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Oxidative Ring Expansion of Spirocyclic Oxindole Derivatives

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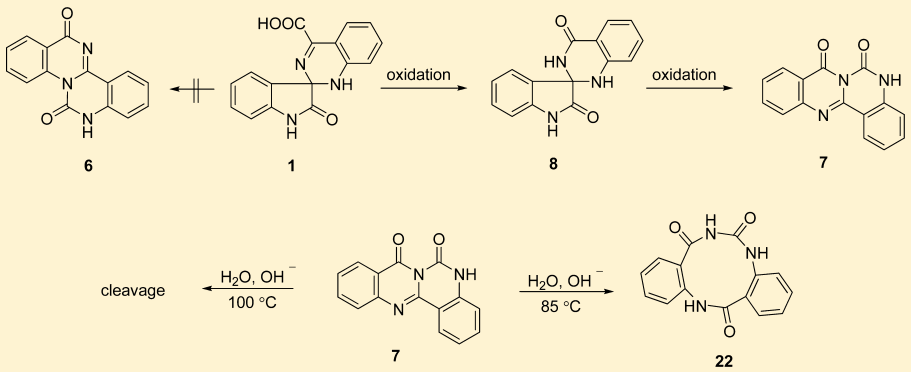
Supporting Information



ABSTRACT: Oxidation of the spirocyclic oxindole derivative, isamic acid **1**, led to decarboxylation and ring expansion to quinazolino[4,5-*b*]quinazoline-6,8-dione **7** rather than, as previously believed, its isomer **6**. The structure of **7** was confirmed by X-ray crystallography. Condensation of isatin (indole-2,3-dione) and 2-aminobenzamide led to the spirocyclic molecule, spiro[3*H*-indole-3,2′(1*H*)quinazoline]-2,4′(1*H*,3*H*)dione **8**, which was also identified as an intermediate in the oxidation of isamic acid. Mild hydrolysis of **7** gave the 10-membered molecule **22**. Isamic acid could easily be converted to *N*-nitrosoisamic acid, which when heated in ethanol underwent a ring expansion to a hydroximino derivative, **38**, of compound **6**. The structure of **38** was confirmed by X-ray crystallography.

INTRODUCTION

Although isamic acid **1**, $C_{16}H_{11}N_3O_3$, which can easily be prepared from isatin **2** in the presence of ammonium ions, has been known since 1842,[1] its true nature as a spirocyclic derivative of oxindole was not revealed until 1969, when Field was the first to assign the correct structure.[2] One year later, this assignment was confirmed by an X-ray crystallographic investigation of *p*-bromophenacyl isamate.[3] Over the years, several research groups have contributed to the study of isamic acid, notably Reissert and Hoppmann,[4] who developed an excellent procedure for the preparation of isamic acid. Jasini,[5−9] in particular, prepared several derivatives (many of them unassigned), and de Mayo and Ryan,[10] who after a comprehensive study in 1967, were the first to suggest a structure (albeit incorrect) with the right composition, namely, **3**, of isamic acid. Previously, Reissert and Hoppmann had assigned structure **4** in 1924. This incorrect formulation was based on the composition $C_{16}H_{13}N_3O_4$, due to the fact that isamic acid strongly adheres one molecule of water (Figure 1).

A few years after the establishment of its true structure, Cornforth in 1976 resolved isamic acid with the help of brucin.[11] Cornforth also noted that the pure enantiomer readily underwent racemization when dissolved in methanol.

RESULTS AND DISCUSSION

Isamic acid could readily be prepared as described by Reissert and Hoppmann by treating isatin with a hot aqueous solution of ammonium chloride and sodium acetate.[4] The ^{13}C NMR spectrum of isamic acid featured a diagnostic signal from the carbon atom in spiro-position at 75.4 ppm.

In connection with attempts to elucidate the structure of isamic acid, Jasini, as well as de Mayo, treated this molecule with hydrogen peroxide in sodium hydroxide under forcing conditions and isolated three compounds A ($C_{14}H_{11}N_2O$), B ($C_{15}H_9N_2O_2$), and C (correctly identified as 2,4(1*H*,3*H*)-quinazolinedione). Compound A was correctly assigned structure **5**, and de Mayo obtained certain evidence that B should have structure **6**. The isomer **7** was also discussed by Jasini as well as by de Mayo but disregarded as an alternative. However, it will now be shown that the correct structure is indeed quinazolino[4,3-*b*]quinazoline-6,8-dione (**7**) (vide infra).

The old experiments just discussed have now been repeated but with careful control of the reaction temperatures. Under such conditions, the known[12] (since 2003) spirocyclic molecule **8**

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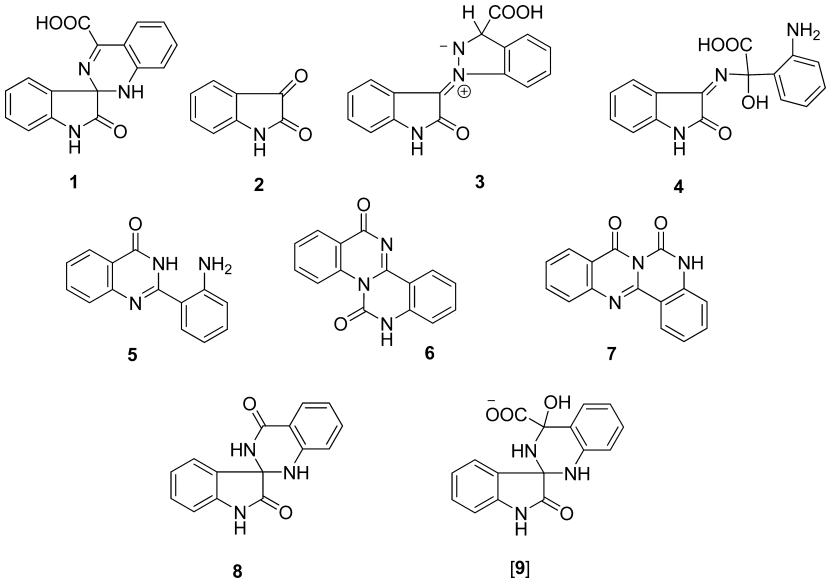
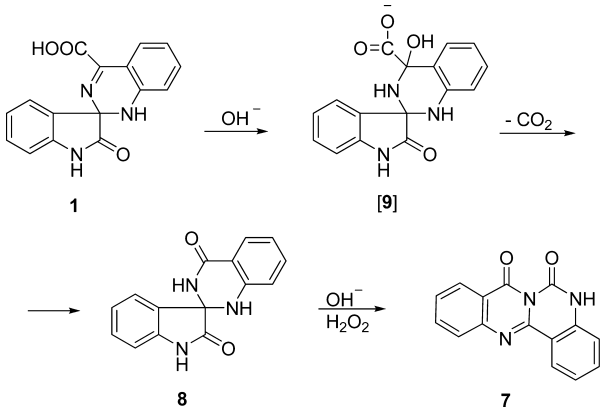


Figure 1. Graphical representation of molecules **1**–**9**.

could now be isolated as an intermediate. Mechanistically, such a reaction pathway is in line with similar oxidative decarboxylations described in the literature.[13] It is assumed, as outlined in Scheme 1, that the addition product **9** is an intermediate.

