Synthesis and Annelation Effect of Tricyclic Fused as-Triazinium Salts

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Two new tricyclic fused as-triazinium salts, the angular as-triazino[3,2-a]isoquinolinium 7 and the linear as-triazino[2,3-b]isoquinolinium system 5 have been prepared starting from a-diaminoisoquinolinium salts and a-dioxo compounds. The ring-closure reaction was extended to various dioxo reagents, e.g., the tetracycle 11 was obtained containing an exo double bond. The angularly fused isomer readily formed a covalent hydrate salt (e.g., 10) whereas the linearly fused salts remained in the heterocumstomatic form even under aqueous conditions which implies a marked anellation effect. The differences in formation and reactivity of the angular and linear ring systems have been interpreted in terms of their aromatic stability.

Dedicated to Professor Salo Gronowitz on the occasion of his 65th birthday.

We have recently reported on the synthesis of the bicyclic pyrido[1,2-b]as-triazinium salts1 3 starting from the 1,2-diaminopyridinium salt 1 and a-dioxo compounds 2. In this previous study we showed that this ring-closure reaction reported first by Kost et al.2,3 can be successfully extended to the synthesis of differently substituted derivatives using numerous symmetrical and unsymmetrical a-dioxo reagents 2.

Scheme 1.

In this paper we describe a further extension of the above cyclization: the synthesis of two differently (angularly and linearly) fused tricyclic analogues of the salts 3: the as-triazino[2,3-b]isoquinolinium (5) and as-triazino[3,2-a]isoquinolinium (7) salts. This study was also undertaken because we wished to clarify the differences in reactivity between the linearly and angularly annelated compounds. Considerable interest is evident in the literature4 about such an ‘annelation effect' and we have also contributed to this area during recent years.5,6

The starting compounds for these syntheses, the 2,3-diamino- (4) and 1,2-diamino-isoquinolinium salts (6), were described by us a few years ago.1,7 When either 4 or 6 was reacted with benzil (2, R' = R" = C6H4) in sulfuric acid under the conditions reported for 3,3 the desired ring closure took place and the diphenyl-substituted derivatives of the two new heteroaromatic cations (5a, A = BF4 and 7a) were obtained as fluoroborate salts in good yields. Spectra of the new yellow crystalline compounds (no NH in the IR spectrum, high down-field shifts in its 1H NMR spectrum) convincingly support the formation of these heteroaromatic systems.

When diacetyl (2, R = CH3) was used as the cyclizing agent we found, however, that only the 2,3-diaminoisoquinolinium salt 4 underwent ring closure under the conditions (methanol, perchloric acid) used3 for the bicyclic analogue 3, R = CH3 to give 5b as the perchlorate salt, whereas the 1,2-diaminoisoquinolinium isomer 6 did not react and was recovered from the reaction mixture. Since the ring closure examined is believed to include a nucleophilic attack of the amino groups at the carbonyl carbon atoms, the failure of the latter reaction was

Scheme 2.

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Fig. 1. Comparison of the aromatic stabilities of 1,2-diamino (a) and 2,3-diaminoisouquinolinium salt (c) as well as their doubly protonated forms (b) and (d), respectively.

obviously due to insufficient nucleophilicity of the amino groups in 6.

This difference in reactivity between the two isomeric diaminoisouquinolinium salts 4 and 6 prompted us to seek a rationalization of this finding, and the following consideration (Fig. 1) may give a satisfactory explanation.

As the ring-closure reactions are carried out in strong acid, the presence of both the starting cations 4 and 6 [Fig. 1, (a) and (c)] and their further protonated doubly positive species [(b) and (d)] should be taken into consideration. Obviously, the latter pair [(b) and (d)] are inactive in the supposed nucleophilic attack.

The relative stabilities of the singly and doubly positive species (a)-(d) can be qualitatively compared by using Clar's notation, i.e., each benzene ring where a π-sextet can be localized is marked with a circle and those isomers having the highest number of such circles are considered the most stable. The structural formulae (a)-(d) in Fig. 1 reveal that, in this respect, there is no essential difference between (a) and (b) (one circle in each) whereas the doubly positive 2,3-diamino isomer (d) has lost its π-sextet on protonation and its formation is therefore unfavourable. In other words, the relative aromatic character of (a)-(d) suggests that the 1,2-isomer occurs in the strongly protonated form (b) whereas the 2,3-isomer remains rather in the more stable form (c).

