Synthesis of Substituted 3-Amino[6,5-*b*]triazinoindoles

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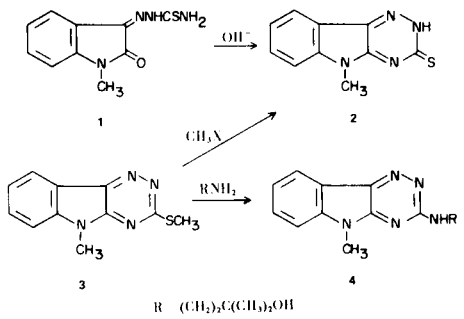
4-[(9-Methyl-*as*-triazino[6,5-*b*]indol-3-yl)amino]-2-methyl-2-butanol (**13**) and the corresponding 2-methyl-3-imino derivative **12** were synthesized and tested *in vitro* against Rhino 2 virus. The two compounds were more active than the known triazino[5,6-*b*]indole **4**. 2,9-Dimethyl-3-methoxy-9*H*-*as*-triazino[6,5-*b*]indolium tosylate (**21**) and the related 3-methylthio compound **9** were prepared. Quaternary **21** formed a pseudo base, **22a**, whereas quaternary **9** did not form a pseudo base.

Reports of the *in vitro* (1) and possible *in vivo* (2) antiviral activity of the 2-amino[5,6-*b*]triazinoindole **4** (Scheme I) and related substances prompted the synthesis and evaluation of the corresponding derivative **13** (Scheme II) of the closely related 3-amino[6,5-*b*]triazinoindole ring system. The [5,6-*b*] ring system has been prepared by cyclization of 1-methylisatin-3-thiosemicarbazone (**1**) to the thioamide **2** (Scheme I) (3). *S*-Methylation of **2** followed by displacement of methyl mercaptan from **3** by the appropriate aminoalcohol yielded **4** (3).

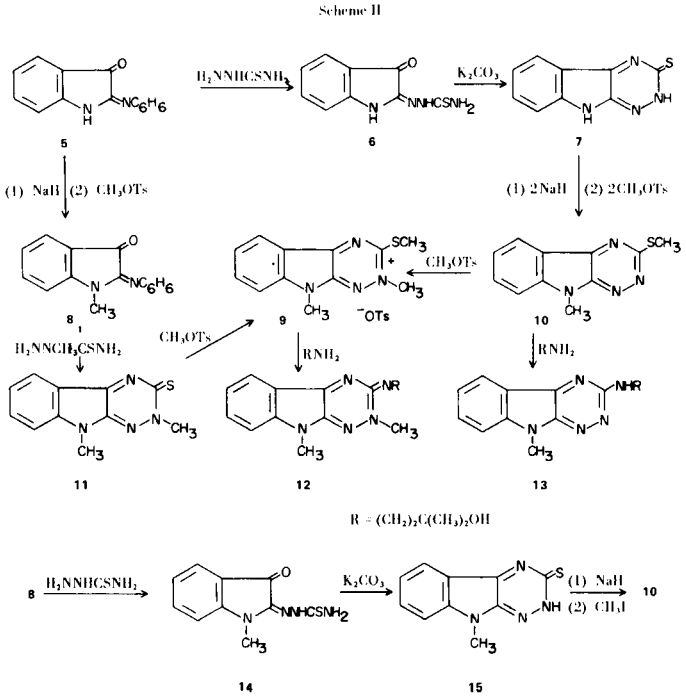
Scheme I



To obtain the [6,5-*b*] ring system isatin-2-thiosemicarbazone (**6**) was required. The report (4) that 2-anilinoisatin (**5**) and semicarbazide react to give isatin-2-semicarbazone rather than isatin-3-semicarbazone directed our attention to this anil as a possible useful intermediate. It proved to be readily available as reported (5). Condensation with thiosemicarbazide yielded the desired **6**. The remaining steps to **13** were uneventful except the final step **10** → **13** which proved to be slow by comparison with the conversion **3** → **4**. Alkylation of **10** with methyl tosylate in the hope of obtaining a sulfonium salt, which would have been more reactive than **10** toward displacement by amines, yielded instead the quaternary **9**. It underwent displacement of methyl mercaptan by amines to give 3-iminotriazinoindoles, for example **12**. Proof of structure of **9** consisted of its unambiguous synthesis by the route **5** → **8** → **11** → **9**. Compound **10** was also prepared from **8** by the sequence **8** → **14** → **15** → **10**.

