Mesoionic 1,2,4-Triazolo[4,3-*c*]quinazolines

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Because of the close structural similarity between triazoloquinazolines and certain 5-membered ring mesoionic heterocycles, all of which possess antiinflammatory activity, we prepared several examples of the novel mesoionic 1,2,4-triazolo[4,3-*c*]quinazoline ring system for their therapeutic potential. These compounds can be prepared by the cyclization of the appropriately substituted 4-hydrazinoquinazolines with phosgene. When the mesoionic product was unsubstituted at the 5-position (*i.e.*, quinazoline 2-position), it could only be isolated as its hydrochloride salt and not as its unstable free base. None of the mesoionic products were sufficiently stable in solution to allow for evaluation of their antiinflammatory activity.

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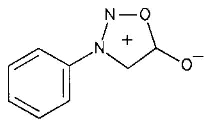
Aryl-substituted and heteroaryl-fused five-membered ring mesoionic heterocycles, such as **1** and **2**, possess antiinflammatory activity [1,2]. Triazoloquinazolines, such as **3** where either A or B is nitrogen (and X is halo or alkoxy, and Y is chloro), also display antiinflammatory activity [3]. There are certain obvious structural similarities between the structures of **1-3**; thus, it was of interest to prepare a series of triazoloquinazoline-fused five-membered mesoionic heterocycles, that would incorporate features common to **1-3** as potential antiinflammatory agents. The first series selected for investigation was **4**.

The general strategy that was to be employed for the synthesis of derivatives of **4** was hydrazinolysis of an appropriately substituted 4-chloroquinazoline, followed by cyclization to the mesoionic compound with phosgene. Accordingly, the 4-chloroquinazolines **6a-c**, prepared by chlorination of the quinazolones **5a-c** using either a phosphoryl chloride/phosphorus pentachloride mixture or phosphoryl chloride in *N,N*-dimethylaniline, were allowed to react with methylhydrazine to afford the 1-methyl-1-arylhydrazines **7a-c**. Attempts to prepare the 2-alkoxy derivatives **6d-f** *via* this method were less successful. Attempted chlorination of **5d** or **5f** under the conditions used for the synthesis of **6a-c**, resulted in the isolation of the dichloro derivative **6b**. A variety of chlorinating agents and conditions were examined; however, these reactions generally resulted in the formation of **6b** (*e.g.* heating with either phosphoryl chloride or thionyl chloride,



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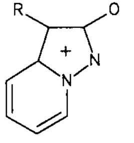

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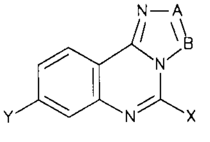

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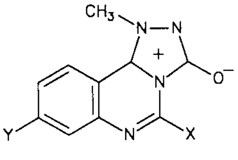

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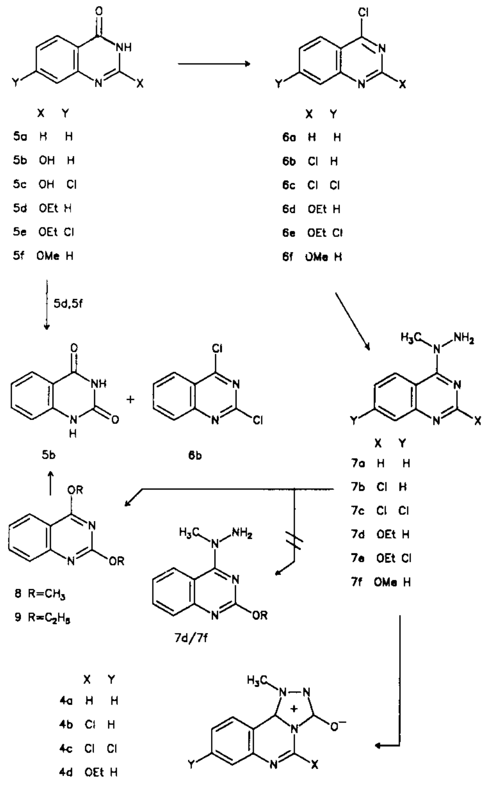