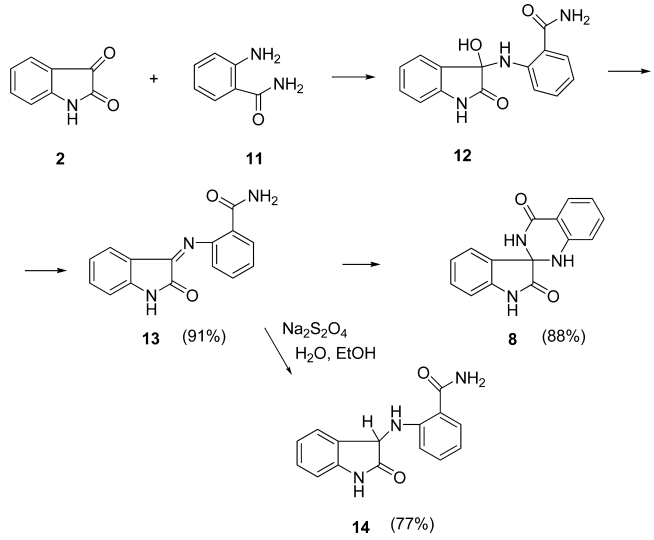
Scheme 1



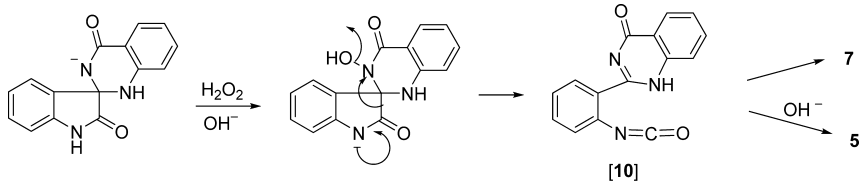
Compound **8**, which featured a diagnostic signal from the carbon atom in the spiro-position at 71.0 ppm in the ^{13}C NMR spectrum, underwent quickly and in almost quantitative yield a ring expansion to the quinazolinoquinoline **7** when treated with potassium permanganate under alkaline conditions at ambient temperature. 2-(2-Aminophenyl)quinazoline-4(3*H*)-one (**5**) was formed as one of the products (together with **7**) when isamic acid was treated with a hot alkaline solution containing considerable amounts of hydrogen peroxide. Compound **5** is not a consecutive product formed by ring cleavage of **7**. Actually, this molecule of low solubility is relatively insensitive to alkaline oxidative conditions. Rather, it is suggested that **5** is formed during the ring expansion process as outlined in Scheme 2. Ring expansions of oxindoles involving isocyanates have been invoked previously in mechanistic discussions.[12,14]

At this stage, it became of interest to resolve the spirocyclic molecule **8**, and in this context, some details of the synthesis of the racemate were studied as outlined in Scheme 3.

Scheme 3



Scheme 2



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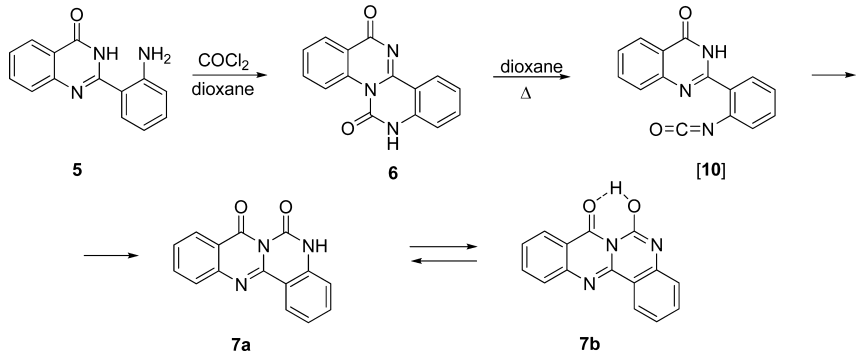
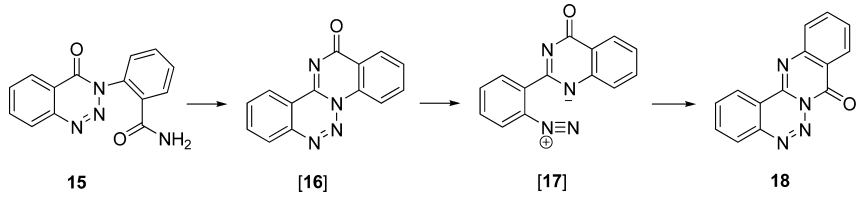
Scheme 4



Scheme 5



The yellow-orange intermediate **13**, which also is the chain tautomer of the spiro-compound **8**, could easily be obtained in high yields by heating **2** and **11** for 3 h in ethanol. The unstable intermediate **12** could be obtained by treating **2** and **11** under ultrasound at 25 °C. When the yellow-orange imine **13** was treated with an aqueous solution of sodium hydroxide at 45 °C, a colorless solution (presumably containing **12** after addition of water) was obtained. Acidification of this solution with acetic acid yielded, however, the spiro-compound **8**. Reduction of the imine with sodium dithionite in aqueous ethanol readily gave the 3-amino-substituted oxindole **14**. The intermediates **12** and **13** could be fully characterized by NMR spectroscopy. Molecule **12** featured a diagnostic singlet at 78.7 ppm and molecule **14** a doublet at 55.6 ppm in their ^{13}C NMR spectra.

Excellent resolution of the racemate of **8** could be effected with supercritical fluid chromatography. The separation of the enantiomers was excellent. Fraction A gave $[\alpha] = -210$, and fraction B gave $[\alpha] = +248$. Both values might be too low due to relatively rapid racemization. One of the enantiomers had previously been prepared using a chiral Brønsted acid in impure form by List *et al.*[15] These workers failed, however, to recognize the signal from the spiro-carbon atom, and hence, we initially believed that their sample mainly contained the chain tautomer.

A closer examination of their published spectrum (in CD_3OD) revealed the presence of a tiny but ignored signal around 73 ppm and more importantly the nonpresence of the chain tautomer. Five years later, Shi *et al.*[16] also obtained an enantiomer of **8** using a similar methodology. However, previous work was not cited.

During the early days of this investigation, it was assumed (following de Mayo) that the oxidation product of **1** (or **8**) had structure **6** (rather than its isomer **7**). This concept started to sway when it was found that treatment of the amino compound **5** with phosgene (or its trimer) in dioxane initially gave **6**, which readily rearranged to the isomer **7** (Scheme 4). These results called for an X-ray investigation which finally proved that **7** (vide infra) is the correct structure of the oxidation product, as already outlined in Scheme 1. In DMSO solution, **7** exists as an equilibrium between **7a** and **7b**, in a 65:35 ratio, as indicated by nice NMR data. In the solid state, the hydroxyl tautomer **7b** is not present. The new results are summarized in Scheme 4. The kinetic molecule **6**, 13*H*-quinazolino[3,4-*a*]quinazolin-5,13-dione, quite readily isomerized to the more stable isomer **7**, for instance, by dissolution in methanol (50 °C) or pyridine (60 °C). The isomer **6** featured a characteristic absorption (C═O) at 1794 cm^{-1} in the IR spectrum, whereas the corresponding signal from the isomer **7** appeared at 1752 cm^{-1}. Both isomers (**6** and **7**) are of low solubility, and DMSO, used as solvent during NMR studies, was aggressive and caused partial decarboxylation to 2-(2-aminophenyl)-4(3*H*)-quinazolinone, **5**.

A similar transformation in the quinazolinobenzotriazine series has been reported by Eddy, Vaughan, and Stevens.[17] Their results are outlined in Scheme 5. It should be noted that only compound **18** actually could be isolated.

The isomers **6** and **7** gave quite different products when treated with sodium hydroxide in water−dioxane. Thus, compound **6** readily underwent ring opening to the known[18] molecule **20**, whereas **7** via the addition product **21** (ring tautomer) gave the 10-membered molecule **22** (chain tautomer). This conversion required a short period of heating at 80−85 °C. Prolonged heating at reflux temperature resulted in cleavage to 2,4(1*H*,3*H*)-quinazolinedione and anthranilic acid. Dissolution of **7** under alkaline conditions at ambient temperature (or even at 60 °C) followed by acidification regenerated **7**. Heating of the pair **21**/**22** in acetic anhydride resulted in recyclization to **7**. The assignment of **22** is based primarily on its conversions but also on a trio of signals (169.6, 159.0, and 155.9 Hz) in the ^{13}C NMR spectrum that should exclude any cyclol (e.g., **21**) as an alternative.

