Ring Transformation of Condensed Dihydro-*as*-triazines

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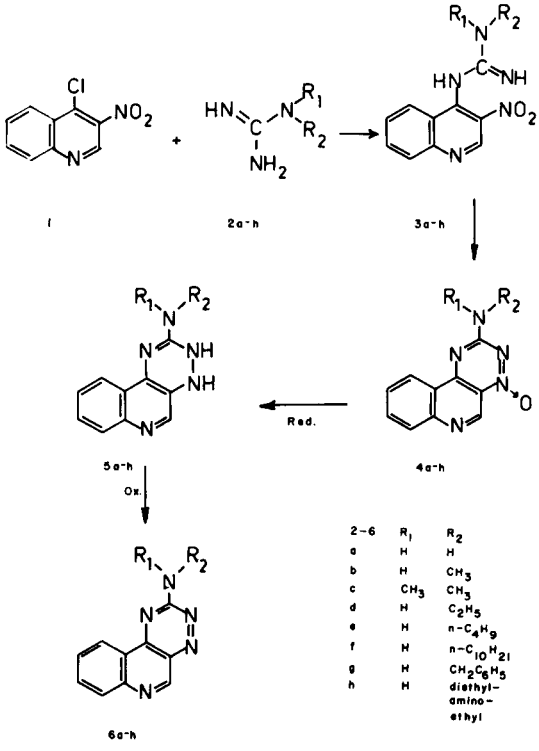
The 2-amino-*as*-triazino[6,5-*c*]quinoline as well as 3-aminopyrido[4,3-*e*]-*as*-triazine had previously been synthetized by Berényi (1) and Benkó *et al* (2). In this paper, the ring transformation occuring in aqueous media of the dihydro intermediates and their salts, respectively appearing during the synthesis of 2-substituted-amino-*as*-triazino[6,5-*c*]quinolines, are reported.

J. Heterocyclic Chem., 18, 1537 (1981).

In the course of preparation of our model compounds, 4-chloro-3-nitroquinoline (**1**) (3) was made to react with the appropriately substituted quanidine **2** and the intermediates obtained (**3**) were cyclized under alkaline conditions to yield *as*-triazino[6,5-*c*]quinoline-4-oxides (**4**).

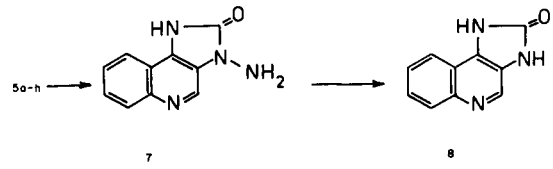
The reduction of the *N*-oxides **4a-h** resulted in the required model compounds **5a-h** which could only be isolated in the form of their salts. Without salt formation, the base underwent oxidation and the ring system became aromatic **6a-h**.

Scheme I

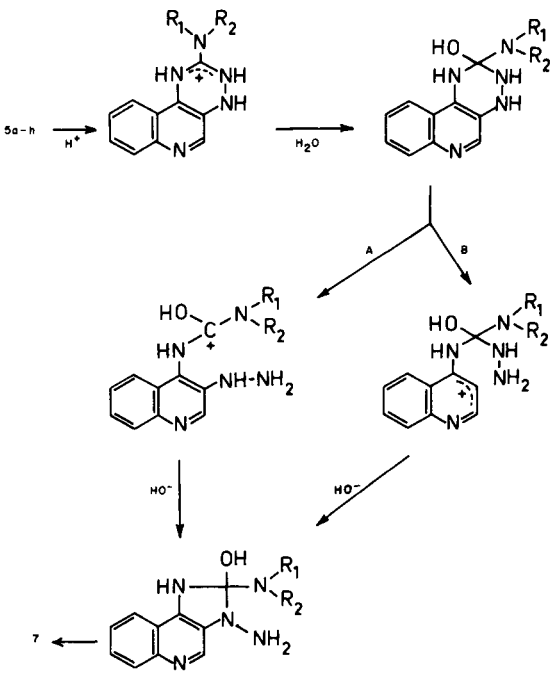


It was observed in our experiments that the salts formed with mineral acids of the dihydro compounds **5a-h** were transformed by heating in aqueous media. This ring transformation resulted in each case in the *N*-aminoimidazoquinoline **7**, the structure of which was proved by chemical, analytical, as well as spectroscopic methods. Thus, the exo-nitrogen was removed from the molecule during this process resulting imidazoquinoline **8**.