neat or with different solvents, for 30 minutes), or, under somewhat milder conditions (*e.g.* phosphoryl chloride in dioxane at room temperature overnight, or heating with PCl_5 in dry toluene for 1.5 hours) in the formation of the dioxo compound **5b**. Presumably, under mild conditions, **5d** and **5f** are hydrolyzed to the dioxo derivative **5b**, whereas under more drastic conditions, this hydrolysis is followed by chlorination to **6b**. Similar reactions have been reported to occur with pyrimidinediones [4]. In several cases, compounds **6e** and **6f** were isolated as minor products; because the crude products were contaminated with large quantities of **5b** and/or **6b** (as identified by thin-layer chromatography, and, occasionally, by isolation), samples of **6e** and **6f** could never be sufficiently purified so as to obtain satisfactory elemental analyses. In one instance, a small quantity of **6d** was isolated as a single product using the phosphoryl chloride/phosphorus pentachloride chlorinating mixture; however, the reaction could not be subsequently replicated.

Compounds **6a-d** were allowed to react with methylhydrazine to provide **7a-d**. Alternative attempts to prepare the 2-alkoxy derivatives **7d** and **7f**, by displacement of the 2-chloro group of **7b** with methoxide or ethoxide were unsuccessful. For example, reaction of the 2-chloro-4-(1-methylhydrazine) derivative **7b** with sodium methoxide or sodium ethoxide afforded the 2,4-dialkoxy derivatives **8** and **9**, respectively, and not the desired **7f** or **7d**. Attempting to take advantage of the greater reactivity of the quinazoline 4-position over that of the 2-position, 2,4-dimethoxyquinazoline (**8**) was allowed to react with methylhydrazine; heating at reflux in dioxane for up to six days, or heating in a sealed tube at 60-80° for up to 3 hours, resulted only in the isolation of quinazolinedione **5b**, and not the desired 2-methoxy-4-(1-methylhydrazine) **7f**. Tomisek and Christensen [5] have previously reported the isolation of **5b** from boiling **8** with a solution of sodium methoxide.

Using the monosubstituted quinazoline derivative **7a**, a series of trial reactions was conducted in order to identify optimal cyclization conditions for **7a-d**. Bubbling phosgene through a toluene solution of **7a** at room temperature resulted only in the isolation of **7a** as its hydrochloride salt. With the possibility that phosgene might be reacting with atmospheric moisture to liberate HCl, the reaction was repeated using several different batches of phosgene, scrupulously anhydrous conditions, and flame-dried glassware. Compound **7a**, as its hydrochloride salt, was isolated in each case. Another likely possibility is that a mesoionic product is formed in the course of the reaction, that liberated hydrogen chloride reacts with residual starting material to give **7a** hydrochloride, and that the mesoionic product somehow eludes isolation. In order to counter this problem, 0.5 equivalents of triethylamine was added to the reaction mixture. Although a small amount of **7a** hydrochloride was formed, the major product was the mesoionic **4a** hydrochloride. In order to obtain **4a** as its free base, and so as to eliminate the formation of **7a** hydrochloride, the amount of triethylamine used in the reaction was increased to at least 1 equivalent. Under these conditions, a crude product was obtained (presumably the free base of **4a**) which underwent decomposition within minutes of isolation. Likewise, all attempts to liberate the free base of **4a** from **4a** hydrochloride, by heating or by treatment with dilute base, also resulted in decomposition. Apparently, **4a** is stable only as its hydrochloride salt and not as its free base. Interestingly, the presence of a 2-substituent appears to stabilize **4b-d** which could be isolated as their free bases. Compounds **4b** and **4c** were prepared either in the absence of triethylamine (which necessitated the liberation of the free base during the course of the reaction) or in the presence of at least 1 equivalent triethylamine. Due to the difficulty in preparing **6d**, and the inability to repeat its synthesis, only a small amount of **4d** could be isolated; quantities were insufficient for microanalysis, however, its structure is supported on the basis of high resolution mass spectroscopy.

With the exception of **4a**, the mesoionic compounds appear to be stable as their solid free bases. However, in the course of our investigations, it became evident that the mesoionic compounds are less stable in solution. Heating **4a** hydrochloride, or **4b** and **4c** as their free bases, in 10% hydrochloric acid for 10-15 minutes, or allowing **4b** and **4c** (free bases) to stand for several hours in the presence of 10% aqueous sodium hydroxide solution, results in decomposition. Whereas **4a-c** appear to be stable to cold water and cold methanol, prolonged heating in methanol also results in decomposition. The decomposition products were neither isolated nor identified. Apparently, these mesoionic compounds are not very stable in solution, and as a consequence, were not submitted for pharmacological evaluation.