Treatment of **7** with amino compounds resulted in a different type of ring cleavage, as exemplified by the formation of the new molecule **23** and the already known molecule **24**. Isomer **6** when treated similarly gave, as expected, identical products. Compound **22** has a low solubility in many solvents, and in connection with a recrystallization experiment with *N*,*N*-dimethylformamide, it was found that another (as distinct from **22** → **7**) transannular reaction occurred, namely, formation of **25**, a known compound.[19−21] The results are outlined in Scheme

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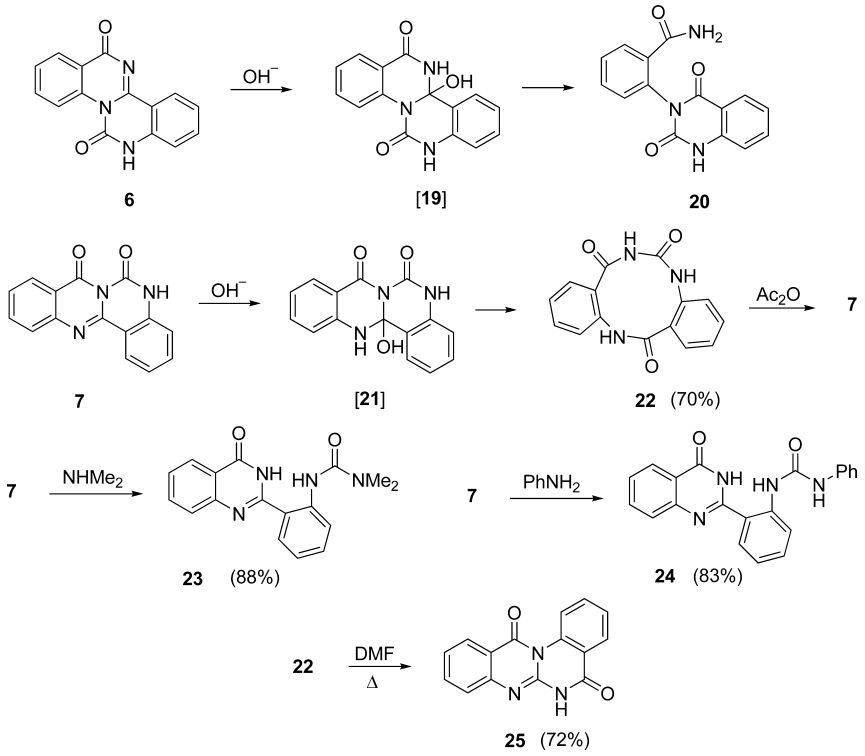
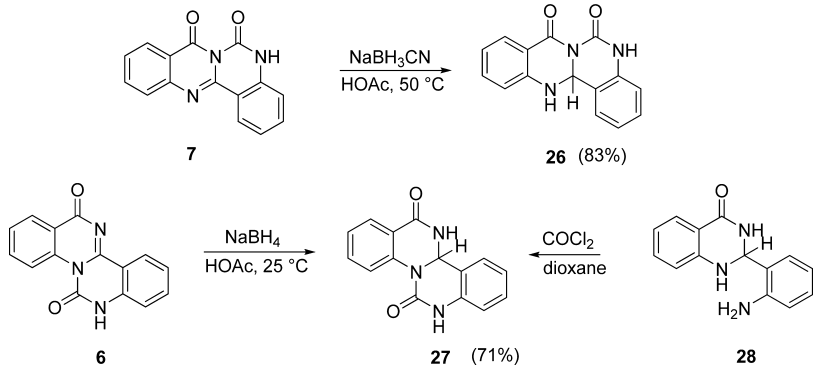
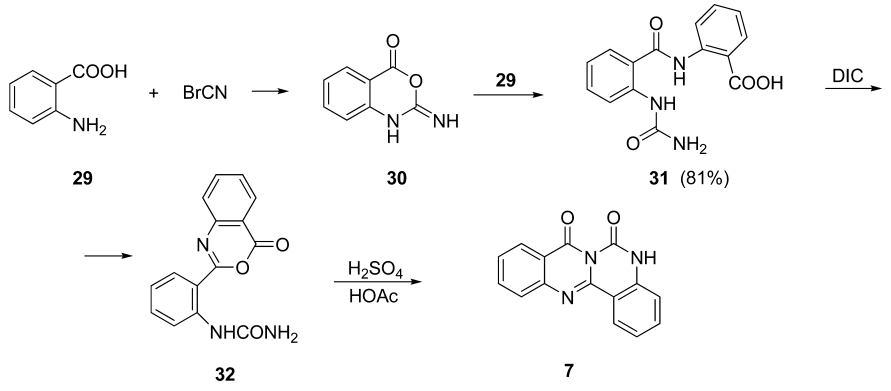
Scheme 6



Scheme 7



Scheme 8[a]



[a]DIC= diisopropylcarbodiimide.

6. Similar cases of 10-membered cycloamides in equilibrium with the corresponding cyclols have been reported by Pinnen.[22,23]

Reduction of the quinazolinoquinazoline **7** with sodium cyanoborohydride in acetic acid gave the dihydro derivative **26**,

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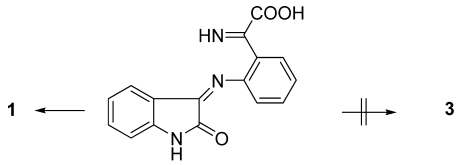
whereas the isomer **6** gave the dihydro derivative **27**, which also could be obtained from the known[24] compound **28** by treatment with phosgene in dioxane (Scheme 7).

During the late 1960s, Doleschall and Lempert[25−27] prepared and correctly identified the quinazolino[4,3-*b*]quinazoline **7** using the route outlined in Scheme 8. Molecule **31** had been prepared by this route already in 1904 by König,[28] although the structure that he assigned to it was incorrect. By this route, large amounts of **7** could readily be prepared.

Nitrosation of **8** readily gave the unstable nitroso derivative **33**, and when heated for 3−5 min in ethanol, a ring expansion occurred with separation of molecule **7**. Isamic acid similarly gave the nitroso derivative **34**, which had been shown by Jasini to undergo a series of transformations under acidic conditions to give a number of unstable intermediates. One of the molecules was described as deeply yellow and considerably more stable than the others. Like isamic acid **1**, its nitroso derivative **34** is a monohydrate, and Jasini,[5] based on Reissert's structure **4**, assigned the incorrect structure **39**, a molecule that never has been isolated nor described (Scheme 9).

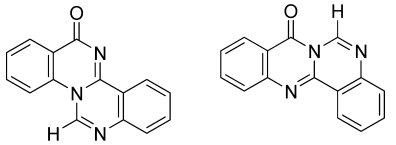
Scheme 9



39

Some of these intermediates have now been studied by NMR spectroscopy (Scheme 9), and in particular, the structure of the yellow stable compound **38** has been determined by X-ray crystallography. The intermediate **35**, formed via *trans*-nitrosation of **34**, could be isolated and featured a signal at 81.8 ppm for the carbon atom in the spiro-position. This intermediate subsequently undergoes ring expansion and an intramolecular oxidative decarboxylation. Intramolecular delivery of the element of hydroxylamine to the carbonyl group in the 13-position is vital for the formation of the 13-hydroximino compound **38** (Scheme 10).

In this paper, we have shown that several papers wherein compound **6** has been claimed were in fact dealing with its isomer **7**. A parallel case has recently been revealed by Venkateswarlu et al.,[29,30] where the originally claimed[31] 13*H*-quinazolino[3,4-*a*]quinazoline-13-one **40** has been shown to be 8*H*-quinazolino-[4,3-*b*]quinazoline-8-one **41** (Figure 2). Compound **41** has been known at least since 1956[32] and is easy to prepare from 2-(2′-aminophenyl)quinazoline-4(3*H*)-one **5** and ethyl orthoformate.[33]



40 **41**

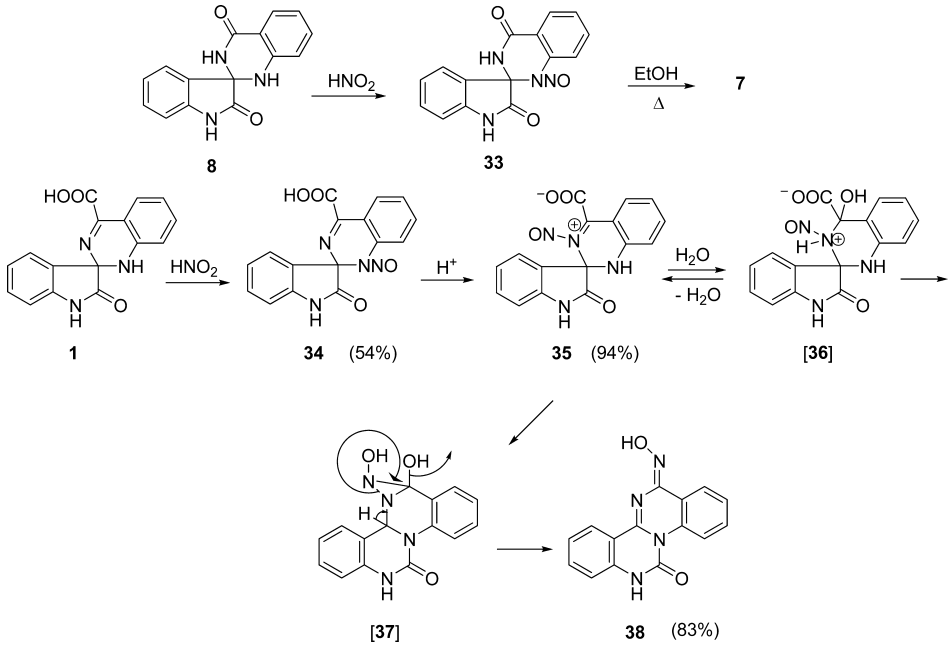
Figure 2. Graphical representation of molecules **40** and **41**.