After this work had been completed we became aware of parallel although less extensive investigations by two groups of Russian workers (6-8). They described the preparation of the intermediates, **6**, **7**, **10**, **11**, **14**, and **15** by essentially the same routes which are outlined in Scheme II.

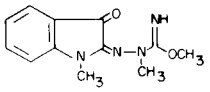
Scheme II



The report (8) that condensation of 2-methylthiosemicarbazone and **8** in hot water yielded an isatin-3-semicarbazone accompanied by the product **11** of the cyclization of the expected isatin-2-semicarbazone in 10% yield contrasts with our observation that the yield of **11** is at least 65% when the condensation is carried out in hot 2-propanol.

In a further investigation of the quaternarization process the oxygen analog **21** of **9** was prepared as outlined in Scheme III. It is particularly important that the pathways to **21** constitute a proof of structure in view of the striking difference in behavior of the two quaternaries toward alkali. Quaternary **9** was unaffected by alkali at room temperature conditions under which quaternary **21** was instantly converted to a pseudo base. The pseudo base returned to the quaternary form after treatment with acid. Upon long standing in methanolic sodium methoxide the SCH_3 quaternary afforded **19**. Although the mechanism of this reaction is obscure, the conversion does serve to interrelate the SCH_3 and OCH_3 quaternaries.

To distinguish the two most likely structures for the pseudo base, **22a** and **23a**, the methoxy pseudo base, **22b** or **23b** was prepared and its nmr spectrum examined. The appearance of separated OCH_3 signals is more in keeping with **22b** than **23b**. It would also be expected that **23a**, which resembles a hemiketal, would revert to **19** rather than **21** upon exposure to acid. We favor, therefore, structures **22a** and **22b** for the pseudo bases. An open chain form **24**, may be excluded since the ultraviolet



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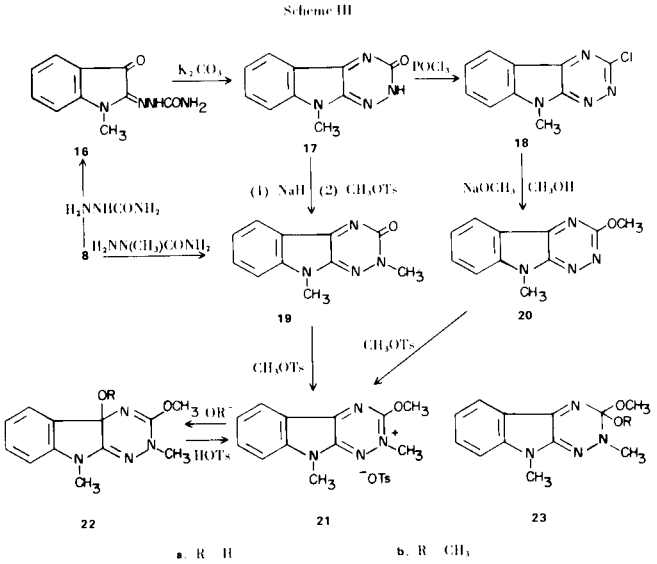
spectrum of the pseudo base does not resemble that of the model semicarbazone **16** (Table I). An explanation of the contrasting behavior of the SCH_3 and OCH_3 quaternaries toward alkali is not apparent.

Comparison of the ultraviolet spectrum (Table I) of **7** with those of **15**, **11**, and **10** support structure **7** as the correct tautomeric representation of this compound. The same conclusion may be reached for structure **17** by comparison with the spectra of models **19** and **20**. The spectra of the amines **12** and **13** are different from one another but no firm conclusion can be reached as to the correct tautomeric structure for **13**. The spectra would have to be studied as a function of *p*H and additional model compounds would be needed.

