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The Synthesis and Reactions of 1,5,6,10b-
Tetrahydroimidazo[5,1-a]isoquinolin-3(2)thione (1)

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It has recently been shown that isoquinaldonitrile and isoquinaldamide are readily available from isoquinoline through the Reissert analogue I (2,3). With this availability we should like to report on the use of isoquinaldamide as a starting point for the imidazo[5,1-a]isoquinoline system.

Hydrogenation of isoquinaldamide hydrobromide gave tetrahydroisoquinaldamide which with lithium aluminum hydride gave 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline (II). The reaction of diamine II with carbon disulfide yielded the dithiocarboxyl derivative III which was converted into the cyclic thiourea IV by heating with acid or by fusion at its melting point, generating hydrogen sulfide in the process. A reasonable mechanism for this cyclization might involve elimination of hydrogen sulfide from III to give an intermediate 1-isothiocyanato-1,2,3,4-tetrahydroisoquinoline which then cyclizes to IV.

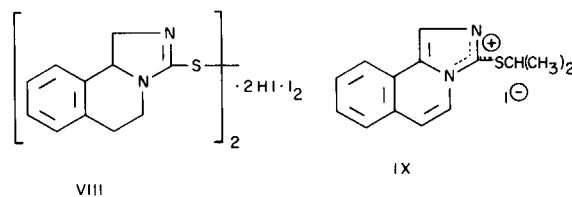
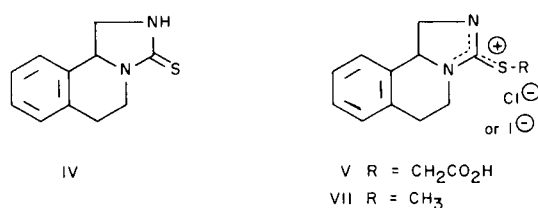
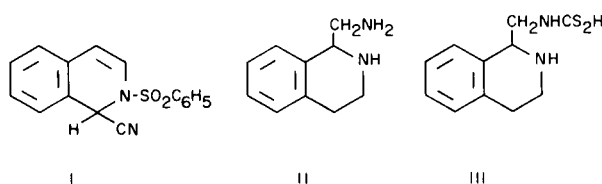
Reaction of the cyclic thiourea (IV) with chloroacetic acid yielded the isothiuronium salt V. Hydrolysis of V with ammonia gave a near quantitative yield of the cyclic urea VI which was also obtained by condensation of phosgene with the diamine II (4). The cyclic thiourea (IV) also reacted with methyl iodide to give the methyl isothiuronium salt VII.

Oxidation of IV with potassium iodide-iodine gave the disulfide periodide VIII (5) which could be hydrolyzed to IV in aqueous acetone. Prolonged refluxing of VIII in aqueous acetone gave IX which also arose when isopropyl iodide was refluxed with IV.

An alternative route to the cyclic urea IV was available from the Reissert analogue X (6). Hydrogenation of X gave the diurethane XI which had previously been prepared by a more tedious process. Hydrolysis and cyclization of XI gave VI.

1,2,3,4-Tetrahydroisoquinaldamide.

Hydrogen bromide was slowly bubbled through a solution of 2.96 g. (0.0174 mole) of 1-isoquinaldamide in 500 ml. of benzene



EXPERIMENTAL (7)

1-Isoquinaldamide.

A mixture of 3.0 g. (0.0098 mole) of 2-benzenesulfonyl-1,2-dihydroisoquinaldonitrile (I) (3) and 45 ml. of 50% sodium hydroxide was heated with stirring on a steam bath for about 8 minutes and poured into 750 ml. of water. Filtration gave 1.6 g. (95%) of the amide which had a melting point 168-170° and an infrared spectrum identical with an authentic sample.



for about 10 minutes. Filtration gave a 97% yield of solid which was used directly in the hydrogenation. To a solution of 4.4 g. (0.017 mole) of this hydrobromide in 230 ml. of 70% ethanol was added 0.15 g. of platinum oxide. The mixture was shaken under 3 atmospheres of hydrogen. After the theoretical uptake of hydrogen the mixture was filtered, evaporated to half volume, and made basic with ammonium hydroxide to give 2.38 g. (78%) of solid, m.p. 180-183° (reported (8) m.p. 181-183°). The hydrochloride was prepared and recrystallized from ethanol, m.p. 285-286°.

Anal. Calcd. for $C_{10}H_{13}ClN_2O$: C, 56.49; H, 6.17; N, 13.15; Cl, 16.63. Found: C, 56.52; H, 6.15; N, 13.15; Cl, 16.62.

1-Aminomethyl-1,2,3,4-tetrahydroisoquinoline (II).

A suspension of 20.1 g. (0.118 mole) of 1,2,3,4-tetrahydroisoquinolaldamide in 200 ml. of tetrahydrofuran was added slowly to 11.4 g. of lithium aluminum hydride in 200 ml. of tetrahydrofuran. After refluxing for 8 hours the volume was reduced and ether, ethyl acetate and 6 *N* hydrochloric acid were added. The solution was then subjected to steam distillation and the residue made basic. Ether extraction of the basic residue followed by distillation of the ether extract gave a 30% yield of the diamine II. Both the hydrochloride dihydrate, m.p. 281° (reported (4) m.p. 281°) and the anhydrous hydrochloride, m.p. 176-182° (reported (9) m.p. 179-184°), were prepared.

1-(1,2,3,4-Tetrahydroisoquinolyl)methylthiocarbamic Acid (III).

