 0.01 mol) in Me_2SO (15 mL) was added $Na_2S·9H_2O$ (5.25 g, 0.022 mol). The resulting mixture was heated under reflux (135 °C) for 30 min and then allowed to cool to room temperature. The NaF which precipitated during the reaction was separated by filtration and washed with fresh Me_2SO (5–10 mL).

2-(2-Aminophenyl)-4*H*-3,1-benzothiazine-4-thione (4). The Me_2SO solution of **2a** (0.01 mol), as described above, was diluted with water (50 mL), and the resulting solution was heated to 85 °C (steam bath) while stirring vigorously with a mechanical stirrer. The pH of this solution was then adjusted to 3.0 by using 2 N HCl. Within 5 min, 4 precipitated as red-orange crystals, which were collected and dried to give 1.2 g (89%). Recrystallization from ethyl acetate–hexane gave 1.1 g (82%) of **4**: mp 153–154 °C; mass spectrum, *m/e* 270 (M^+); ^1H NMR ($CDCl_3$) δ 6.45 (br s, 2 H), 6.69–6.75 (t, 2 H), 7.23 (t, 1 H), 7.46 (t, 1 H), 7.65–7.72 (d, 2 H), 7.77 (t, 1 H), 8.75 (d, 1 H); IR (Nujol) 3280, 3420 (NH_2) cm^{-1}.

Anal. Calcd for $C_{14}H_{10}N_2S_2$: C, 62.19; H, 3.73; N, 10.36. Found: C, 62.42; H, 3.62; N, 10.40.

Mixtures of **4** and **5a** were obtained from this procedure when the temperature during acidification was lowered (Table I). The two products were separated by chromatography (silica gel) with CH_2Cl_2 to elute **4** and EtOAc to elute **5a**.

2,1-Benzisothiazoline-3-thione (5a). The Me_2SO solution of **2a** (0.01 mol), as described above, was diluted with water (100 mL), and to it was added K_2CO_3 (1.51 g, 0.011 mol). The resulting solution was cooled to 0 °C with an ice bath. To this solution, with vigorous stirring, was added over 0.5 h a solution of I_2 (2.79 g, 0.01 mol) dissolved in ethanol (50 mL). After the mixture stirred at 25 °C for 18 h, the pH was adjusted to 2.5 with 2 N HCl, and then the mixture was extracted with Et_2O (2 × 100 mL). The combined Et_2O portions were filtered through phase-separating filter paper and evaporated in vacuo. The residue was chromatographed (silica gel, EtOAc) to give 1.2 g (72%) of pure **5a**. Recrystallization from dichloromethane–hexane gave yellow-orange crystals: mp 106–107 °C; mass spectrum, *m/e* 167 (M^+); ^1H NMR ($CDCl_3$) δ 7.18 (t, 1 H), 7.73 (d, 1 H), 7.57 (t, 1 H), 7.8 (br s, 1 H, NH), 8.02 (d, 1 H); UV (90% EtOH) λ_{max} 210 nm (sh, log ε 4.11), 245 (4.18), 287 (4.83), 305 (sh, 3.48), 422 (4.05); IR (Nujol) 3120 (NH) cm^{-1}.

Anal. Calcd for $C_7H_5NS_2$: C, 50.27; H, 3.01; N, 8.37; S, 38.34. Found: C, 49.98; H, 2.79; N, 8.47; S, 38.44.

2*H*-3,1-Benzothiazine-2,4(1*H*)-dithione (9). The Me_2SO solution of **2a** (0.01 mol), as prepared above, was cooled to 0 °C with an ice bath, and then CS_2 (3.04 g, 0.04 mol) was added dropwise and the solution stirred for 30 min. The reaction was diluted with water (450 mL) and the resulting precipitate collected and dried. Recrystallization from acetone gave 1.5 g (71%) of **9** as dark red crystals, mp 236–237 °C (lit.[7] mp 238–240 °C). Mass spectrum, *m/e* 211 (M^+); ^1H NMR (Me_2SO-d_6) δ 7.36 (t, 1 H), 7.49 (d, 1 H), 7.82 (t, 1 H), 8.24 (d, 1 H); IR (Nujol) 3135 (NH) cm^{-1}.

Anal. Calcd for $C_8H_5NS_3$: C, 45.47; H, 2.38; N, 6.63; S, 45.52. Found: C, 45.63; H, 2.59; N, 6.68; S, 45.30.