Comparison of the antiviral activity of **4**, **12** and **13** *in vitro* revealed that **13** and **12** were respectively two and four times as active as **4** when tested against Rhino 2 virus (7).

Scheme III



EXPERIMENTAL

Nmr spectra were determined with a Varian Model A-60 nmr spectrometer; TMS was used as the internal standard. The nmr, uv (95% ethanol), and ir spectra of most of the compounds were determined and are in accord with the structures written.

Isatin-2-thiosemicarbazone (**6**).

2-Anilinoisatin (22.2 g., 0.100 mole) was added to a hot, stirred solution of thiosemicarbazide (9.2 g., 0.105 mole) in 50 ml. of water and 200 ml. of alcohol and the mixture refluxed for 20 minutes. The red crystals were recrystallized from alcohol, yield, 17.9 g. (82%), m.p. 215-217°; lit. (6) m.p. 216-217°.

Anal. Calcd. for $C_9H_8N_4OS$: C, 49.08; H, 3.66; N, 25.44. Found: C, 49.13; H, 3.67; N, 25.34.

2,9-Dihydro-9H-*as*-triazino[6,5-*b*]indole-3-thione (**7**).

To a hot solution of 8 g. of potassium carbonate in 180 ml. of water was added 8 g. of **6** and the mixture refluxed for 24 hours. The filtered solution was cooled and acidified with dilute hydrochloric acid to give red crystals which were recrystallized from dimethylformamide-ether, yield 6.4 g. (87%), m.p. $>330°$; lit. (7) m.p. $>330°$.

Anal. Calcd. for $C_9H_6N_4S$: C, 53.45; H, 2.99; N, 27.70. Found: C, 53.45; H, 2.99; N, 27.69.

9-Methyl-3-methylthio-9*H*-*as*-triazino[6,5-*b*]indole (**10**).

Compound **7** (64 g., 0.316 mole) in 1.6 liters of dimethylformamide was converted to the disodium salt by addition of sodium hydride (28.2 g. of a 57% oil suspension, 0.66 mole) and then treated with methyl iodide (41.2 ml., 0.66 mole) in 100 ml. of dimethylformamide in one portion. After stirring for four hours the reaction mixture was diluted with four volumes of ether and the red solid recrystallized from 2-propanol, yield, 55 g. (76%), m.p. 194-195°; lit. (8) m.p. 193.5°.

Anal. Calcd. for $C_{11}H_{10}N_4S$: C, 57.37; H, 4.38; N, 24.33. Found: C, 57.26; H, 4.47; N, 24.15.

By the same procedure compound **15** yielded compound **10**.

2,9-Dihydro-9-methyl-3*H*-*as*-triazino[6,5-*b*]-indole-3-thione (**15**).

1-Methylisatin-2-thiosemicarbazone (**14**) was prepared from **8**

TABLE I

Ultraviolet Spectra

Compound	Wavelength of the maxima in mμ (extinction coefficient)
7	229 (13,600), 252 (7400), 268 (5440), 299 (41,800), 514 (1660)
15	230 (14,300), 257 (9300), 264 (9590), 300 (44,100), 525 (1600)
11	232 (15,300), 255sh (8980), 266 (10,300), 297 (47,300), 520 (1800)
10	219 (23,900), 270 (35,400), 297sh (6910), 340 (7330), 424 (2080)
17	226 (20,900), 265 (26,700), 315 (8630), 474 (2190)
19	224 (20,700), 265 (21,000), 330 (9300), 475 (2300)
20	214 (30,000), 259 (19,200), 324 (18,500), 415 (2270)
12	218 (16,200), 237 (19,100), 267 (33,600), 325 (11,900), 524 (1500)
13	227sh (20,600), 237 (22,300), 270 (23,000), 343 (7640), 455 (2780)
9	222 (29,600), 283 (37,100), 336 (13,600), 483 (1720)
21	224 (27,000), 282 (10,900), 334sh (4030), 371sh (7400), 387 (9450), 540 (898)
22a	220sh (13,700), 281 (13,000), 322 (3000)
22b	220sh (14,100), 282 (13,000), 325 (3050)
16	243 (14,200), 268 (19,300), 329 (13,400), 507 (4570)