EXPERIMENTAL

Melting points were determined on Thomas Hoover melting point apparatus and are uncorrected. Infrared and ^1H-nmr spectra were obtained using a Nicolet 5ZDX FT-IR and a JEOL FX 90Q spectrometer (with tetramethylsilane as an internal standard), respectively. Mass spectra were determined on a Finnigan 4015 spectrometer at 70 eV. Thin-layer chromatography was performed with silica gel GLF plates (250 microns) using ultraviolet light and iodine vapor for visualization. Elemental analyses were performed by Atlantic Microlab. Compounds **6a-6c** were prepared according to published procedures [11-13].

1-Methyl-1,2,4-triazolo[4,3-*c*]quinazolium-3-olate Hydrochloride (**4a**).

A solution of phosgene (10 ml of a 12.5% solution in toluene) was added to a stirred solution of **7a** (0.5 g, 2.87 mmoles) and triethylamine (0.32 g, 3.1 mmoles) in dry toluene at room temperature. The reaction mixture was allowed to stir at room temperature for 15 minutes and the solid material was collected by filtration and heated with 2-propanol. The solid product was collected by filtration, washed with warm 2-propanol and air-dried to give 70 mg (12%) of **4a**; mp 270-272°; ^{1}H-nmr (DMSO-d$_6$): 4.58 (s, 3H, CH$_3$), 7.60-8.15 (m, 3H, Ar-H), 8.57 (d, 1H, C$_{10}$-H), 10.06 (s, 1H, C$_5$-H).

Anal. Calcd. for $C_{10}H_8N_4O{\cdot}HCl{\cdot}\frac{1}{3}H_2O$: C, 49.48; H, 4.01; N, 23.09. Found: C, 49.52; H, 4.10; N, 22.75.

5-Chloro-1-methyl-1,2,4-triazolo[4,3-*c*]quinazolium-3-olate (**4b**).

Method A.

A solution of phosgene (3 ml of a 12.5% toluene solution) was added in a dropwise manner to a stirred suspension of **7b** (0.3 g, 1.4 mmoles) in dry toluene (10 ml) at room temperature. After the addition was complete, the solution was heated at reflux for 10 minutes, allowed to cool to room temperature, and the solid material was collected by filtration. The crude product was dissolved in water (*ca.* 10 ml) and the insoluble portion was collected by filtration. This material was washed with boiling 2-propanol and air-dried to give 0.1 g (30%) of **4b**, mp 301-303°; ^{1}H-nmr (DMSO-d$_6$): 4.12 (s, 3H, CH$_3$), 7.71-8.05 (m, 3H, Ar-H), 8.38 (d, 1H, C$_{10}$-H).

Anal. Calcd. for $C_{10}H_7ClN_4O$: C, 51.17; H, 3.00; N, 23.88. Found: C, 51.38; H, 3.24; N, 23.42.

Method B.

Compound **4b** was prepared following the same procedure used for the synthesis of **4a** and 1 equivalent of triethylamine. The product was obtained in 42% yield after washing with boiling 2-propanol, mp 301-303°. The products from Methods A and B were found to be identified by thin-layer chromatography and ^{1}H-nmr.

5,8-Dichloro-1-methyl-1,2,4-triazolo[4,3-*c*]quinazolinium-3-olate (**4c**).

Method A.

Compound **4c** was prepared from **7c** following the procedure used for **4b**. The yield of product was 30% (Method A) after recrystallization from absolute ethanol, mp 273-275°; ^{1}H-nmr (DMSO-d$_6$): 4.21 (s, 3H, CH$_3$), 7.33-7.96 (m, 2H, Ar-H), 8.38 (d, 1H, C$_{10}$-H).

Anal. Calcd. for $C_{10}H_6Cl_2N_4O$: C, 44.60; H, 2.23; N, 20.81. Found: C, 44.83; H, 2.44; N, 21.09.

Method B.

A solution of phosgene (1 ml of a 12.5% solution in toluene) was added to a stirred solution of **7c** (0.1 g, 0.41 mmole) and triethylamine (0.1 g, 0.98 mmole) in dry toluene (5 ml) at room temperature. The reaction mixture was allowed to stir at room temperature for 15 minutes and the solid product was collected by filtration. The filtrate was allowed to stand at room temperature for 1 hour; needle-like crystals that separated from solution were collected by filtration, air-dried, and recrystallized from absolute ethanol to give **4c** in 43% yield, mp 274-275°. The products prepared by Methods A and B were found to be identical by thin-layer chromatography and ^{1}H-nmr.