Finally, one can ask the question why de Mayo's suggested structure for isamic acid was the indazole derivative **3**. Actually, the immediate precursor to **3** was suggested to be **39**, which is the chain tautomer of isamic acid **1**. In other words, de Mayo was quite close to the truth.

CRYSTALLOGRAPHIC SECTION

The structure of **7** was confirmed by a single-crystal X-ray analysis. The details of the X-ray analysis can be found in the Experimental Section. The molecular and crystal structure of **7** is visualized in Figure 3. The molecule forms dimers via hydrogen bonding in the [010] direction, and in the [100] direction, the molecules have significant $\pi-\pi$ stacking interactions. The packing coefficient (percent filled van der Waals space in the

Scheme 10



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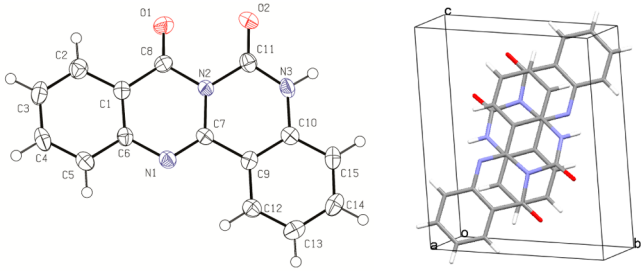

Figure 3. (a) Molecular and (b) crystal structure of **7**. A more detailed version can be found in the Supporting Information.

unit cell) is 73%, indicating an efficient molecular framework in the solid state.

The structure of the hydroximino compound **38** was confirmed by X-ray analysis, the details of which are given in the Experimental Section. The molecular and crystal structure is shown in Figure 4. The molecules are linked together via

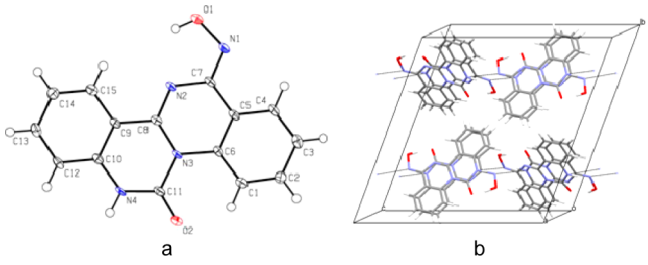

Figure 4. (a) Molecular and (b) crystal structure of **38**. Panel a shows one of the four symmetry-independent molecules in the asymmetric unit. Panel b also displays the hydrogen bonds in the [001] direction. More detailed versions of panels a and b can be found in the Supporting Information.

hydrogen bonds ([001] direction) and strong $\pi-\pi$ stacking interactions ([100] direction) (Figure 4) to form a 3D network. The packing coefficient (percent filled van der Waals space in the unit cell) is 74%, indicating a very efficient molecular framework in the solid state.

EXPERIMENTAL SECTION

^{1}H and ^{13}C NMR spectra were recorded on an instrument at 300.1 MHz for ^{1}H and 75.5 for ^{13}C using the residual (DMSO-d_6) resonances as reference, unless otherwise stated. The IR spectra were obtained on a 300 FT-IR spectrometer. All chemicals originated from commercial sources and were used as received, except THF, which was distilled from sodium and stored under nitrogen.

Isamic Acid (1). Isatin (14.7 g, 0.1 mol) was added to a stirred solution of ammonium chloride (10.0 g) and sodium acetate (16.5 g) in water (150 mL) at 70 °C. After a period (20 min) at 95 °C, the reaction mixture (now containing the yellow-beige sodium−ammonium salt of isamic acid) was allowed to reach 30−45 °C when the mixture was acidified with hydrochloric acid and cooled with crushed ice. The title compound was isolated as a red solid: 12.6 g (88%); IR 3385, 3170, 3122, 1726, 1643, 1619, 1473, 1389, 1189, 1136, 1029, 752 cm^{-1}; ^{1}H NMR δ 3.5 (br s, 1H), 6.59 (m, 2H), 6.87 (d, 1H), 7.00 (dd, 1H), 7.20 (m, 2H), 7.30 (m, 2H), 10.3 (s, 1H); ^{13}C NMR δ 75.4 (s), 110.1 (d), 111.5 (s), 113.6 (d), 116.9 (d), 122.3 (d), 126.8 (d), 130.3 (d), 133.2 (s), 134.1 (d), 140.6 (s), 145.6 (s), 159.7 (s), 165.9 (s), 175.1 (s).

Spiro[3*H*-indole-3,2′(1*H*)quinazoline]-2,4′(1*H*,3′*H*)-dione (8). Isatin (14.7 g, 0.1 mol) and 2-amino benzamide (13.6 g, 0.1 mol) were heated in acetic acid (110 mL) at reflux temperature for 1 h, whereupon the clear solution was evaporated and treated with 2-propanol, which resulted in a whitish solid: 23.8 g (88%); mp 277−278 °C (lit.[12] 277−278 °C); the spectroscopic data were identical to those in the literature;[12] IR 3488, 3233, 2967, 1709, 1685, 1646, 1610, 1524, 1474, 1327, 1195, 1050, 877, 757 cm^{-1}; ^{1}H NMR δ 6.62 (d, 1H, J = 7.8 Hz), 6.09 (m, 1H), 6.85 (d, 1H, J = 6.8 Hz), 7.05 (m, 1H), 7.25 (m+d, 3H, J = 1.16 Hz), 7.46 (d, 1H, J = 6.8 Hz), 7.60 (d, 1H, J = 7.8 Hz), 8.33 (d, 1H, J = 1.16 Hz), 10.3 (br s, 1H); ^{13}C NMR δ 71.0 (s), 110.1 (d), 113.9 (d), 114.3 (s), 117.2 (d), 122.3 (d), 125.3 (d), 126.8 (d), 129.5 (s), 130.8 (d), 133.3 (d), 142.1 (s), 146.8 (s), 163.9 (s), 176.0 (s).

Quinazolino[4,5-*b*]quinazoline-6,8-dione (7). Method A. Oxidation of the spiro-compound **8** occurred with addition of potassium permanganate (vide infra). Method B. Isomer **6** (100 mg) was heated in dioxane (25 mL) for 5 min; the solid was obtained upon cooling, isolated, washed with dioxane, and dried to yield 98 mg of isomer **7**. Method C. The benzoxazinone **32** was added to acetic acid (60 mL) containing sulfuric acid (10 mL) and heated to 110 °C for 15 min, whereupon the solution was added to ice/water. The solid formed was collected, washed with water, and dried. Method D. The *N*-nitroso compound **33** (294 mg, 1 mmol) was dissolved in ethanol and heated at reflux temperature for 5 min. The solid formed was collected after being cooled and washed: 228 mg (91%); mp 291−293 °C (lit.[10] 291−293 °C); in solution, **7** appears as a mixture of tautomers (**7a** and **7b**); IR 3205, 3148, 3009, 2933, 1752, 1689, 1581, 1563, 1372, 1258, 1125, 891, 757, 747 cm^{-1}; ^{1}H NMR (**7a**) δ 7.15 (d, 1H), 7.26 (dd, 1H), 7.55 (dd, 1H), 7.61 (dd, 1H), 7.69 (d, 1H), 7.86 (dd, 1H), 8.15 (dd, 1H), 8.38 (dd, 1H), 11.50 (s, 1H); ^{1}H NMR (**7b**) δ 7.23 (dd, 1H), 7.31 (dd, 1H), 7.61 (dd, 1H), 7.71 (dd, 1H), 7.83 (dd, 1H), 8.17 (dd, 1H), 8.36 (dd, 1H), 8.96 (d, 1H), 12.10 (s, 1H); ^{13}C NMR (**7**) δ 110.5 (s), 115.3 (d), 119.9 (d), 121.5 (d), 121.6 (d), 123.8 (d), 125.8 (s), 129.8 (d), 131.1 (d), 133.3 (d), 141.2 (s), 142.5 (s), 155.9 (s), 158.9 (s), 169.6 (s).