Because of the difficulties experienced, the synthesis of the dimethyl-substituted angularly fused as-triazino-[3,2-a]isouquinolinium salt 7c was accomplished through a different route. The diamino salt 6 was first deprotonated to its conjugate base 8. In contrast with the analogous conversion of the monocyclic diamino compound 1 described by Potts using fairly careful conditions (ion-exchange column) this bicyclic imino-amino compound (8) could be simply obtained by treatment of 6 with aqueous sodium hydroxide solution and was isolated in the form of stable colourless crystals. Reaction of 8 with diacetyl (2, R = CH₃) yielded the pseudo base 9c which, when treated with dilute acid, afforded the protonated salt 10c. With concentrated perchloric acid this salt (10c) underwent a facile dehydration to give the dimethyl-substituted heterocyclic perchlorate salt 7c in the form of pale yellow crystals.

When the perchlorate anion of 7c was exchanged for chloride, we observed that the yellow colour disappeared and a colourless chloride salt was obtained showing strong NH bands in the IR. The ¹H NMR pattern of this compound revealed that the chloride salt of the covalent hydrate 10c (A = Cl) was obtained. The facile covalent hydration of as-trazines is well documented in the literature and was also found by us with related ring systems.

Extension of the above synthetic route, i.e., under neutral conditions, to the angularly fused as-triazino-[3,2-a]isouquinolinium salts allowed the synthesis of various additional substituted compounds. Thus, aqueous glyoxal afforded the unsubstituted heteroaromatic compound as the perchlorate salt 7b. Exchange of the perchlorate anion for ethanesulphonate, however, resulted in formation of the ethanesulphonate derivative of the hydrate 10b. The ring closure was also accomplished with 1,2-cyclohexadiene. The orange condensation product which separated from this reaction mixture proved to be the tetracyclic compound 11 containing, interestingly, a double bond in the terminal ring. A similar conversion was observed with isatin: in this case, a new pentacyclic heteroaromatic derivative indolo[2,3':5,6'-as-triazino[3,2-a]isouquinoline (12) was obtained in good
yield as red crystals. Observation of formation of the stable 'exo' double bond in 11 prompted us to try this cyclization with glyoxylic acid esters which could also allow the introduction of a C=O function into position 2 of the target heterocycle. Thus, reaction of 8 with ethyl pyruvate, as expected, resulted in elimination of both water and ethanol and, accordingly, gave the triazinone compound 13 as a stable crystalline product.

\[ \text{Scheme 4.} \]

We have carried out detailed investigations of the covalent hydration of the above triazinium salts (e.g., 10). These experiments revealed that, depending on the substituents and counter ions, the addition of water may take place extremely easily. These examples and other related compounds obtained by us\(^{12}\) show that, generally, complex anions such as tetrafluoroborate or perchlorate favour the removal of water from the hydrates, whereas halides or sulfates tend to form covalent hydrates. Since formation of the covalent hydrates can be considered as a nucleophilic attack of the water molecule on the heteroaromatic cation, we were also interested in reactions of these heteroaromatic salts with hydroxide ion. We found that treatment of either 7 or 10 with sodium hydroxide solution afforded pseudo base 9 and therefore the following equilibria exist:

\[
\begin{align*}
\text{Aromatic salt} & \quad \xrightarrow{\text{Pseudo base}} \quad \xrightarrow{\text{Hydrate salt}} \\
7 & \quad 9 \quad \xrightarrow{=} \quad 10
\end{align*}
\]

which can be regarded as a ternary equilibrium. The first equilibrium (protonation of 9 to 10) can clearly be adjusted by changing the pH and the second (dehydration of 10 to 7) seems to be sensitive to the factors mentioned above (e.g., substituent, anion).

In contrast with the successful alternative synthesis starting from 1,2-diaminoisoquinolinium salt under neutral conditions, the 2,3-isomer does not react under analogous conditions: efforts to isolate the conjugate base (3-imino-2-amino compound) from 4 failed, probably because of the necessary formation of an unstable quinonoid structure and only a limited number of derivatives have been prepared. We wished, however, to compare the reactivity of the linearly fused \textit{ax}-triazino[2,3-b]isoquinolinium salt towards nucleophiles like water and hydroxide anion with that of the angularly fused isomer.