Scheme 2



Scheme 3



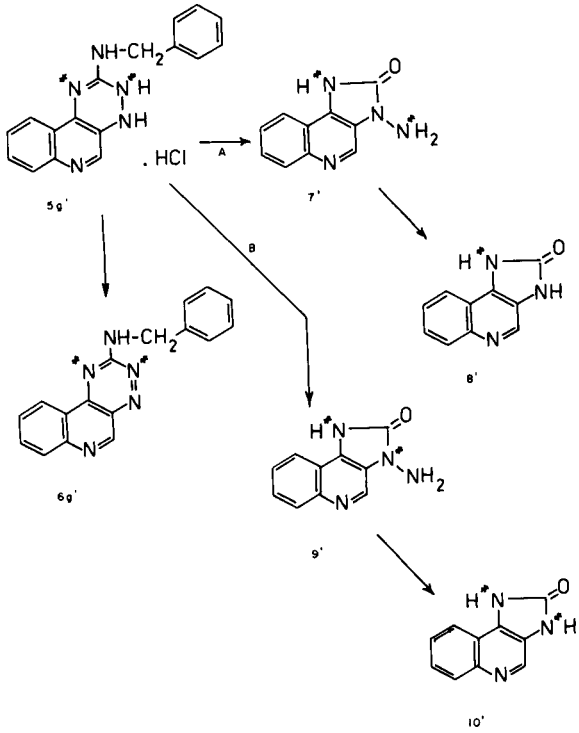
When the reaction of 3-amino-1,2-dihydropyrido[4,3-*e*]-*as*-triazine having a structure analogous to **5a** was carried out under the same conditions, an interesting difference was observed: 3-amino-1,3-dihydro-2*H*-imidazo[4,5-*c*]pyridin-2-one, having an analogous structure to **7** was obtained only in trace amounts, while the oxidized form, 3-aminopyrido[4,3-*e*]-*as*-triazine was obtained in a 97% yield.

The transformation of **5a** hydrochloride to **7** could proceed in two alternative ways (pathways A and B, respectively).

In order to decide the mechanism of the reaction, a partial ^{15}N labelling was used. Therefore, the reaction sequence **1**→**5** was started from **1** as well as from **2g** (1,2-$^{15}N_2$) (4) and proceeded through the intermediate **3g′**. Thus 2-benzylamino-3,4-dihydro-*as*-triazino[6,5-*c*]quinoline-(1,3-$^{15}N_2$) (**5g′**) was obtained.

From our labelled model compound **5g′**, a product **8′** containing one ^{15}N atom would be obtained through pathway A, while a product **10′** containing ^{15}N atoms in two positions would appear through the pathway B (ANRORC mechanism),

Scheme 4



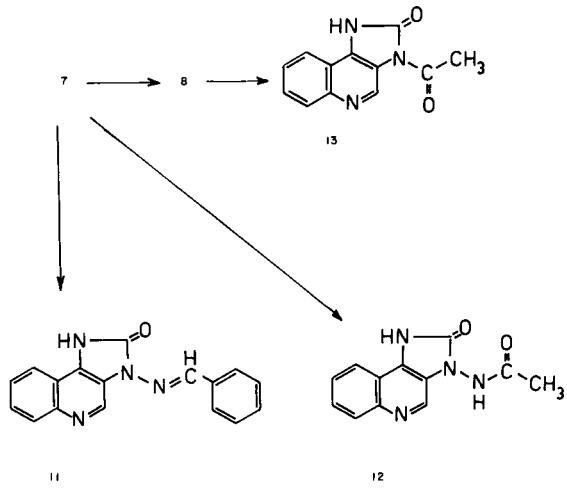
The ^{15}N content of the labelled compounds was determined on the basis of the mass spectra resulting from the electron irradiation of the products (5).

Instead of the starting dihydro model compound (**5g′**), the more stable oxidized derivative **6g′** was studied and it was stated that the mass number and isotopic distribution of the molecular ion beam were statistically 96 ±1% in two positions when the natural isotopic correlation was taken into consideration, a fact showing that the structure was 1,3-dihydro-2*H*-imidazo[4,5-*c*]quinolin-2-one-(1-^{15}N) (**8′**).

Thus, the experimental results showed that the transformation **5g**→**7** proceeded exclusively through the pathway A, *i.e.* the process started with splitting of the bond between C-2 and N-3 and the nitrogen atom being in the original position 3 became an element of the primary amino group of the compound **7** obtained.