5-Ethoxy-1-methyl-1,2,4-triazolo[4,3-*c*]quinazolium-3-olate (**4d**).

Methylhydrazine (0.28 g, 6 mmoles) was added in a dropwise manner to a solution of **6d** (0.13 g, 0.62 mmole) in methylene chloride (5 ml) while maintaining the temperature below 30°. The reaction mixture was allowed to stir for 30 minutes and was evaporated under reduced pressure. The residue was suspended in ice-water, stirred for 10 minutes, collected by filtration, air-dried, and recrystallized from a methanol/methylene chloride mixture to give 88 mg (67%) of crude **7d** (mp 181-183°). A solution of phosgene (1 ml of a 12.5% solution in toluene) was added in a dropwise manner to a stirred solution of crude **7d** (20 mg, 0.9 mmole) and triethylamine (5 drops) in dry toluene (20 ml). The reaction mixture was allowed to stir at room temperature for 15 minutes; the precipitated solid was collected by filtration, and allowed to stir with chloroform for 10 minutes. The solid material was collected by filtration and air-dried to give 15 mg (68%) of **4d** which was homogeneous by thin-layer chromatography; mp 208-210°; ^{1}H-nmr (DMSO-d$_6$): 1.38 (t, 3H, ethyl CH$_3$), 4.1 (s, 3H, CH$_3$), 4.59 (q, 2H, CH$_2$), 7.42-7.81 (m, 3H, Ar-H), 8.25 (d, 1H, C$_{10}$-H).

High resolution ms. Calcd. for $C_{12}H_{12}N_4O_2$: m/z 244.0960. Found: m/z 244.0967.

1,2,3,4-Tetrahydro-2,4-dioxoquinazoline (**5b**).

A mixture of 2,4-dimethoxyquinazoline (**8**) (50 mg, 0.26 mmole) and methylhydrazine (0.4 ml) was heated in a sealed tube at 60-80° for 3 hours. The excess methylhydrazine was removed *in vacuo* and the resultant oil was triturated with benzene and allowed to stir with ice-cold water (15 ml) for 15 minutes. The solid product was collected by filtration and air-dried to give 30 mg (70%) of the title compound **5b**, mp >350° (Lit [6] mp >360°). The product co-chromatographed with an authentic sample of **5b** prepared according to the literature [6] procedure.

2-Ethoxy-3,4-dihydro-4-oxoquinazoline (**5d**).

Sodium metal (1.7 g) was dissolved in absolute ethanol (50 ml) at 0°; 2-chloro-3,4-dihydro-4-oxoquinazoline (1 g, 5.5 mmoles) was added in several small portions with stirring at room temperature. The reaction mixture was heated at reflux for 24 hours, allowed to cool to room temperature, and the solvent was removed under reduced pressure. Water (20 ml) was carefully added to the residue and acetic acid was added to *p*H 5. The product was collected by filtration, washed with cold water (10 ml), air-dried, and recrystallized from ethyl acetate to give 0.89 g (85%) of **5d**, mp 179-181° (Lit [7] mp 179°).

7-Chloro-2-ethoxy-3,4-dihydro-4-oxoquinazoline (**5e**).

Compound **5e** was prepared from 2,7-dichloro-3,4-dihydro-4-oxoquinazoline [8] using the same procedure employed for the synthesis of **5d**. The product was obtained in 86% yield after recrystallization from ethyl acetate; mp 222-224°; ^{1}H-nmr (DMSO-d$_6$): 1.38 (t, 3H, CH$_3$), 4.40 (q, 2H, CH$_2$), 7.21-8.00 (m, 3H, Ar-H).

Anal. Calcd. for $C_{10}H_9ClN_2O_2$: C, 53.45; H, 4.00; N, 12.47. Found: C, 53.57; H, 4.03; N, 12.43.

2-Methoxy-3,4-dihydro-4-oxoquinazoline (**5f**).

Compound **5f** was prepared in the same manner as **5d** except that absolute methanol was used as the reaction solvent. The product was obtained in 85% yield after recrystallization from ethyl acetate, mp 233-235° (Lit [7] mp 218°).

4-Chloro-2-ethoxyquinazoline (**6d**).