This linear ring system unlike the angularly fused isomer, failed to form a covalent hydrate under similar conditions. Thus, 2,3-diphenyl-\textit{ax}-triazino[2,3-b]isoquinolinium ethanesulfonate (5a, \(A = C_2H_5SO_2\)) was recovered from its aqueous acetonitrile solution after several hours, and the unchanged UV spectrum also revealed the stability of the aromatic form.

The linearly fused system 5, however, reacted very rapidly with sodium hydroxide: from the aqueous reaction mixture a very unstable greenish blue solid was isolated which decomposed very easily when allowed to stand. Only a very crude \(^1\)H NMR spectrum could be recorded from the solution of this product which suggested (singlet at 6.58) that the OH group is attached to C-6 (14 was formed) rather than to C-2 and, thus, the structure of this pseudo base (14) is totally different from that (9) obtained from the angularly fused analogue.

\[ \text{Scheme 5.} \]

This annelation effect may again be due to the different aromatic character of the linearly and angularly fused ring systems 5 and 7, and, in this respect, Fig. 2 may give a satisfactory explanation for the selectivity experienced with pseudo-base formation. In Fig. 2 we compare the structures of the possible pseudo bases, and again the representations using the 'Clar-circles' were used in order to mark the localized \(\pi\)-sextet units.

Inspection of Fig. 2 reveals that, with the angularly fused compounds (a), (c), the 2-substituted isomer [(a), circle in the structure] should be more stable than the 6-substituted one [(c) no aromatic substructure]. With the linear system, in turn, a different conclusion can be drawn: of the two pseudobases (b), (d) only the 6-substituted one (d) is partially aromatic and, thus,
formation of this isomer (d) is more favourable. We have shown above that the compounds which are formed experimentally, (a) and (d), are exactly those which can be predicted using these considerations.

A further study of the selectivity problem in the ring closure to fused as-triazinium salts as well as further extensions of the ring-closure reaction discussed here is in progress and will be published elsewhere.

**Experimental**

Melting points were determined on a Büchi apparatus and are uncorrected. The IR spectra were recorded with a Nicolet 205 FT apparatus. The NMR spectra were registered on Varian XL-400 equipment. Me$_4$Si was used as an internal standard.

**2,3-Dimethyl-as-triazino[2,3-b]isoquinolinium tetrafluoroborate** (5b). To a mixture of 2,3-diaminoisouquinolinium tosylate (4, 0.4 g, 1.2 mmol), methanol (6 ml) and diacetyl (0.12 g, 1.4 mmol) was added 70% perchloric acid (1 ml) and the mixture was allowed to stand at room temperature for 4 h. Pale yellow crystals separated which were filtered off and recrystallized from acetonitrile to give 0.25 g (74%) of the product; m.p. 238–240°C. Anal. C$_{11}$H$_{12}$ClN$_3$O$_4$; C, H, N.

**2,3-Diphenyl-as-triazino[3,2-a]isoquinolinium tetrafluoroborate** (7a). This compound was prepared according to the procedure given for 5a (see above). Starting from 1,2-diaminoisouquinolinium tosylate (6, 0.4 g, 1.2 mmol), benzil (0.27 g, 1.2 mmol) and sulfuric acid (4 ml), a yellow solid was obtained which was recrystallized from acetonitrile to give yellow needles: 0.38 g, 75%, m.p. 266–267°C. IR (KBr): 3110, 3060, 1630, 1550, 1460, 1440, 1390, 1320, 1280, 1160, 1100, 1060, 1040, 1010, 970, 820, 760, 700 cm$^{-1}$. Anal. C$_{22}$H$_{18}$BF$_4$N$_3$; C, H, N.

**2-Amino-1-iminoisouquinoline** (8). To a suspension of 1.0 g (3 mmol) of 1,2-diaminoisouquinolinium tosylate (6) in 3 ml water was added aqueous sodium hydroxide (10%, 3 ml) whereupon a clear solution was formed. After a few seconds a light yellow solid precipitated and the crystals were filtered off and recrystallized from toluene to give 0.34 g of light yellow needles 71%, m.p. 81–82°C. IR (KBr): 3310, 3295, 3180, 1644, 1610, 1570, 1545, 1480, 1460, 1420, 1360, 1290, 1270, 1250, 1185, 1150, 970, 940, 770, 755 cm$^{-1}$. H NMR (100 MHz, DMSO-d$_6$): 6 8.27 (d, 1 H, H-8, 8.0 Hz), 8.15 (br s, 2 H, NH$_2$), 7.60–7.25 (m, 3 H, H-5,6,7), 7.17 (d, 1 H, H-3, 7.5 Hz), 6.02 (d, 1 H, H-4, 7.5 Hz), 5.53 (s, 1 H, NH). Anal. C$_9$H$_8$N$_3$; C, H, N.