3-(Ethylthio)-2,1-benzisothiazole (6). To a stirring solution of **5a** (1.30 g, 0.0078 mol) in aqueous ethanol (50 mL, 1:1) was added K_2CO_3 (1.07 g, 0.0078 mol), followed by ethyl iodide (1.21 g, 0.0078 mol). The resulting solution was stirred at 25 °C for 1 h. The ethanol was then evaporated in vacuo, and the oil, which separated from the water, was extracted with dichloromethane. The combined extracts were filtered through phase-separating paper and evaporated in vacuo. The residue was chromatographed (silica gel, 3:2 pentane–dichloromethane) to give 1.5 g (98%) of yellow oil: mass spectrum, *m/e* 195 (M^+); NMR ($CDCl_3$) δ 1.37 (t, 3 H), 3.07 (q, 2 H), 7.17 (t, 1 H), 7.38 (t, 1 H), 7.68 (d, 1 H), 7.73 (d, 1 H); UV (90% EtOH) λ_{max} 208 nm (sh, log ε 4.13), 228 (4.32), 293 (3.79), 304 (3.83), 353 (3.85).

Anal. Calcd for $C_9H_9NS_2$: C, 55.35; H, 4.65; N, 7.17; S, 32.83. Found: C, 55.61; H, 4.39; N, 7.32; S, 32.91.

Thermal Conversion of 5a to 4. The $CDCl_3$ was evaporated from the NMR sample of **5a** (ca. 50 mg) with a nitrogen stream. The residue remaining in the tube was then heated in an oil bath (105–110 °C) until the conversion of **5a** (R_f 0.38) to **4** (R_f 0.95) was completed as followed by TLC (9:1 CH_2Cl_2-EtOAc). After cooling, the red residue was dissolved in $CDCl_3$, and the NMR spectrum obtained was identical with that of **4**.

General Procedure for the Preparation of N-Substituted 2,1-Benzisothiazoline-3-thiones. To a stirring solution of 0.01 mol of the appropriate N-substituted aminobenzotrifluoride (**1b,c**)[12] in 15 mL of Me_2SO was added $Na_2S·9H_2O$ (5.25 g, 0.022 mol). Each reaction was then heated under reflux (130–140 °C). After 15 min an aliquot was removed, diluted into water, and extracted with CH_2Cl_2. Heating was discontinued when TLC of the CH_2Cl_2 extract suggested none of the starting benzotrifluoride remained. After the reactions cooled, the NaF was separated by filtration and washed with fresh Me_2SO. The Me_2SO filtrate was then diluted with water (50 mL), the pH adjusted to 3.5 with 2 N HCl, and the mixture extracted with CH_2Cl_2 (2 × 75 mL). The combined extracts were filtered through phase-separating paper and stirred at 25 °C for 18 h. The CH_2Cl_2 was allowed to evaporate, and the products were isolated by chromatography.

1-Methyl-2,1-benzisothiazoline-3-thione (5b). Isolation was accomplished by chromatography (silica gel, 3:2 hexane–dichloromethane) to give 0.6 g (33%) of **5b**. Recrystallization from dichloromethane–hexane gave orange crystals, mp 138–139 °C (lit.[8] mp 139 °C); mass spectrum, *m/e* 181 (M^+); NMR ($CDCl_3$) δ 3.63 (s, 3 H), 7.15 (t, 1 H), 7.23 (d, 1 H), 7.63 (t, 1 H), 8.06 (d, 1 H); UV (90% EtOH) λ_{max} 210 nm (sh, log ε 4.08), 253 (4.22), 290 (3.81), 312 (3.24), 437 (4.11), 445 (4.10).

Anal. Calcd for $C_8H_7NS_2$: C, 53.01; H, 3.89; N, 7.73; S, 35.38. Found: C, 52.80; H, 3.88; N, 7.74; S, 35.56.

1-Phenyl-2,1-benzisothiazoline-3-thione (5c). Purification was achieved by chromatography (silica gel, 3:2 dichloromethane–hexane) to give 1.23 g (50%) of pure **5c** as a red oil. Crystallization from MeOH gave orange crystals: mp 59–60 °C (lit.[8] mp 50 °C); mass spectrum, *m/e* 243 (M^+); NMR ($CDCl_3$) δ 7.18 (t, 1 H), 7.28 (d, 1 H), 7.38–7.62 (m, 6 H), 8.12 (d, 1 H).

Anal. Calcd for $C_{13}H_9NS_2$: C, 64.16; H, 3.73; N, 5.76; S, 26.35. Found: C, 63.92; H, 3.58; N, 5.79; S, 26.06.

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Registry No. **1a**, 88-17-5; **1b**, 14925-10-1; **1c**, 14925-11-2; **2a**, 83816-88-0; **4**, 83816-86-8; **5a**, 83816-87-9; **5b**, 23310-52-3; **5c**, 23310-50-1; **6**, 67943-94-6; **9**, 16081-97-3; $Na_2S·9H_2O$, 1313-84-4; ethyl iodide, 75-03-6.

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