3-Hydroxy-3-(2-carboxamido)phenylamino-oxindole (12). Isatin (1.47 g, 10 mmol) and 2-amino-benzamide (1.36 g, 10 mmol) were added to ethanol (20 mL), and the mixture was stirred at ambient temperature under the influence of ultrasound until all isatin was consumed (4 h): 1.10 g (38%); mp 150 °C decomp (loss of water); IR 3585, 3440, 3225, 1710, 1655, 1584, 1508, 1470, 1211, 1044, 750 cm^{-1}; ^{1}H NMR δ 5.66 (d, 1H), 6.50 (dd, 1H), 6.91 (m, 3H), 7.20 (m, 3H), 7.54 (d, 1H), 7.91 (s, 1H), 9.07 (s, 1H), 10.64 (s, 1H), 78.7 (s), 109.8 (d), 112.3 (d), 115.6 (d), 116.8 (s), 121.3 (d), 125.4 (d), 127.1 (s), 128.9 (d), 129.1 (d), 131.9 (d), 142.6 (s), 147.0 (s), 171.4 (s), 174.7 (s). Anal. Calcd for $C_{15}H_{13}N_3O_3$: C, 63.59; H, 4.63; N, 14.83. Found: C, 63.65; H, 4.35; N, 14.86.

Isatin-2′-carboxamidophenylimine (13). Isatin (2.94 g, 20 mmol) and 2-aminobenzamide (2.72 g, 20 mmol) were heated in ethanol (40 mL) at reflux temperature for 3 h. The orange-yellow solid formed was collected, washed with ethanol, and dried: 4.85 g (91%); mp >260 °C; IR 3372, 3209, 3080, 2975, 1725, 1655, 1605, 1483, 1462, 1394, 1339, 1210, 1147, 736 cm^{-1}; ^{1}H NMR δ 6.37 (d, 1H), 6.89 (dd, 1H), 6.88 (d, 1H), 6.99 (d, 1H), 7.31−7.70 (m, 7H), 7.83 (d, 1H), 11.0 (s, 1H); ^{13}C NMR δ 111.6 (d), 116.1 (s), 117.9 (d), 121.9 (d), 125.0 (s), 125.1 (d), 125.7 (d), 129.6 (d), 131.6 (d), 134.7 (d), 147.1 (s), 148.4 (s), 155.2 (s), 163.5 (s), 167.5 (s). Anal. Calcd for $C_{15}H_{11}N_3O_2$: C, 67.91; H, 4.18; N, 15.84. Found: C, 67.77; H, 4.30; N, 15.61. When dissolved in DMSO, compound **13** readily underwent cyclization to its ring tautomer, **8**.

3-(2-Carboxamido)phenylamino-oxindole (14). Method A. The imine **13** (265 mg, 1 mmol) was added to acetic acid (5 mL) followed by sodium cyanoborohydride (125 mg, 2 mmol). The mixture was stirred at 40 °C, which changed the yellow-orange coloration to colorless within 30 min, whereupon the solution was diluted with water and the precipitate formed was collected, washed, and dried: 230 mg (77%); mp 118−120 °C. Anal. Calcd for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.32; H, 5.00; N, 15.63. Method B. The imine **13** (2.65 g, 10 mmol) was added to a stirred solution of ethanol (30 mL) and water (30 mL), wherein sodium dithionite (3.50 g) had been dissolved. The mixture was kept at 50 °C until it became almost colorless when it was concentrated and then diluted with water. The precipitate was collected, washed, and dried: 2.25 g (81%); mp 118−120 °C; IR 3413, 3197, 3078, 1702, 1615, 1578, 1513, 1473, 1378, 1324, 1274, 1233, 1192, 1139, 1119, 836, 731 cm^{-1}; ^{1}H NMR δ 5.35 (d, 1H, J = 6.2

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Hz), 6.54 (dd, 1H), 6.63 (dd, 1H), 6.92−6.99 (m, 2H), 7.19−7.32 (m, 4H), 7.68 (d, 1H), 7.97 (s, 1H), 8.67 (d, 1H, J = 6.2 Hz); the signal from the NH in the oxindole ring was not observed; ^{13}C NMR δ 55.6 (d), 110.0 (d), 112.5 (d), 114.9 (s), 115.3 (d), 121.9 (d), 124.0 (d), 127.8 (s), 128.9 (d), 129.1 (d), 132.4 (d), 141.9 (s), 148.8 (s), 171.6 (s), 176.8 (s).

Oxidation of Isamic Acid (1) under Previously Used Conditions. Isamic acid (1.0 g) was dissolved in aqueous sodium hydroxide (10%, 10 mL), and hydrogen peroxide (30%, 2 mL) was added. A vigorous reaction ensued, and a yellowish precipitate was formed after approximately 5 min. After 4 h at rest, this precipitate was collected and recrystallized from acetic acid (210 mg, 24%). This compound was later identified as molecule **7** (vide infra). Acidification of the aqueous phase with acetic acid gave a precipitate of 2-(*o*-aminophenylquinazoline-4(3*H*)-one **5** (180 mg, 33%) (vide infra).

Oxidation of Isamic Acid (1) under Controlled Conditions. Isamic acid (7.0 g, 25 mmol) was dissolved in water (300 mL) containing potassium hydroxide (7.0 g), whereupon hydrogen peroxide (30%, 7.0 mL) was added in portions during 45 min, keeping the temperature in the stirred solution between 30 and 40 °C. After a period of 3 h, the precipitate that formed was collected (2.10 g, 51%) and identified as the spiro-compound **8**. Acidification of the mother liquor gave a precipitate of the starting material (i.e., isamic acid, 3.80 g).

Oxidation of the Spiro-Compound 8 with Potassium Permanganate under Alkaline Conditions. The spiro-compound **8** (2.65 g, 10 mmol) was dissolved in water (120 mL) containing potassium hydroxide (2.5 g). A solution of potassium permanganate (0.75 g) dissolved in water (150 mL) was added dropwise to the stirred solution at 25 °C, during 10 min. An initial green coloration was observed; however, soon, manganese(IV) oxide appeared. The precipitates that formed were collected and treated with a solution of sodium hydrogensulfite. The manganese(IV) oxide quickly dissolved, and the whitish precipitate of compound **7** could be observed and collected (2.15 g, 87%).

2-(2-Aminophenyl)quinazoline-4(3*H*)-one (5). Method A. 2-(2-Nitrophenyl)quinazolin-4(3*H*)-one[34] (2.68 g, 10 mmol) was added to a stirred solution composed of sodium dithionite (3.0 g) in water (25 mL) and ethanol (25 mL). The mixture was heated at 65 °C and within 15 min resulted in a clear solution. Concentration followed by dilution with water gave the crude product which was crystallized from ethanol: 2.05 g (89%); mp 236−237 °C (lit. 236−237 °C).[35] Method B. 2-(2-Nitrophenyl)quinazolin-4(3*H*)-one[34] (2.68 g, 10 mmol) was catalytically (Pd/C, 5%) hydrogenated and dissolved in 1:1 ethanol/dioxane (100 mL). Filtration and evaporation gave a crude product, which was crystallized from ethanol: 1.85 g (79%); the spectral data of molecule **5** were in agreement with data in the literature;[35,36] ^{1}H NMR δ 6.61 (dd, 1H), 6.87 (d, 1H), 7.1 (br s, 2H), 7.22 (dd, 1H), 7.46 (dd, 1H), 7.71 (d, 1H), 7.76−7.80 (m, 2H), 8.15, (d, 1H), 12.1 (br s, 1H); ^{13}C NMR δ 112.5 (s), 115.1 (d), 116.7 (d), 120.5 (s), 125.8 (d), 126.2 (d), 126.9 (d), 128.9 (d), 131.9 (d), 134.5 (d), 148.1 (s), 149.5 (s), 153.6 (s), 162.1 (s).

13*H*-Quinazoline[3,4-*a*]quinazolin-5,13-dione (6). 2-(2-Aminophenyl)quinazoline-4(3*H*)one **5** (237 mg, 1 mmol) was dissolved in dioxane (12 mL), and phosgene (150 mg, 1.5 mmol) dissolved in dioxane (10 mL) was added at 35 °C to the stirred solution. A yellowish precipitate formed within 1−2 min. After a stirring period of 30 min, the product was collected and dried: 245 mg (93%); mp >260 °C, decomp; IR 3350, 1794, 1732, 1626, 1561, 1482, 1392, 1253, 1165, 1081, 820, 755, 746 cm^{-1}; ^{1}H NMR δ 7.15 (m, 1H), 7.26 (d, 1H), 7.55−7.76 (m, 3H), 8.05 (d, 1H), 8.30 (d, 1H), 8.89 (d, 1H), 11.5 (s, 1H); ^{13}C NMR δ 115.0 (d), 121.4 (s), 122.9 (d), 126.6 (d), 126.7 (d), 126.8 (d), 126.9 (d), 133.7 (d), 135.0 (d), 137.6 (s), 138.1 (s), 145.6 (s), 147.3 (s), 159.2 (s). Anal. Calcd for $C_{15}H_9N_3O_2$: C, 68.43; H, 3.45; N, 15.96. Found: C, 68.22; H, 3.26; N, 15.82.