A mixture of **5d** (0.5 g, 2.6 mmoles), phosphoryl chloride (6 ml), and phosphorus pentachloride (1 g) was heated at reflux for 4 hours. Excess phosphoryl chloride was removed under reduced pressure and the crude product was poured onto crushed ice (*ca.* 10 g). The solution was neutralized by the addition of concentrated ammonium hydroxide solution and the solid product was collected by filtration, washed with water, air-dried, and dissolved in boiling benzene. The benzene solution was dried (magnesium sulfate), filtered, and the filtrate was evaporated to dryness; the product was recrystallized from hexanes to afford 0.3 g (60%) of **6d**, mp 55-57°. This material, which was homogeneous by thin-layer chromatography, was used in the synthesis of **4d** without further characterization.

1-Methyl-1-(1-quinazolyl)hydrazine (**7a**).

Methylhydrazine (1.4 g, 30 mmoles) was added in a dropwise manner to a stirred solution of **6a** (0.65 g, 4 mmoles) in methylene chloride; the temperature was maintained below 30° by an ice-bath (when necessary). The reaction mixture was allowed to stir for 45 minutes under these conditions and was then allowed to stand at 0° overnight. The solvent was evaporated under reduced pressure; the residue was suspended in ice-water (*ca.* 25 ml), and was allowed to stir for 20 minutes. The solid product was collected by filtration, dried, and recrystallized from a methanol/methylene chloride mixture to afford 0.55 g (80%) of **7a**, mp 126-128°; ^{1}H-nmr (deuteriochloroform): 3.6 (s, 3H, CH_3), 4.4 (broad s, 2H, NH_2, exchangeable with deuterium oxide), 7.29-7.91 (m, 3H, Ar-H), 8.65 (s, 1H, C_2-H), 8.9 (d, 1H, C_5-H).

Anal. Calcd. for $C_9H_{10}N_4 \cdot HCl \cdot ½H_2O$: C, 49.20; H, 5.46; N, 25.51. Found: C, 49.27; H, 5.30; N, 25.50.

1-(2-Chloro-4-quinazolyl)-1-methylhydrazine (**7b**).

The title compound was prepared from **6b** using the same procedure used for the synthesis of **7a**. The product was obtained in 64% yield after recrystallization from methanol, mp 153-155°; ^{1}H-nmr (DMSO-d_6): 3.44 (s, 3H, CH_3), 5.50 (s, 2H, NH_2, exchangeable with deuterium oxide), 7.32-7.86 (m, 3H, Ar-H), 9.65 (d, 1H, C_5-H).

Anal. Calcd. for $C_9H_9ClN_4$: C, 51.79; H, 4.34; N, 26.85. Found: C, 51.92; H, 4.36; N, 26.75.

1-(2,7-Dichloro-4-quinazolyl)-1-methylhydrazine (**7c**).

Compound **7c** was prepared from **6c** following the same procedure used for **7a**. The product was obtained in 70% yield after recrystallization from methanol/methylene chloride mixture, mp 188-190°; ^{1}H-nmr (DMSO-d_6): 3.44 (s, 3H, CH_3), 5.50 (s, 2H, NH_2, exchangeable with deuterium oxide), 7.36-7.60 (m, 2H, Ar-H), 9.65 (d, 1H, C_5-H).

Anal. Calcd. for $C_9H_8Cl_2N_4$: C, 44.44; H, 3.31; N, 23.04. Found; C, 44.52; H, 3.35; N, 22.97.

2,4-Dimethoxyquinazoline (**8**).

Compound **8** was prepared in exactly the same manner, and on the same scale, as compound **9**, except that absolute methanol was used in place of ethanol as the reaction solvent. The title compound was obtained in 76% yield, mp 74-76° (Lit [9] mp 67°). The product co-chromatographed with an authentic sample of **8** prepared according to a literature [9] procedure.

2,4-Diethoxyquinazoline (**9**).

Sodium metal (23 mg, 1 mmole) was dissolved in absolute ethanol (4 ml) at 0°; compound **7b** (100 mg, 0.47 mmole) was added at room temperature and the reaction mixture was then heated at reflux for 2 hours. The cooled reaction mixture was poured into ice-cold water (10 ml), and the solid product was collected by filtration, washed with cold water (10 ml), air-dried, and recrystallized from 95% ethanol to afford 75 mg (72%) of **9**, mp 54-56° (Lit [10] mp 55°).

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