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DERIVATIVES OF TETRAZA-INDOLIZINES

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Tetraza-indolizines have been prepared by interaction between 5-amino-tetrazole and 2-hydroxymethylene-cyclohexanone and cyclopentanone, ethyl cyclohexanone-2-carboxylate, and potassium o-iodobenzoate. The last-named substance gave a known hydroxy-benztetrazaindolizine, previously obtained by another type of method. A diethylaminoethylaminotetraza-indolizine was found to have no therapeutic action in experimental try-panosomiasis.

In an earlier communication [1]) we have reported the synthesis of a series of tricyclic triaza-indolizines from 3-aminotriazole. We now record analogous reactions with 5-aminotetrazole (I), which *Bülow* [2]) has previously shown to form dicyclic pyrimidines by interaction with simple β-diketones and β-ketoesters. 5-Aminotetrazole reacted smoothly with 2-hydroxymethylenecyclohexanone. By analogy with the corresponding reaction with 3-aminotriazole, the product is regarded as 5,6-tetramethylene-1,2,3,8-tetrazaindolizine (II; X = H) [3]). This was also obtained by condensation of 5-aminotetrazole with ethyl cyclohexanone-2-carboxylate to the hydroxy derivative (II; X = OH), followed by conversion into the chloro-compound (II, X = Cl) and then catalytic dechlorination.

7-Chloro-5,6-tetramethylene-1,2,3,8-tetrazaindolizine (II; X = Cl) reacted with aniline to give the corresponding anilino compound (II; X = NHPh) and with N,N-diethylethylenediamine to give the hydrochloride of the substituted base (II; X = $NH.CH_2CH_2NEt_2$). This salt was found by Professor *C. H. Browning*, F.R.S. and Miss *H. Adamson*, B.Sc., to be lethal for mice in doses exceeding 2 mg per 20 g body weight, and had no therapeutic effect on *T. congolense* or *T. brucei* in sub-lethal doses.

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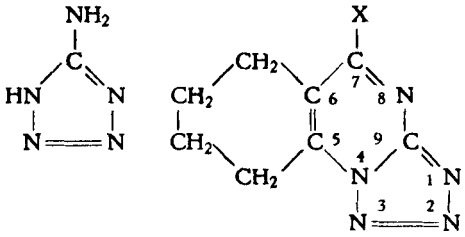
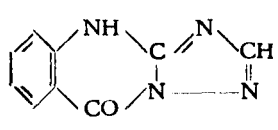
[1]) *J. W. Cook, R. P. Gentles* and *S. H. Tucker*, Rec. trav. chim. **69**, 343 (1950).

[2]) *C. Bülow*, Ber. **42**, 4429 (1909).

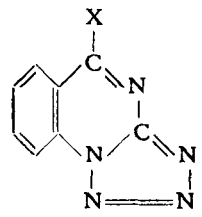
[3]) We adopt the numbering of "The Ring Index" for indolizine (*A. M. Patterson* and *L. T. Capell*), New York, 1940.



(I.) (II.) (III.)



(IV.)



(V.)

We have shown [1]) that 3-amino-1,2,4-triazole condenses with 2-hydroxymethylenecyclopentanone to give a trimethylenetriazaindolizine to which an angular structure (corresponding with III) was assigned, whereas ethyl cyclopentanone-2-carboxylate, in contrast to ethyl cyclohexanone-2-carboxylate, gave the alternative linear structure. With 5-aminotetrazole a further divergence has been encountered. For, whereas this amine reacted normally with 2-hydroxymethylenecyclopentanone to give a compound presumed to be 5,6-trimethylene - 1,2,3,8 - tetrazaindolizine (III), ethyl cyclopentanone-2-carboxylate gave a compound, $C_{10}H_{16}O_2N_{10}$, evidently formed by interaction of one molecule of ketoester with two molecules of aminotetrazole.