in the usual manner. The crude product was not characterized but instead was cyclized to **15** in hot aqueous potassium carbonate; m.p. >300°; lit. (8) m.p. 311°.

Anal. Calcd. for $C_{10}H_8N_4S$: C, 55.54; H, 3.73; N, 25.91. Found: C, 55.26; H, 3.65; N, 25.83.

2,9-Dimethyl-3-methylthio-9*H*-*as*-triazino[6,5-*b*]indolium *p*-Toluenesulfonate (**9**).

A. By Methylation of **10**.

A mixture of **10** (39.6 g.) and 150 ml. of methyl *p*-toluenesulfonate was stirred on the steam bath for 75 minutes. The cold solution was poured into 600 ml. of ether and the orange product recrystallized from methanol-2-propanol, yield, 51.3 g. (82%), m.p. 222-223° dec.

Anal. Calcd. for $C_{19}H_{20}N_4O_3S_2$: C, 54.79; H, 4.84; N, 13.45. Found: C, 54.66; H, 4.81; N, 13.43.

B. By Methylation of **11**.

A mixture of 0.1 g. of **11** and one ml. of methyl *p*-toluenesulfonate was heated on the steam bath for 10 minutes and then diluted with 60 ml. of ether, yield, 0.17 g. (96%). The recrystallized product was identical with that prepared by method A.

1-Methyl-2-anilinoisatin (**5**).

The preparation given here is an improvement over that reported in the literature (10). A cold (-5°) solution of 2-anilinoisatin (222 g., 1 mole) in 1 liter of dimethylformamide was treated in portions with sodium hydride (46 g. of a 57% oil emulsion, 1.09 moles). The mixture was warmed to 40° for 30 minutes and then kept at -10° while methyl tosylate (170 ml., 1.09 moles) was added. The mixture was stirred at room temperature for 3 hours, at 40° for 30 minutes, and then poured into ice water. The red crystals were dissolved in methylene dichloride, the solution dried, concentrated and the residue crystallized from cyclohexane to give 179 g. (76%) of **5**, m.p. 129-130°; lit. (10), m.p. 132°.

2,9-Dihydro-2,9-dimethyl-3*H*-*as*-triazino[6,5-*b*]indole-3-thione (**11**).

The intermediate thiosemicarbazone could not be isolated but the cyclized product **11** was isolated after prolonged reflux of the reaction mixture. 2-Methyl-thiosemicarbazide (11) (11.6 g., 0.11 mole) and **8** (23.6 g., 0.1 mole) in 400 ml. of 2-propanol was stirred and refluxed for 18 hours. The product separated from the cold reaction mixture and was recrystallized from methanol-2-propanol, yield, 16.2 g. (65%) of a dark red solid, m.p. 253° dec; lit. (8) m.p. 245.5°.

Anal. Calcd. for $C_{11}H_{12}N_4OS$: C, 57.37; H, 4.38; N, 24.33; S, 13.92. Found: C, 57.00; H, 4.42; N, 24.16; S, 13.84.

4-[(2,9-Dihydro-2,9-dimethyl-3*H*-*as*-triazino[6,5-*b*]-indol-3-ylidene)-amino]-2-methyl-2-butanol (**12**).

A solution of **9** (10.4 g., 0.025 mole) and 3-hydroxy-3-methylbutylamine (3 g., 0.029 mole) was refluxed for 2 hours. The solution was concentrated *in vacuo* and the residue crystallized from methanol-ether. The crystals were dissolved in water and the solution made basic with dilute sodium hydroxide. The precipitated solid was recrystallized twice from cyclohexane to give 3.4 g. (50%) of purple crystals, m.p. 136-137°.