To a solution of 0.225 g. (0.00104 mole) of 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride dihydrate in 10 ml. of 50% ethanol refluxing on a steam bath was added 2 ml. of carbon disulfide and 1 ml. of ammonium hydroxide. After refluxing for a short time 0.12 g. (48%) of a white solid, m.p. 130-132° (with evolution of hydrogen sulfide - the melting point of pure products with identical infrared spectrum varied from 130-132° to 147-150° and were very sensitive to rate of heating).

Anal. Calcd. for $C_{11}H_{14}N_2S_2$: C, 55.42; H, 5.92; N, 11.73. Found: C, 55.69; H, 5.79; N, 11.56.

This same compound could also be obtained by treating the free base II with carbon disulfide in ethanol.

1,5,6,10b-Tetrahydroimidazo[5,1-*a*]isoquinoline-3-(2) thione (IV).

To 2.43 g. (0.0150 mole) of 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline in 17.5 ml. of 55% ethanol refluxing on a steam bath was added 2 ml. of carbon disulfide. (If the reaction is stopped shortly after this addition III can be isolated). After refluxing for 4 hours, 0.2 ml. of concentrated hydrochloric acid was added and reflux was continued for an additional 18 hours. After cooling 2.21 g. (72%) of solid, m.p. 150-152°, was obtained. Recrystallization from benzene gave m.p. 155-156°.

Anal. Calcd. for $C_{11}H_{12}N_2S$: C, 64.66; H, 5.92; N, 13.71; S, 15.69. Found: C, 64.56; H, 5.81; N, 13.71; S, 15.73.

When III was heated slightly above its melting point, hydrogen sulfide was generated and upon cooling the melt IV could be obtained.

Reaction of IV with Chloroacetic Acid (Preparation of V).

To 0.50 g. of chloroacetic acid in 2 ml. of water was added 0.07 g. (0.00034 mole) of the cyclic thiourea (IV). After heating on a steam bath for 3 hours the solution was evaporated and triturated with hot benzene to yield 0.10 g. (99%) of solid, m.p. 243-247°. Recrystallization from ethanol gave m.p. 242-246°.

Anal. Calcd. for $C_{13}H_{15}ClN_2O_2S$: C, 52.25; H, 5.05; N, 9.38; Cl, 11.87; S, 10.73. Found: C, 51.96; H, 5.07; N, 9.25; Cl, 11.72; S, 10.76.

1,5,6,10b-Tetrahydroimidazo[5,1-*a*]isoquinoline-3-(2)-one (VI).

To 0.061 g. (0.00025 mole) of V in 1 ml. of hot water was added 4 drops of concentrated ammonium hydroxide. After cooling 0.045 g. (95%) of solid was obtained. Washing with ether and water gave m.p. 146-147° (reported (4) m.p. 148°).

This same compound (VI) was obtained by bubbling phosgene through an ether solution of II. The sample prepared in this manner was identical in all respects with that obtained by the hydrolysis of V.

Reaction of IV with Methyl Iodide (Preparation of VII).

To 0.085 g. of IV was added 0.85 g. of methyl iodide and the mixture was refluxed for 20 minutes. After cooling and recrystallization from ethanol a solid, m.p. 193-196°, was obtained.

Anal. Calcd. for $C_{12}H_{15}N_2IS$: C, 41.65; H, 4.37. Found: C, 41.30; H, 4.29.

Preparation of VIII.

To 0.115 g. (0.00056 mole) of IV in 20 ml. of 1:1 aqueous acetone was added dropwise a solution of 4*N* aqueous potassium iodide-iodine with vigorous stirring. Partial evaporation gave 0.23 g. (78%) of solid, m.p. 153-154.5°. A sample was purified by slow evaporation of an acetone solution and washed with ether to give m.p. 157-160°.

Anal. Calcd. for $C_{22}H_{24}N_4I_4S_2$: C, 28.83; H, 2.64; N, 6.12; I, 55.41; S, 6.98. Found: C, 28.91; H, 2.73; N, 6.20; I, 55.50; S, 7.10.

When 0.07 g. of this compound (VIII) in 5 ml. of water with just sufficient acetone to effect solution was refluxed for 5 hours a 47% yield of IV was obtained.

Preparation of IX.

(a) From VIII.

A solution of 0.07 g. of VIII in 40 ml. of 1:1 aqueous acetone was refluxed for 18 hours and the acetone evaporated by a stream of warm air to give 0.023 g. of solid, m.p. 240-243°. Recrystallization from ethanol gave m.p. 242-244°.

Anal. Calcd. for $C_{14}H_{15}IN_2S$: C, 45.41; H, 4.08; N, 7.58; I, 34.29; S, 8.65. Found: C, 45.50; H, 4.17; N, 7.71; S, 8.51; I, 34.16.

(b) From IV.

A few milligrams of the thiourea IV was refluxed in a large excess of isopropyl iodide for 1 hour and the solvent evaporated to give a solid with an identical infrared spectra to the material obtained from VIII.

1,5,6,10b-Tetrahydro[5,1-*a*]isoquinoline-3(2)-one from X.

A solution of 1.14 g. (0.005 mole) of X (6) in 50 ml. of glacial acetic acid and 0.1 g. of platinum oxide was shaken under 4 atmospheres hydrogen for 20 hours. Filtration, concentration, trituration with benzene-hexane, and recrystallization from benzene-hexane gave 0.72 g. (47%) of XI, m.p. 95-97°, (reported (4) m.p. 103°).

A mixture of 10 ml. of 50% sodium hydroxide and 0.05 g. (0.0002 mole) of XI was heated on the steam bath for 20 minutes. After standing several days, 0.025 g. (81%) of VI was obtained. This product was identical in respect to melting point and infrared spectrum with that obtained in the two preparations noted above.

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