A further difference in behaviour between 3-aminotriazole and 5-aminotetrazole was revealed in their reacton with potassium *o*-iodobenzoate. In the case of aminotriazole this led to the linear compound (IV) [1]). 5-Aminotetrazole, however, reacted with the iodobenzoate to give mostly diphenylamine-2,2'-dicarboxylic acid [4]), together with a smaller amount of the angular condensation product, 7-hydroxy-5,6-benz-1,2,3,8-tetrazaindolizine (V; X = OH). This compound proved to be identical with the tetrazolo-hydroxyquinazolinedihydride of *Stollé* and *Hanusch* [5]), whose work established its structure (V; X = OH). Unlike the linear benztriazaindolizine derivative (IV), the

[4]) *F. Ullmann*, Ann. **355**, 352 (1907).
[5]) *R. Stollé* and *Fr. Hanusch*, J. prakt. Chem. *136*, 9, 120 (1933).

angular benztetrazaindolizine derivative (V; X = OH) reacted readily with phosphoryl chloride to give the corresponding chloro-compound (V: X = Cl).

In the course of this work, 2-amino-5,6,7,8-tetrahydroquinazoline [6]) was unexpectedly obtained (a) by slow pyrolysis of 5,6-tetramethylene-1,3,8-triazaindolizine (II; CH in place of N^2; X = H), (b) by hydrogenation of 7-chloro-5,6-tetramethylene-1,2,3,8-tetrazaindolizine (II; X = Cl) followed by sublimation of the product, and (c) in an attempt to condense 5-aminotetrazole with ethyl cyclohexanone-2-glyoxylate.

Experimental part.

5,6-Tetramethylene-1,2,3,8-tetrazaindolizine (II; X = H). 5-Aminotetrazole (I) (10 g) was dissolved in alcohol (100 cm^3) and 2-hydroxymethylenecyclohexanone (12.6 g) added, the mixture being boiled for several hours. On cooling the solution the product crystallised in colourless plates, m.p. 122—123°. Yield, 14 g, 80 %.

Oxidation with boiling potassium permanganate solution gave adipic acid and ammonia (isolated as ammonium chloride).

Analysis:

Found: C 54.9 %, H 5.3 %, N 40.1 %.

Calculated for $C_8H_9N_5$: C 54.8 %, H 5.2 % N 40.0 %.

7-Hydroxy-5,6-tetramethylene-1,2,3,8-tetrazaindolizine (II; X = OH). A solution of 5-aminotetrazole (1 g) and ethyl cyclohexanone-2-carboxylate (1.7 g) in acetic acid (5 cm^3) was boiled for 3 hours, and the solvent removed under reduced pressure. The residual hydroxy-compound (I; X = OH) crystallised from water after treatment with charcoal in colourless needles, m.p. 200° (dec.). Yield, 1.6 g, 84 %.

Analysis:

Found: C 50.5 %, H 4.9 %, N 36.7 %.

Calculated for $C_8H_9ON_5$: C 50.3 %, H 4.7 %, N 36.7 %.

7-Chloro-5,6-tetramethylene-1,2,3,8-tetrazaindolizine (II; X = Cl). The hydroxy-compound (I; X = OH) (5 g) was heated under reflux with phosphoryl chloride (20 cm^3) for 4 hours and the excess reagent removed under reduced pressure. The residue, mixed with ice, was almost neutralised with ammonia and, after trituration, the solid was collected, dried, and sublimed at 110—120°/3 mm. The fine colourless needles obtained were crystallised from ligroin (b.p. 100—120°), m.p. 97—99°. Yield, 3 g, 54 %.

Analysis:

Found: C 46.0 %, H 4.0 %, N 33.2 %.

Calculated for $C_8H_8N_5Cl$: C 45.8 %, H 3.9 %, N 33.4 %.

[6]) *E. Benary*, Ber. **63**, 2606 (1930).

5,6-Tetramethylene-1,2,3,8-tetrazaindolizine (II; X = H). A solution of the chloro-compound (I; X = Cl) (0.2 g) in acetone (15 cm^3) was dehalogenated by shaking with hydrogen and 2% palladised strontium carbonate (0.2 g). After crystallising the product from ligroin (b.p. 100—120°), colourless needles were obtained, m.p. 122—123° alone or mixed with a specimen prepared as described above. Yield, 0.08 g, 44%.