Ring Opening of Compound 6 and Formation of Compound 20. Compound **6** (262 mg, 1 mmol) was dissolved in water (15 mL) containing sodium hydroxide (80 mg, 2 mmol) under stirring at 40 °C for 10 min, whereupon acetic acid was added and the precipitate of the known amide **20** was collected, washed, and dried: 212 mg (80%); mp 261−263 °C (lit.[18] 265−266 °C); IR 3390, 3207, 2900−2700, 1715, 1657, 1605, 1572, 1462, 1397, 1292, 1162, 868, 753 cm^{-1}; ^{1}H NMR δ 7.20−7.24 (s+d, 3H), 7.40 (d, 1H), 7.52 (dd, 1H), 7.61 (dd, 1H), 7.67 (dd, 1H), 7.75 (d, 1H), 7.81 (s, 1H), 7.94 (d, 1H), 11.5 (s, 1H); ^{13}C NMR δ 114.3 (s), 115.2 (d), 122.4 (d), 127.6 (d), 128.4 (d), 128.5 (d), 130.8 (d), 130.9 (d), 133.5 (s), 134.4 (s), 135.2 (d), 139.9 (s), 150.2 (s), 162.2 (s), 167.8 (s).

5,6,9,10-Dibenzo-1,3,7-triaza-2,4,8-trioxodecane (22). Compound **7** (1.32 g, 5 mmol) was dissolved in water (30 mL) containing potassium hydroxide (2.0 g) at 50 °C. This solution was then heated to 80−85 °C for 5 min. The solution was allowed to cool and acidified with acetic acid, and the precipitate of **22** was collected, washed with water, and dried: 0.98 g (70%); mp 150 °C decomp; IR 3116, 2848, 1647, 1581, 1498, 1455, 1427, 1379, 1340, 1291, 824, 750 cm^{-1}; ^{1}H NMR δ 6.98 (dd, 1H), 7.02−7.18 (m, 2H), 7.35 (dd, 1H), 7.58 (dd, 1H), 8.05 (d, 1H), 8.19 (d 1H), 9.13 (d, 1H), 10.8 (s, 1H); ^{13}C NMR δ 110.5 (s), 115.3 (d), 119.9 (d), 121.5 (d), 121.6 (d), 123.9 (d), 125.8 (s), 129.8 (d), 131.1 (d), 133.3 (d), 141.2 (s), 142.5 (s), 155.9 (s), 159.0 (s), 169.6 (s). Anal. Calcd for $C_{15}H_{11}N_3O_3$: C, 64.05; H, 3.94; N, 14.95. Found: C, 63.92; H, 4.05; N, 14.92.

Cyclization of 22 to 7. Compound **22** (281 mg, 1 mmol) was heated at reflux temperature in acetic anhydride (3.0 mL) for 5 min. The solid that formed on cooling was collected and identified as compound **7** (220 mg, 83%).

Cyclization of 22 to 25. Compound **22** (282 mg, 1 mmol) was dissolved in DMF (4.0 mL) and heated at 120 °C for 15 min. Cooling and addition of some water precipitated compound **25**: 195 mg (72%). This compound was identical to a sample of **25** prepared according to ref 18.

Ring Opening of Compound 7 with Dimethylamine and Formation of the Urea Derivative 23. Compound **7** (263 mg, 1 mmol) was added to dioxane (6 mL), whereupon dimethylamine (30% in water, 1 mL) was added to the stirred suspension. Light heating to 70 °C resulted in a clear solution which was diluted with water and acidified with acetic acid which immediately resulted in the formation of a precipitate, which was collected, washed with water, and dried: 294 mg (88%); mp 230−232 °C; IR 3150, 1668, 1533, 1443, 1265, 771 cm^{-1}; ^{1}H NMR δ 3.03 (s, 6H), 3.9 (br, 2H), 7.08 (dd, 1H), 7.45 (dd, 1H), 7.52 (dd, 1H), 7.67 (d, 1H), 7.81 (dd, 1H), 7.92 (d, 1H), 8.17 (d, 1H), 8.33 (d, 1H); ^{13}C NMR δ 36.2 (q), 119.6 (s), 120.6 (d), 120.9 (d), 121.5 (s), 125.9 (d), 126.1 (d), 126.4 (d), 129.3 (d), 131.3 (d), 134.4 (d), 140.5 (s), 147.4 (s), 154.5 (s), 155.3 (s), 162.7 (s). Anal. Calcd for $C_{17}H_{16}N_4O_2$: C, 66.22; H, 5.23; N, 18.17. Found: C, 65.99; H, 5.35; N, 18.03.

Ring Opening of Compound 7 with Aniline and Formation of Compound 24. Compound **7** (263 mg, 1 mmol) was added to aniline (4 mL) and after a period of heating (140 °C, 30 min), and the reaction mixture was allowed to cool and then treated with water (35 mL) containing acetic acid (3 mL). The solid formed was collected, washed with water, and dried: 294 mg (83%); mp 208−210 °C (lit.[37] 208−210 °C).

2,4(1*H*,3*H*)-Quinazolinedione. Compound **7** (1.32 g, 5 mmol) was treated as described for the preparation of compound **22** but now under more severe conditions (heating at reflux for 15 min). Acidification with acetic acid gave the title compound: 0.72 g (88%); the spectral properties were in agreement with those in the literature;[38] ^{1}H NMR δ 7.13−7.17 (m, 2H), 7.59 (dd, 1H), 7.87 (d, 1H), 11.1 (s, 1H), 11.3 (s, 1H); ^{13}C NMR δ 114.2 (s), 115.3 (d), 122.5 (d), 127.1 (d), 134.7 (d), 138.4 (s), 148.8 (s), 159.4 (s).

Urea Derivative 31. Anthranilic acid (68.5 g, 0.5 mol) was dissolved in water (1800 mL) at 96−98 °C, whereupon a solution of bromocyanogene in water was added. This solution was prepared as follows. Sodium cyanide (12.3 g, 0.25 mol) dissolved in water (110 mL) was added to bromine (12.7 mL, 0.25 mol) in water (120 mL) under stirring, while keeping the temperature at 5−8 °C. Upon addition of this solution to the solution of anthranilic acid, a slurry of the product was quickly obtained. The mixture was allowed to cool, and product **31** was collected, washed with water, and dried; 70.5 g (81%); mp 208−210 °C (lit.[25] 208−210 °C); the analytical sample was recrystallized from DMF/H_2O; IR 3414, 3300, 3225, 1648, 1609, 1525, 1448, 1363, 1314, 1228, 1027, 901, 7784, 740 cm^{-1}, ^{1}H NMR δ 6.5 (br, s, 2H), 7.07 (dd,

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1H), 7.20 (dd, 1H), 7.49 (dd, 1H), 7.63 (dd, 1H), 7.75 (d, 1H), 8.05 (d, 1H), 8.30 (d, 1H), 8.60 (d, 1H), 9.57 (s, 1H), 11.94 (s, 1H); ^{13}C NMR δ 117.4 (s), 120.5 (d), 121.0 (d), 121.1 (d), 121.5 (s), 123.3 (d), 127.3 (d), 131.3 (d), 132.2 (d), 134.0 (d), 140.6 (s), 140.8 (s), 155.8 (s), 167.0 (s), 169.8 (s).

Cyclization of 31 to the Benzoxazinone 32. The urea derivative **31** (14.2 g, 50 mmol) in DMF (45 mL) was treated with diisopropylcarbodiimide (8.0 g) and heated to 130 °C for 20 min. Upon cooling, the product precipitated. After dilution with methanol, the benzoxazinone **32** was collected, washed with methanol, and dried: 7.1 g (61%); mp 238−240 °C (lit.[26] 238−240 °C); IR 3362, 3195, 1771, 1666, 1604, 1566, 1536, 1467, 1449, 1245, 1219, 1167, 1035, 1005, 873, 768 cm^{-1} (lit. 1780, 1675 cm^{-1});[26] ^{1}H NMR δ 6.7 (s, 2H), 7.07 (dd, 1H), 7.51 (dd, 1H), 7.63 (dd, 1H), 7.93 (dd, 1H), 8.02 (d, 1H), 8.13−8.16 (m, 2H), 8.44 (d, 1H), 11.0 (s, 1H); ^{13}C NMR δ 114.1 (s), 116.6 (s), 120.0 (d), 127.3 (d), 127.8 (d), 128.9 (d), 133.1 (d), 136.6 (d), 142.0 (s), 145.3 (s), 155.5 (s), 156.6 (s), 158.3 (s).