Anal. Calcd. for $C_{16}H_{21}N_5O$: C, 64.19; H, 7.07; N, 23.40. Found: C, 64.19; H, 7.01; N, 23.14.

4-[(9-Methyl-*as*-triazino[6,5-*b*]indol-3-yl)amino]-2-methyl-2-butanol (**13**).

A mixture of **10** (11 g., 0.051 mole) and 3-hydroxy-3-methylbutylamine (16.2 g., 0.156 mole) was heated at 180-185° for 18 hours. The excess amine was removed *in vacuo* and the residue recrystallized from alcohol to give 4.8 g., (33%) of yellow crystals, m.p. 145-146°.

Anal. Calcd. for $C_{15}H_{19}N_5O$: C, 63.14; H, 6.70; N, 24.49. Found: C, 63.14; H, 6.70; N, 24.55.

1-Methylisatin-2-semicarbazone (**16**).

To a solution of semicarbazide hydrochloride (24.5 g., 0.22 mole), potassium acetate (21.6 g., 0.22 mole) in 60 ml. of water was added **8** (47.3 g., 0.20 mole) in 600 ml. of methanol. The mixture was refluxed for 30 minutes with good stirring. The product was collected and recrystallized from methanol, yield, 30.8 g. (71%) of red crystals, m.p. 232-233°.

Anal. Calcd. for $C_{10}H_{10}N_4O_2$: C, 55.04; H, 4.62; N, 25.68. Found: C, 54.83; H, 4.59; N, 25.67.

2,9-Dihydro-9-methyl-3*H*-*as*-triazino[6,5-*b*]indol-3-one (**17**).

To a hot solution of 40 g. of potassium carbonate in 800 ml. of water was added 43.6 g. of crude **16** and the whole refluxed and stirred for 18 hours. The hot solution was filtered, cooled and acidified with dilute hydrochloric acid. The product was purified by solution in alkali and precipitation with acid, yield, 33.8 g. (84.5%) of yellow crystals, m.p. 330-332°.

Anal. Calcd. for $C_{10}H_8N_4O$: C, 59.99; H, 4.03; N, 27.89. Found: C, 59.68; H, 4.03; N, 27.89.

3-Chloro-9-methyl-9*H*-*as*-triazino[6,5-*b*]indole (**18**).

A suspension of 20 g. of **17** in 50 ml. of phosphorus oxychloride was stirred and refluxed for two hours and then poured into one liter of ice water. The crystals were dissolved in chloroform to remove insoluble tar, the solution concentrated, and the residue crystallized from methylene chloride-hexane, yield, 15.5 g. (71%) of yellow crystals, m.p. 189-190°.

Anal. Calcd. for $C_{10}H_7ClN_4$: C, 54.93; H, 3.23; N, 35.62. Found: C, 54.76; H, 3.15; N, 35.33.

3-Methoxy-9-methyl-9*H*-*as*-triazino[6,5-*b*]indole (**20**).

A hot solution of **18** (7.15 g., 0.033 mole) and sodium methoxide (2.7 g., 0.050 mole) in 600 ml. of methanol was refluxed for 4 hours, filtered, and cooled to give yellow needles, 5 g. (71%), m.p. 178-179°.

Anal. Calcd. for $C_{11}H_{10}N_4O$: C, 61.67; H, 4.71; N, 26.15. Found: C, 61.45; H, 4.64; N, 26.34.

2,9-Dihydro-2,9-dimethyl-3*H*-*as*-triazino[6,5-*b*]indol-3-one (**19**).

A. By Methylation of **17**.

Sodium hydride (7.5 g. of a 57% oil suspension, 0.178 mole) and 20 g. (0.1 mole) of **17** in dry dimethylformamide was heated at about 55° for 30 minutes. The solution was cooled to -10° and treated with methyl tosylate (27.8 ml., 0.18 mole). The mixture was stirred for four hours at room temperature, poured into water, and the product collected, yield, 19 g. (89%), m.p. 308-310°. An analytical sample was prepared by recrystallization from methanol with no change in melting point.