The structure of **7** and **8** arising from the ring transformation was also proved in a preparative way. In the case of **7**, the reactive amino group was transformed to the Schiff's base **11** with benzaldehyde, and on the other hand, it was acetylated with acetic acid anhydride to yield the amide **12**. Both compounds were obtained in excellent yields.

Scheme 5



The *N*-acylation of 1,3-dihydro-2*H*-imidazo[4,5-*c*]quinolin-2-one (**8**) gave the *N*-acetyl compound **13** in good yield.

EXPERIMENTAL

The melting points are uncorrected. The infrared spectra were obtained with a Perkin Elmer 157 G spectrophotometer, while the proton nmr spectra were taken up with a Hitachi Perkin Elmer R-24/A 60 mHz spectrometer by using tetramethylsilane as internal standard. The mass spectra were prepared with an Ms-902 type AEI spectrometer by the direct introduction method. The energy of ionization was 70 eV.

General Method for the Preparation of Guanidinonitroquinolines (**3**).

The base was made free from 1 mole of the salt of the appropriately substituted guanidine **2** by an equivalent amount of sodium ethoxide in ethanol. The precipitated inorganic salt was filtered and 0.5 mole of 4-chloro-3-nitroquinoline (**1**) (3) was added to the solution. After a short period, the product appeared in the form of orange-coloured crystals. The data of **3a-g** obtained are summarized in Table I.

General Method for the Preparation of Amino-*as*-triazino[6,5-*c*]quinoline-4-oxide Derivatives (**4**).

Table I

4-Substituted Guanidino-3-nitroquinolines (**3a-h**)

Compound			Empirical formula	Yield	Mp	Analysis C		H		N	
3	R_1	R_2	(Mol. wt.)	%	°C	Calcd.	Found	Calcd.	Found	Cald.	Found
a	H	H	$C_{10}H_9N_5O_2$ (231.2)	95	230-231	51.94	51.81	3.92	4.00	30.30	30.40
b	H	CH_3	$C_{11}H_{11}N_5O_2$ (244.3)	54	206-207	53.87	53.84	4.52	4.67	28.56	28.80
c	CH_3	CH_3	$C_{12}H_{13}N_5O_2$ (259.3)	53	222-223	55.59	55.73	5.06	5.06	27.02	26.95
d	H	C_2H_5	$C_{12}H_{13}N_5O_2$ (259.3)	28	187-189	55.59	55.62	5.06	5.02	27.02	27.15
e	H	*n*-C_4H_9	$C_{14}H_{17}N_5O_2$ (287.3)	28	192-193	58.53	58.56	5.96	6.17	24.37	24.37
f	H	*n*-$C_{10}H_{21}$	$C_{20}H_{29}N_5O_2$ (371.5)	31	136-138	64.66	64.48	7.87	8.01	18.85	18.97
g	H	$CH_2C_6H_5$	$C_{17}H_{15}N_5O_2$ (321.3)	98	205-207	63.53	63.51	4.70	4.62	21.80	21.69
h	H	diethylaminoethyl	$C_{16}H_{22}N_6O_2$ (330.4)	71	173-174	58.18	58.11	6.71	6.91	25.44	25.33

Table II

as-Triazino[6,5-*c*]quinoline 4-Oxide Derivatives (**4a-h**)

Compound			Empirical formula	Yield	Mp	Analysis C		H		N	
4	R_1	R_2	(Mol. wt.)	%	°C	Calcd.	Found	Calcd.	Found	Calcd.	Found
a	H	H	$C_{10}H_7N_5O$ (213.2)	95	309-311	56.35	56.13	3.31	3.32	32.85	32.69
b	H	CH_3	$C_{11}H_9N_5O$ (227.3)	78	275-277	58.14	58.32	3.99	4.11	30.83	30.78
c	CH_3	CH_3	$C_{12}H_{11}N_5O$ (241.3)	81	220-221	59.74	59.64	4.60	4.65	29.01	29.15
d	H	C_2H_5	$C_{12}H_{11}N_5O$ (241.3)	68	230-232	59.74	59.64	4.60	4.62	29.01	29.00
e	H	*n*-C_4H_9	$C_{14}H_{15}N_5O$ (269.4)	67	212-213	62.43	62.57	5.62	5.64	26.01	25.91
f	H	*n*-$C_{10}H_{21}$	$C_{20}H_{27}N_5O$ (353.5)	85	153-155	67.95	67.80	7.70	7.65	19.82	19.97
g	H	$CH_2C_6H_5$	$C_{17}H_{13}N_5O$ (303.3)	93	235-237	67.31	67.23	4.32	4.42	23.09	22.99
h	H	diethylaminoethyl	$C_{16}H_{20}N_6O$ (312.3)	62	158-159	61.51	61.69	6.45	6.44	26.91	27.05

To the boiling solution of 0.5 mole of **3** in 100 ml of ethanol, 100 ml of 5% sodium hydroxide solution was added while stirring. The mixture was boiled for 30 minutes to give a crystalline precipitate. The data of **4a-g** obtained are shown in Table II.