***N*-Nitrosospiro[indolo-3,2′-quinazoline]-2,4′-dione (33).** The spiro-compound **8** (2.65 g, 10 mmol) was dissolved in acetic acid (30 mL), and sodium nitrite (0,84 g, 12 mmol) was added in portions to the stirred solution at 30 °C. Within 5−10 min, the product started to appear as a whitish solid. After 45 min, water (30 mL) was added and the product (**33**) collected, washed with water, and dried: 2.65 g (83%); mp 150 °C decomp; IR 3343, 3183, 3100, 1748, 1727. 1650, 1604, 1469, 1450, 1376, 1271, 1182, 1115, 1074, 936, 751 cm^{-1}; ^{1}H NMR δ 6.90−7.04 (m, 3H), 7.31 (dd, 1H), 7.56 (dd, 1H), 7.79 (dd, 1H), 8.10 (d, 1H), 8.14 (dd, 1H), 9.5 (s, 1H), 11.1 (s, 1H); ^{13}C NMR δ 75.7 (s), 110.5 (d), 114.7 (d), 114.8 (s), 122.5 (d), 122.7 (d), 124.4 (s), 127.5 (d), 128.2 (d), 130.9 (d), 134.9 (d), 138.2 (s), 142.2 (s), 159.0 (s), 169.1 (s). Anal. Calcd for $C_{15}H_{10}N_4O_3$: C, 61.22; H, 3.43; N, 19.04. Found: C, 61.00; H, 3.28; N, 18.88.

***N*-Nitrosoisamic Acid (34).** Isamic acid **1** (2.93 g, 10 mmol) was added to a stirred solution of sodium nitrite (1.05 g, 15 mmol) in water at 35 °C for 2 h. After that period of time, the solution was filtered and cooled in ice/water. Acidification with hydrochloric acid precipitated the product, which was washed with water and dried: 1.76 g (54%); mp ∼150 °C decomp; this monohydrate could be dried in an exciccator to yield **34** free of water; IR 3276, 1723, 1618, 1604, 1443, 1193, 1142, 1095, 1051, 948, 753, 693 cm^{-1}; ^{1}H NMR δ 6.92−7.01 (m, 3H), 7.31 (dd, 1H), 7.55 (dd, 1H), 7.74−7.81 (m, 2H), 8.20 (d, 1H), 11.2 (s, 1H); ^{13}C NMR δ 80.4 (s), 110.4 (d), 111.3 (s), 114.4 (d), 122.7 (d), 122.7 (d), 124.3 (s), 127.8 (d), 128.3 (d), 130.8 (d), 135.4 (d), 135.8 (s), 141.8 (s), 156.3 (s), 164.6 (s), 168.8 (s). Anal. Calcd for $C_{16}H_{10}N_4O_4\cdot H_2O$: C, 56.47; H, 3.55; N, 16.47. Found: C, 56.48; H, 3.31; N, 16.46.

Zwitterionic Molecule 35. *N*-Nitrosoisamic acid **34** (644 mg, 2 mmol) in ethanol (20 mL) was treated (5 min) with hydrochloric acid (2 mL) at 60 °C. The solid product obtained was washed with water and dried: 610 mg (94%); mp 180 °C decomp; this decomposition is sudden and violent; experiments with large amounts should be avoided; IR 3060−2900 (br), 1733, 1643, 1609, 1572, 1496, 1333, 1289, 1226, 1083, 760 cm^{-1}; ^{1}H NMR δ 7.13 (d, 1H), 7.19−7.25 (m, 2H), 7.33 (d, 1H), 7.37−7.44 (m, 2H), 7.56 (dd, 1H), 8.32 (d, 1H), 11.4 (s, 1H); ^{13}C NMR δ 81.8 (s), 114.7 (s), 114.8 (d), 123.0 (d), 124.0 (s), 125.3 (d) 125.6 (d), 125.6 (d), 126.4 (d), 129.8 (d), 133.4 (d), 137.4 (s), 138.5 (s), 143.9 (s), 148.8 (s), 170.5 (s). Anal. Calcd for $C_{16}H_{10}N_4O_4$: C, 59.63; H, 3.13; N, 17.39. Found: C, 59.42; H, 3.01; N, 17.02.

Hydroximino Compound 38. The zwitterionic molecule **35** (322 mg, 1 mmol) or *N*-nitrosoisamic acid **34** (293 mg, 1 mmol) was heated in ethanol (15 mL) containing NH_3 (aqueous, 1 mL) for 15 min. The yellow precipitate that formed was collected and dried: 295 mg (83%); mp >260 °C; the analytical sample was recrystallized from DMF; IR 3110, 2950, 1716, 1618, 1605, 1533, 1442, 1410, 1382, 1269, 938, 750 cm^{-1}; ^{1}H NMR δ 7.12 (d, 1H), 7.21 (dd, 1H), 7.37 (dd, 1H), 7.47 (dd, 1H), 7.59 (dd, 1H), 7.83 (d, 1H), 8.30 (d, 1H), 8.42 (d, 1H), 10.3 (s, 1H), 11.5 (s, 1H); ^{13}C NMR δ 114.7(d), 115.0 (s), 120.2 (s), 121.4 (d), 122.7 (d), 122.9 (d), 126.94 (d), 126.96 (d), 129.1 (d), 133.4 (s), 134.1 (s), 138.0 (s), 144.5 (s), 147.4 (s), 147.7 (s). Anal. Calcd for $C_{15}H_{10}N_4O_2$: C, 64.74; H, 3.62; N, 20.14. Found: C, 64.69; H, 3.60; N, 20.08.

2-(2-Aminophenyl)-1,2-dihydroquinazoline-4(3*H*)one (28). 2-(2-Nitrophenyl)-1,2-dihydroquinazoline-4(3*H*)one (2.69 g, 10 mmol) was added to a stirred mixture of ethanol (40 mL) and water (40 mL), wherein sodium dithionate (5.0 g) had been dissolved. The mixture was heated to 65 °C for 45 min, concentrated, and diluted with water and the solid formed collected, washed with water, and dried: 1.85 g (77%); mp 171−173 °C (lit. 170−173 °C);[24] ^{1}H NMR δ 6.28 (d, 1H, J = 7.8 Hz), 6.58 (m, 2H), 7.16−7.97 (m, 9H), 9.14 (d, 1H, J = 7.8 Hz); ^{13}C NMR δ 66.6 (d), 111.8 (d), 115.3 (s), 115.4 (d), 124.3 (d), 128.46 (d), 128.49 (d), 129.3 (d), 132.6 (d), 132.7 (d), 133.0 (s), 147.8 (s), 150.5 (s), 171.6 (s). This molecule has very recently also been described by Patil et al.[39]

13,14-Dihydroquinazolino[4,3-*b*]quinazolinedione (26). Compound **7** (0.53 g, 2 mmol) was added to acetic acid (12 mL) at 50 °C, whereupon sodium cyanoborohydride (0.5 g) in portions was added to the suspension. A clear solution was obtained after 15 min, but soon, the product started to partially precipitate. After 1 h, the mixture was cooled, water added, and the product collected: 0.45 g (83%); mp >260 °C; IR 3250, 2888, 1747, 1644, 1629, 1575, 1497, 1357, 1282, 763 cm^{-1}; ^{1}H NMR δ 6.76 (d, 1H, J = 6.6 Hz), 6.89 (d, 1H), 7.14−7.56 (m, 7H), 8.26 (d, 1H, J = 6.6 Hz), 11.2 (s, 1H); ^{13}C NMR δ 71.2 (d), 114.9 (d), 115.4 (s), 122.7 (d), 124.7 (s), 124.8 (d), 125.4 (d), 125.9 (d), 127.5 (d), 129.3 (d), 132.9 (d), 137.6 (s), 139.9 (s), 144.2 (s), 149.2 (s). Anal. Calcd for $C_{15}H_{11}N_3O_2$: C, 67.91; H, 4.18; N, 15.84. Found: C, 67.66; H, 4.30; N, 15.66.