Analysis:

Found:	C 54.9%, H 5.2%, N 40.1%.
Calculated for $C_8H_9N_5$:	C 54.8%, H 5.2%, N 40.0%.

5,6-Trimethylene-1,2,3,8-tetrazaindolizine (III). To a solution of 5-aminotetrazole (2 g) in acetic acid (10 cm^3) was added a solution of 2-hydroxymethylenecyclopentanone (2 g) in acetic acid (10 cm^3). After several hours' boiling, during which the initial precipitate redissolved, the solvent was removed under reduced pressure and the dark residue extracted with ligroin (b.p. 100—120°). Repeated crystallisation from this solvent gave short colourless needles, m.p. 152—153°. Yield, 1.9 g, 60%.

Analysis:

Found:	C 52.2%, H 4.5%, N 43.4%.
Calculated for $C_7H_7N_5$:	C 52.2%, H 4.4%, N 43.5%.

Condensation of 5-aminotetrazole with ethyl cyclopentanone-2-carboxylate. 5-Aminotetrazole (5 g) and ethyl cyclopentanone-2-carboxylate (7.8 g) in alcohol (50 cm^3) were refluxed for 24 hours. When cold the product was filtered from the mother liquor which yielded more material on concentration. Crystallisation from alcohol gave rectangular plates, m.p. 162° (effervescence) after softening at 158°. Yield, 6.2 g.

Analysis:

Found:	C 38.9%, H 5.0%, N 45.4%.
Calculated for $C_{10}H_{16}O_2N_{10}$:	C 39.0%, H 5.2%, N 45.4%.

When the reaction was carried out in acetic acid, 5-acetylaminotetrazole was isolated; without a solvent, charring took place and a little 5-aminotetrazole was recovered.

7-Anilino-5,6-tetramethylene-1,2,3,8-tetrazaindolizine (II; X = NHPh). This was obtained by heating a solution of the chloro-compound (II; X = Cl) (1 g) and aniline (1 g) in alcohol (5 cm^3) for 2 hours. After washing the product with water, crystallisation from alcohol yielded colourless needles, m.p. 192—194°. Yield, 0.7 g, 55%.

Analysis:

Found:	C 63.0%, H 5.3%, N 31.4%.
Calculated for $C_{14}H_{14}N_4$:	C 63.1%, H 5.3%, N 31.6%.

Hydrochloride of 7-(β-diethylaminoethylamino)-5,6-tetramethylene-1,2,3,8-tetrazaindolizine (II; X = $NHCH_2CH_2NEt_2$). A solution of the chloro-compound (II; X = Cl) (1 g) and N,N-diethylethylenediamine (1 cm^3) in alcohol (10 cm^3) was boiled for 3 hours. After the solvent had been removed on a water bath the pressure

was reduced to remove unreacted diamine. The residue crystallised from alcohol/dioxan in colourless prisms, m.p. 220—232° (dec.). Yield, 1.3 g, 84 %.

Analysis:

Found: C 52.0 %, H 7.2 %.
Calculated for $C_{14}H_{23}N_7 . HCl$: C 51.6 %, H 7.4 %.

7-Hydroxy-5,6-benz-1,2,3,8-tetrazaindolizine (V; X = OH). Anhydrous 5-amino-tetrazole (4.3 g), potassium o-iodobenzoate (14.3 g), potassium carbonate (3.5 g), copper bronze (0.1 g), and amyl alcohol (15 cm^3) were stirred under reflux in an oil bath for 12 hours. The solid was filtered, washed with ether, dissolved in water (50 cm^3) and the solution, filtered free from copper bronze, was acidified with hydrochloric acid. Extraction of the precipitate with boiling water left a residue which after crystallisation from ethylene glycol, and then glacial acetic acid, yielded pale yellow prisms of diphenylamine-2,2'-dicarboxylic acid, m.p. 290—295° (dec.). Yield, 0.6 g. *Ullmann* [4]) gives m.p. 295°.