Anal. Calcd. for $C_{11}H_{10}N_4O$: C, 61.67; H, 4.71; N, 26.16. Found: C, 61.68; H, 4.66; N, 26.09.

B. By Condensation of 2-Methylsemicarbazide with **8**.

The intermediate semicarbazone could not be isolated but prolonged heating of the reaction mixture lead directly to **19**. A solution containing **8** (1.3 g., 0.055 mole), acetic acid (0.3 ml.), 2-methylsemicarbazide (12) (0.56 g., 0.06 mole) in 16 ml. of 2-propanol was refluxed for 18 hours. The product separated after the reaction mixture was cooled; it was recrystallized from 2-propanol to give 0.28 g., m.p. 310-311°, identical in all respects with **19** prepared by method A.

C. By "Hydrolysis" of **9**.

From a solution of **9** (2.08 g., 0.005 mole) and sodium methoxide (0.27 g., 0.05 mole) in methanol which had been left at room temperature for 18 hours there was isolated 0.31 g. (29%) of product which was identical with that prepared by method A.

2,9-Dimethyl-3-methoxy-9*H*-*as*-triazino[6,5-*b*]indolium *p*-Toluenesulfonate (**21**).

A. By Methylation of **19**.

A mixture of 17.1 g. of **19** in 365 ml. of methyl tosylate was stirred under nitrogen at 80° for two hours. The clear solution was poured slowly into 1.5 liters of ether and the product recrystallized from 2-propanol-ether, yield, 29 g. (90%) of purple crystals, m.p. 174-175°.

Anal. Calcd. for $C_{19}H_{20}N_4O_4S$: C, 56.99; H, 5.03; N, 13.98. Found: C, 56.84; H, 4.91; N, 14.19.

B. By Methylation of **20**.

Application of the same procedure to **20** yielded a quaternary salt which was identical with that obtained by methylation of **19**.

2,9-Dihydro-3-methoxy-2,9-dimethyl-4a-*H*-*as*-triazino[6,5-*b*]indol-4a-ol (**22a**).

A purple solution of 0.8 g. of **21** in 3 ml. of water and 30 ml. of acetone was stirred with 5.6 g. of Amberlite IRA-410 (OH^- form) for 15 minutes. The colorless solution was filtered and concentrated *in vacuo* at room temperature. The residue was recrystallized twice from acetone; yield, 0.3 g. (61%) of yellow crystals, m.p. 139-141°; nmr (DMSO-d_6): δ 3.13, 3.18, 3.28 (s, 9H), 6.7-7.7 (m, 4H).

Anal. Calcd. for $C_{12}H_{13}N_4O_2$: C, 58.52; H, 5.72; N, 22.75. Found: C, 58.65; H, 6.02; N, 22.81.

2,9-Dihydro-3,4a-dimethoxy-2,9-dimethyl-4a-*H*-*as*-triazino[6,5-*b*]-indole (**22b**).

A purple solution of 1 g. of **21** in 30 ml. of methanol was stirred under nitrogen with 10 g. of Amberlite IRA-410 (OH^- form) until colorless (about 10 minutes); The solution was filtered, concentrated *in vacuo*, and the residue recrystallized from hexane to give 0.46 g. (71%) of yellow crystals, m.p. 115-115.5°; nmr (DMSO-d_6): δ 2.88, 3.17, 3.22, 3.30 (s, 12H), 6.5-7.7 (m, 4H).

Anal. Calcd. for $C_{13}H_{16}N_4O_2$: C, 60.08; H, 6.26; N, 21.38. Found: C, 59.98; H, 6.20; N, 21.53.

Addition of a mole-equivalent of *p*-toluenesulfonic acid monohydrate to an acetone solution of either **22a** or **22b** resulted in the precipitation of the quaternary **21** in good yield.

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