5,6-Dihydroquinazolino[3,4-*g*]quinazoline-6,13(7*H*)-dione (27). Method A. Compound **6** (0.53 mg, 2 mmol) was added to acetic acid (12 mL) at 25 °C, wherein sodium borohydride (0.5 g) had been dissolved. The mixture was stirred for 4 h and then quenched with water and the precipitate formed collected: 0.39 mg (71%); mp >260 °C. Anal. Calcd for $C_{15}H_{11}N_3O_2$: C, 67.91; H, 4.18; N, 15.84. Found: C, 67.81; H, 4.28; N, 15.72. Method B. The amino compound **28** (237 mg, 1 mmol) was dissolved in dioxane (8 mL), and triphosgene (210 mg, 0.7 mmol) in dioxane (3 mL) was added to the stirred solution at 25 °C. After 1 h, water (5 mL) was added and the precipitate collected, washed with water, and dried: 240 mg (90%); ^{1}H NMR δ 6.27 (s, 1H), 6.99 (d, 1H), 7.05 (dd, 1H), 7.32−7.41 (m, 3H), 7.59 (m, 2H), 7.93 (d, 1H), 8.80 (s, 1H), 10.2 (s, 1H); ^{13}C NMR δ 65.6 (d), 114.1 (d), 114.4 (s), 122.0 (d), 125.2 (s), 125.6 (d), 125.7 (d), 127.2 (d), 128.0 (d), 130.2 (d), 131.8 (d), 136.0 (s), 140.4. (s) 149.6 (s), 163.2 (s).

Single-Crystal X-ray Analysis. The crystal structures were determined by direct methods and refined by full matrix least-squares analyses with anisotropic temperature factors for all atoms except protons. Proton positions were calculated using known molecular geometries, refined in riding mode with fixed isotropic temperature factors.

Crystal data for **7**: $C_{15}H_9N_3O_2$, M_r = 263.25 g/mol, triclinic, $P\bar{1}$ (No. 2), a = 7.0598(4) Å, b = 8.4940(5) Å, c = 10.5944(6) Å, α = 97.816(3)°, β = 93.664(2)°, γ = 113.447(3)°, V = 572.54(6) Å^3, Z = 2, ρ_{calc} = 1.527 g cm^{-1}, μ = 0.105 mm^{-1}, $R1$ = 0.0415, $wR2$ = 0.1117, GOF = 1.056. The data were collected at 200 K on a diffractometer with graphite-monochromated Mo Kα radiation and employing a 0.15 × 0.05 × 0.05 mm crystal (R_{int} = 0.045).

Crystal data for **38**: $C_{15}H_{10}N_4O_2$, M_r = 278.27 g/mol, triclinic, space group $P\bar{1}$ (No. 2), a = 8.1500(4) Å, b = 17.7300(8) Å, c = 17.8700(9) Å, α = 111.230(1)°, β = 90.190(1)°, γ = 98.070(2)°, V = 2379.0(2) Å^3, Z = 8, ρ_{calc} = 1.554 g cm^{-3}, μ = 0.108 mm^{-1}, $R1$ = 0.07, $wR2$ = 0.22, GOF = 1.00. The data were collected at 100 K on the Grenoble synchrotron (beamline ID29) and employing a 0.11 mm × 0.02 mm × 0.01 mm crystal (R_{int} = 0.05). CCDC-957012 and CCDC-915864 contains the supplementary crystallographic data for **7** and **38**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Crystal structural data of compounds **7** and **38** have been deposited at Cambridge Data Centre and allocated the deposition numbers CCDC-957012 and CCDC-915864, respectively, CIFs for these two molecules are included in the

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Supporting Information, where also copies of NMR spectra are provided for all new compounds and also for some already known key compounds (like **1** and **8**). The chromatogram obtained during the resolution of the spiro-compound **8** is also provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

REFERENCES

(1) Laurent, A.; Erdmann, O. L. *J. Prakt. Chem.* **1842**, *25*, 430.
(2) Field, G. F. *J. Chem. Soc. D* **1969**, *15*, 886.
(3) Blount, J. F. *J. Chem. Soc. D* **1970**, 432.
(4) Reissert, A.; Hoppmann, H. *Ber. Dtsch. Chem. Ges. B* **1924**, *57B*, 972.
(5) Jacini, G. *Gazz. Chim. Ital.* **1947**, *77*, 295.
(6) Jacini, G. *Gazz. Chim. Ital.* **1942**, *72*, 510.
(7) Jacini, G. *Gazz. Chim. Ital.* **1943**, *73*, 85.
(8) Jacini, G. *Gazz. Chim. Ital.* **1943**, *73*, 306.
(9) Jacini, G. *Gazz. Chim. Ital.* **1944**, *74*, 3.
(10) de Mayo, P.; Ryan, J. J. *Can. J. Chem.* **1967**, *45*, 2177.
(11) Cornforth, J. W. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2004.
(12) Bergman, J.; Engqvist, R.; Stalhandske, C.; Wallberg, H. *Tetrahedron* **2003**, *59*, 1033.
(13) Blay, G.; Fernandez, I.; Monje, B.; Montesinos-Magraner, M.; Pedro, J. R. *Tetrahedron* **2011**, *67*, 881.
(14) Bergman, J.; Rehn, S. *Tetrahedron* **2002**, *58*, 9179.
(15) Cheng, X.; Vellalath, S.; Goddard, R.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 15786.
(16) Jiang, Y.; Liu, Y.; Tu, S.-J.; Shi, F. *Tetrahedron: Asymmetry* **2013**, *24*, 1286.
(17) Eddy, F. D.; Vaughan, K.; Stevens, M. F. G. *Can. J. Chem.* **1978**, *56*, 1616.
(18) Bitter, I.; Szocs, L.; Toke, L. *Acta Chim. Acad. Sci. Hung.* **1981**, *107*, 57.
(19) Butler, K.; Partridge, M. W. *J. Chem. Soc.* **1959**, 1512.
(20) Prashad, M.; Chen, L.; Repic, O.; Blacklock, T. J. *Synth. Commun.* **1998**, *28*, 2125.
(21) Palazzo, S.; Giannola, L. I.; Neri, M. *J. Heterocycl. Chem.* **1975**, *12*, 1077.
(22) Pinnen, F.; Zanotti, G.; Lucente, G. *Tetrahedron Lett.* **1984**, *25*, 5201.
(23) Pinnen, F.; Zanotti, G.; Lucente, G. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1311.
(24) Yale, H. L.; Kalkstein, M. *J. Med. Chem.* **1967**, *10*, 334.
(25) Doleschall, G.; Lampert, K. *Monatsh. Chem.* **1964**, *95*, 1083.
(26) Doleschall, G.; Lempert, K. *Tetrahedron* **1968**, *24*, 5529.
(27) Doleschall, G.; Lempert, K. *Tetrahedron* **1969**, *25*, 2539.
(28) Konig, W. *J. Prakt. Chem.* **1904**, *69*, 1.
(29) Venkateswarlu, S.; Satyanarayana, M.; Ravikiran, P.; Vijayakumar, A. *Tetrahedron Lett.* **2013**, *54*, 4512.
(30) Venkateswarlu, S.; Satyanarayana, M.; Ravikiran, P.; Siddaiah, V. *J. Heterocycl. Chem.* **2013**, *50*, 1089.
(31) Marinho, E.; Araujo, R.; Proenca, F. *Tetrahedron* **2010**, *66*, 8681.
(32) Stephen, T.; Stephen, H. *J. Chem. Soc.* **1956**, 4173.
(33) Butler, K.; Partridge, M. W.; Waite, J. A. *J. Chem. Soc.* **1960**, 4970.
(34) Roy, A. D.; Subramanian, A.; Roy, R. *J. Org. Chem.* **2006**, *71*, 382.
(35) Waibel, M.; Hasserodt, J. *Tetrahedron Lett.* **2009**, *50*, 2767.
(36) Sneddon, H. F.; Lynn, S. M. *Synlett* **2011**, 573.
(37) Parfitt, R. T.; Partridge, M. W.; Vipond, H. J. *J. Chem. Soc.* **1963**, 3062.
(38) Li, J.; Xian, C.; Shi, D.; Ma, S.; Qing, L.; Qi, Z.; Tang, J. *Org. Lett.* **2009**, *11*, 1193.
(39) Patil, N. T.; Konala, A.; Sravanti, S.; Singh, A.; Ummanni, R.; Sridhar, B. *Chem. Commun.* **2013**, *49*, 10109.