**2H-as-Triazino[3,2-a]isoquinolin-2-ol** (9b). To a suspension of 2-amino-1-iminoisouquinoline (8, 3.2 g, 20 mmol) in acetonitrile (20 ml) was added glyoxal (3.75 ml, 30% in water) at room temperature. A solution was formed first, then a white solid precipitated. The solid was filtered off and washed with acetonitrile to give 2.88 g of the pseudo base 9b. 72%, m.p. 150–152°C (DMF). IR (KBr): 3430, 3110, 3100, 3080, 3060, 3030, 2890, 1650, 1630, 1610, 1570, 1550, 1480, 1320, 1180, 1145, 1010, 970, 955, 930, 780, 680 cm$^{-1}$. H NMR (400 MHz, DMSO-d$_6$): 6 8.45 (d, 1 H, H-11, 8.0 Hz), 7.65 (t, 1 H, H-9, 7.0 Hz), 7.59 (d, 1 H, H-8, 8.0 Hz), 7.51 (t, 1 H, H-10, 7.0, 8.0 Hz), 7.42 (d, 1 H, H-6, 7.5 Hz), 7.24 (d, 1 H, H-3, 7.20 Hz), 6.49 (d, 1 H, H-7, 7.5 Hz), 6.20 (d, 1 H, H-10, 7.0 Hz), 5.48 (m, 1 H, H-2, 7.0, 2.0 Hz). Anal. C$_{14}$H$_{12}$N$_3$O; C, H, N.

as-Triazino[3,2-a]isoquinolinium perchlorate (7b). To a suspension of the pseudo base 9b (2.0 g, 10 mmol) in acetonitrile (5 ml) was added 70% perchloric acid (1.5 ml). A clear solution was formed and after a few minutes white crystals precipitated. The product was
filtered with washed with ethyl acetate to give 2.0 g of the salt 7b. 71%, m.p. 245–248°C. IR (KBr): 3130, 3110, 3090, 3080, 3060, 1640, 1590, 1440, 1410, 1350, 1330, 1160, 1100, 910, 890, 830, 800, 760, 720, 620 cm⁻¹. ¹H NMR (400 MHz, CD₂CN): δ 8.96 (d, 1 H, H-2, J 2.0 Hz), 8.92 (d, 1 H, H-3, J 2.0 Hz), 8.99 (d, 1 H, H-11, J 8.0 Hz), 8.83 (d, 1 H, H-6, J 7.5 Hz), 8.64 (d, 1 H, H-7, J 8.0 Hz), 8.34 (d, 1 H, H-8 J 8.0 Hz), 8.09 (m, 1 H, H-9), 7.97 (d, 1 H, H-8, J 7.0 Hz), 7.93 (d, 1 H, H-3, J 3.0 Hz), 7.84 (d, 1 H, H-6, J 7.5 Hz), 7.84 (m, 1 H, H-10, J 7.0, 8.0 Hz), 7.31 (d, 1 H, H-7, J 7.5 Hz), 5.92 (d, 1 H, H-2, J 3.0 Hz. Anal. C₁₃H₁₅N₂O₄S: C, H, N.

7,9,10,11-Tetrahydroisoquinolino[2,1-b]benzo-as-triazine (11). To a suspension of 2-amino-1-iminoisoquinoline (8, 1.59 g, 10 mmol) in acetonitrile (10 ml) was added 1,2-cyclohexanediol (1.2 g, 11 mmol) with stirring. A colourless precipitate was formed first which slowly turned to orange-yellow. After 2 h of stirring water (10 ml) was added to the suspension and the crystals were filtered off and washed with ethyl acetate to give 1.9 g of the salt 10c. 56%, m.p. 75–78°C. ¹H NMR (100 MHz, DMSO-d₆–CDCl₃): δ 11.0 (br s, 1 H, NH), 8.80 (d, 1 H, H-11, J 8.0 Hz), 8.70 (m, 3 H, H-8,9,10), 7.72 (d, 1 H, H-6, J 8.0 Hz), 7.30 (d, 1 H, H-7, J 8.0 Hz), 2.57 (q, 2 H, CH₂CH₂), 1.85 (s, 3 H, CH₃), 1.53 (s, 3 H, CH₃), 1.15 (s, 3 H, CH₂CH₂). Anal. C₃₃H₂₉N₁₉O₅: C, H, N.