General Method for the Preparation of 2-Amino-*as*-triazino[6,5-*c*]quinoline Derivatives (**6**).

The solution of **4** in ethanol was hydrogenated in the presence of palladium on carbon catalyst at 1 atmosphere and at room temperature until hydrogen consumption ceased. After removing the catalyst, ethanolic hydrochloric acid was added to the solution to yield the hydrochloride of the appropriate 3,4-dihydro compound **5a-g**. When the solution was evaporated to dryness without the addition of acid, **6a-g** were obtained as a consequence of spontaneous oxidation. The corresponding data are contained in Table III.

3-Amino-1,3-dihydro-2*H* imidazo[4,5-*c*]quinoline-2-one (**7**).

A mixture of 3.6 g (0.01 mole) of **5g** with 30 ml of 10% hydrochloric acid was boiled for 2 hours. The initially precipitated material was dissolved on heating for a few minutes. After cooling, the precipitated hydrochloride of **7** was filtered and washed with ethyl acetate to yield 2.2 g (86%), mp 320-322° (from water). The same product was obtained by starting from **5a** or **5b** under similar conditions. The base liberated by sodium bicarbonate from the hydrochloride of **7** had mp 344-345° (from DMSO); ir (potassium bromide): 3310-3210 (NH_2), 3100-2300 (NH-imidazole), 1700 cm^{-1} (CO); ^{1}H-nmr (HMPA-d_{18}): 5.6 (s, br, NH_2), 7.1-7.5 (m, 2, H-7 H-8), 7.7 (dd, 1, H-9), 8.25 (dd, 1, H-6), 8.45 (s, 1, H-4), 13.0 (s, 1, NH).

Anal. Calcd. for $C_{10}H_8N_4O$ 200.2 and 202.2 for the ^{15}N-labelled compound: C, 60.00; H, 4.03; N, 27.98. Found: C, 60.11; H, 4.06; N, 27.85.

1,3-Dihydro-2*H*-imidazo[4,5-*c*]quinolin-2-one (**8**).

To the solution of 2.0 g (0.01 mole) **7** in 22 ml 36% sodium hydroxide (from which a part of the sodium salt crystallized out), a concentrated aqueous solution of 1.0 g of sodium nitrite was added, the mixture was cooled to 0° and 15 ml of 18% hydrochloric acid was added. The mixture

Table III

as-Triazino[6,5-*c*]quinoline Derivatives **6a-h**

Compound			Empirical formula	Yield	Mp	Analysis C		H		N	
6	R_1	R_2	(Mol. wt.)	%	°C	Calcd.	Found	Calcd.	Found	Calcd.	Found
a	H	H	$C_{10}H_7N_5$ (197.2)	80	290-291	60.91	60.85	3.58	3.57	35.51	35.64
b	H	CH_3	$C_{11}H_9N_5$ (211.2)	72	260-262	62.55	62.43	4.29	4.34	33.16	33.02
c	CH_3	CH_3	$C_{12}H_{11}N_5$ (225.3)	84	143-144	63.98	63.76	4.92	4.79	31.10	30.98
d	H	C_2H_5	$C_{12}H_{11}N_5$ (225.3)	77	218-219	63.98	63.87	4.92	4.97	31.10	30.92
e	H	*n*-C_4H_9	$C_{14}H_{15}N_5$ (253.3)	77	189-190	66.38	66.41	5.97	6.04	27.65	27.66
f	H	*n*-$C_{10}H_{21}$	$C_{20}H_{27}N_5$ (337.5)	87	114-117	71.18	71.02	8.07	8.14	20.75	20.61
g	H	$CH_2C_6H_5$	$C_{17}H_{13}N_5$ (287.3)	72	194-196	71.06	70.97	4.56	4.60	24.38	24.50
h	H	diethylaminoethyl	$C_{16}H_{20}N_6$ (296.4)	72	141-143	64.84	65.00	6.80	6.69	28.36	28.51

was stirred for one half hour at 0°, then 2 hours at room temperature and filtered. The crystals were suspended in water and adjusted to *p*H 7 by sodium bicarbonate to yield 1.5 g (82%) of the title compound, mp 360°; ir (potassium bromide): 3300-2400 (NH), 1720 cm^{-1} (CO); ^{1}H-nmr (HMPA-d_{18}): 7.2-7.7 (m, 3, H-7,8,9), 8.3 (dd, 1, H-6), 8.4 (s, 1, H-4), 12.0 (s, 1, NH), 12.8 (s, 1, NH).