Analysis:

Found: C 65.6 %, H 4.5 %, N 5.6 %.
Calculated for $C_{14}H_{11}O_4N$: C 65.4 %, H 4.3 %, N 5.45 %.

The above aqueous extract after treatment with charcoal and fractional crystallisation from water, to remove unchanged iodobenzoic acid gave colourless prisms of (V; X = OH), m.p. 243° (dec.). Yield, 0.2 g.

Analysis:

Found: C 51.5 %, H 2.9 %, N 37.6 %.
Calculated for $C_8H_5ON_5$: C 51.3 %, H 2.7 %, N 37.4 %.

7-Chloro-5,6-benz-1,2,3,8-tetrazaindolizine (V; X = Cl). The hydroxy-compound (V; X = OH) (0.15 g) was dissolved in phosphoryl chloride (5 cm^3) and heated under reflux for 2 hours. The reagent was removed under reduced pressure, ice added to the residue and the pale yellow precipitate was filtered, washed with water, dried, and crystallized from benzene. It formed colourless prisms, m.p. 184—185°. Yield, 0.14 g, 84 %.

Analysis:

Found: C 46.7 %, H 2.2 %, N 34.5 %.
Calculated for $C_8H_4N_5Cl$: C 46.7 %, H 2.0 %, N 34.1 %.

The same chloro-compound (identified by m.p. and mixed m.p.) was also obtained from a sample of the hydroxy-compound (V; X = OH) prepared by the method of *Stollé* and *Hanusch* [5]).

Formation of 2-Amino-5,6,7,8-tetrahydroquinazoline.

a) 5,6-Tetramethylene-1,3,8-triazaindolizine [1]) (0.1 g) dissolved in light petroleum (b.p. 80—100°) (10 cm^3) was distilled to dryness over a small flame and allowed to char. The residue and sublimate were extracted with benzene and the extract evaporated to dryness. The residue on vacuum sublimation yielded white crystals, m.p. 208—210°.

b) 7-Chloro-5,6-tetramethylene-1,2,3,8-tetrazaindolizine (II; X = Cl) (0.2 g) was shaken with hydrogen and palladised strontium carbonate (0.2 g) in alcohol (25 cm^3). Removal of the solvent and vacuum sublimation of the residue followed

by crystallisation from benzene/light petroleum yielded very small prisms, m.p. 210—211°.

c) A solution of 5-aminotetrazole (2.5 g) in alcohol (20 cm^3) was added to ethyl cyclohexanone-2-glyoxylate (5 g) and the solution refluxed for 5 hours. After removal of the solvent the gummy residue was heated at 140° at 2 mm pressure to remove unchanged ketoester. The residue was extracted with benzene and the extract, passed through an alumina column, was concentrated and the solid so obtained was sublimed in vacuo, m.p. 205—207°.

Analysis:

Found (a):	C 64.3 %, H 6.9 %, N 29.0 %.
,, (b):	C 65.2 %, H 7.5 %, N 27.7 %.
,, (c):	C 65.1 %, H 7.4 %, N 27.3 %.
Calculated for $C_8H_{11}N_3$:	C 64.4 %, H 7.4 %, N 28.2 %.

Mixed melting point in each case with a specimen of 2-amino-5,6,7,8-tetrahydroquinazoline, prepared as described by *Benary* [6], who gives m.p. 206—210°, showed no depression below the lower melting point.

A picrate of the authentic specimen was prepared and did not depress the melting point of a picrate prepared from material obtained under (c). It crystallised from much alcohol in yellow micro-prisms, m.p. 232° (dec.) after softening at 220°.

Analysis:

Found:	C 44.6 %, H 3.9 %, N 22.1 %.
Calculated for $C_{14}H_{14}O_7N_6$:	C 44.4 %, H 3.7 %, N 22.2 %.

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