1,2-Dihydro-2,3-dimethyl-2-hydroxy-as-triazino[3,2-a]isoquinolinium ethanesulfonate (10e). To a suspension of the pseudo base 9e (2.0 g, 10 mmol) in acetonitrile (5 ml) was added ethanesulfonic acid (0.9 ml, 11 mmol). After a few minutes, white crystals separated, which were filtered off and washed with ethyl acetate to give 2.1 g of the salt 10e: 65%, m.p. 136–138°C. IR (KBr): 3230, 3050, 2990, 2840, 2850, 1660, 1650, 1580, 1530, 1490, 1190, 1180, 1170, 1150, 1050, 800, 740, 680, 570 cm⁻¹. ¹H NMR (400 MHz, CD₂CN): δ 8.85 (d, 1 H, H-11, J 8.0 Hz), 8.01 (m, 1 H, H-9), 7.95 (d, 1 H, H-8, J 7.0 Hz), 7.93 (d, 1 H, H-3, J 3.0 Hz), 7.84 (d, 1 H, H-6, J 7.5 Hz), 7.84 (m, 1 H, H-10, J 7.0, 8.0 Hz), 7.31 (d, 1 H, H-7, J 7.5 Hz), 5.92 (d, 1 H, H-2, J 3.0 Hz). Anal. C₁₃H₁₅N₂O₄S: C, H, N.

Indolo[2',3':5,6]-as-triazino[3,2-a]isoquinoline (12). To a suspension of 2-amino-1-iminoisoquinoline (8, 3.2 g, 20 mmol) in acetonitrile (40 ml) was added isatin (3.2 g) with stirring. A red deep solution was formed. After 2 h of stirring at room temperature the red precipitate was filtered off and recrystallized from dimethylformamide to give 4.2 g (77%) of the product; m.p. 300–303°C. IR (KBr): 3100, 1620, 1590, 1550, 1490, 1410, 1300, 1190 cm⁻¹. Anal. C₂₂H₁₉N₁₀: C, H, N.

3-Methyl-as-triazino[3,2-a]isoquinolin-2(5H)-one (13). To a suspension of 2-amino-1-iminoisoquinoline (8, 3.2 g, 20 mmol) in acetonitrile (50 ml) was added ethyl pyruvate (2.62 ml, 1.2 g, 24 mmol) dropwise with stirring. A crystalline precipitate was formed which was filtered off after 30 min of stirring at 0°C. The product was recrystallized from acetonitrile to give 2.3 g of 13: 54%, m.p. 240–241°C. ¹H NMR (100 MHz, DMSO-d₆–CDCl₃): δ 8.70 (d, 1 H, H-11, J 7.0 Hz), 7.95 (d, 1 H, H-6, J 8.0 Hz), 7.90–7.40 (m, 3 H, H-8,9,10), 7.30 (d, 1 H, H-7, J 8.0 Hz), 2.39 (s, 3 H, CH₃). Anal. C₁₃H₁₁N₉O: C, H, N.

Reaction of 2,3-diphenyl-as-triazino[2,3-b]isoquinolinium tetrafluoroborate (5a, A = BF₄⁻) with sodium hydroxide (formation of the pseudo base 14). To a solution of 2,3-diphenyl-as-triazino[2,3-b]isoquinolinium ethanesulfonate (5a, A = C₂H₅SO₃, 0.45 g, 1 mmol) in water (10 ml), was added 2M aqueous sodium hydroxide solution, whereupon a dark greenish blue solid precipitated immediately. The crude pseudo base 14 (0.23 g; 71%) was separated by filtration; m.p. 221–223°C. ¹H NMR (60 MHz, CDCl₃): δ 8.70–7.2 (m, 15 H), 5.8 (s, 1 H, H-6).
References


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