Anal. Calcd. for $C_{10}H_7N_3O$ 185.2 and 186.2 for the ^{15}N-labelled compound, respectively: C, 64.86; H, 3.81; N, 22.69. Found: C, 65.06; H, 3.68; N, 22.49.

3-Benzylideneamino-1,3-dihydro-2*H*-imidazo[4,5-*c*]quinolin-2-one (**11**).

The suspension of 2.0 g (0.01 mole) **7**, in 20 ml of water was adjusted to *p*H 4 with hydrochloric acid. On heating to 40° the mixture became a clear solution, and the solution of 1.06 g (0.01 mole) benzaldehyde in 2 ml of ethanol was added while stirring. The crystals were filtered after 5 minutes to yield 2.7 g (94%) of the title compound, mp 349-350° (from dimethylformamide); ir (potassium bromide): 3100-2300 (NH), 1720 (CO); ^{1}H-nmr (HMPA-d_{18}): 7.2-7.8 (m, 5, aryl-H), 7.6-7.8 (m, 3, H-7,8,9), 8.35 (dd, 1, H-6), 8.7 (s, 1, H-4), 9.7 cm^{-1} (s, 1, CHC_6H_5).

Anal. Calcd. for $C_{17}H_{12}N_4O$ (288.3): C, 70.82; H, 4.20; N, 19.43. Found: C, 70.92; H, 4.36; N, 19.64.

3-Acetylamino-1,3-dihydro-2*H*-imidazo[4,5-*c*]quinolin-2-one (**12**).

The mixture of 2.0 g (0.01 mole) of **7** and 20 ml of acetic anhydride was boiled for one hour and a half and then poured into 20 ml of water. The *p*H of the solution was adjusted to 6 with 40% sodium hydroxide. The precipitated white crystals were filtered and washed with water to give 2.0 g (77%) **12**, mp 360° from water-ethanol; ir (potassium bromide): 3260 (NH), 3100-2300 (NH-imidazole), 1740 (CO), 1675, 1520 cm^{-1} (NH); ^{1}H-nmr (DMSO-d_6): 2.25 (s, 3, CH_3), 7.5-7.8 (M, 2, H-7,8), 8.0-8.3 (m, 2, H-6,9), 8.75 (s, 1, H-4), 11.1 (s, br, NH).

Anal. Calcd. for $C_{12}H_{10}N_4O_2 \cdot H_2O$ (260.3): C, 55.38; H, 4.65; N, 21.53; H_2O, 6.92. Found: C, 55.60; H, 4.73; N, 21.40; H_2O, 7.10.

3-Acetyl-1,3-dihydro-2*H*-imidazo[4,5-*c*]quinolin-2-one (**13**).

The mixture of 1.1 g (6 mmoles) of **8** and 11 ml of acetic anhydride was stirred and boiled for one hour, cooled and the precipitated product was filtered, washed with ethyl acetate and dried to give 1.0 g (73%) of **13**, mp 358-360° (from methyl cellosolve); ir (potassium bromide): 3200-2600 (NH), 1700 cm^{-1} (CO); ^{1}H-nmr (HMPA-d_{18}): 2.7 (s, 3, CH_3), 7.3-7.9 (m, 3, H-7,8,9), 8.4 (dd, 1, H-6), 9.2 (s, 1, H-4), 13.8 (s, br, NH).

Anal. Calcd. for $C_{12}H_9N_3O_2$ (227.2): C, 63.43; H, 4.00; N, 18.49. Found: C, 63.64; H, 4.06; N, 18.46.

REFERENCES AND NOTES

(1) E. Berényi, P. Benkó and L. Pallos, *Acta Chim. Acad. Sci. Hung.*, **90**, 399 (1976).

(2) P. Benkó, E. Berényi, A. Messmer, Gy. Hajós and L. Pallos, *ibid.*, **90**, 405 (1976).

(3) G. B. Bachman, D. E. Welton, G. L. Jenkins and J. E. Christian, *J. Am. Chem. Soc.*, **69**, 365 (1947).

(4) This compound was prepared from thiourea-$^{15}N_2$ (Isocommerz).

(5) The mass spectrometric behaviour of the compounds will later be analysed in detail.