SYNTHESIS AND ANTI-INFLAMMATORY ACTIVITY OF SUBSTITUTED 2-STYRYL-4-(δ-DIETHYLAMINO-α-METHYLBUTYLAMINO)-6-NITRO- AND 2-STYRYL-4-(δ-DIETHYLAMINO-α-METHYLBUTYLAMINO)-6-AMINOQUINAZOLINES

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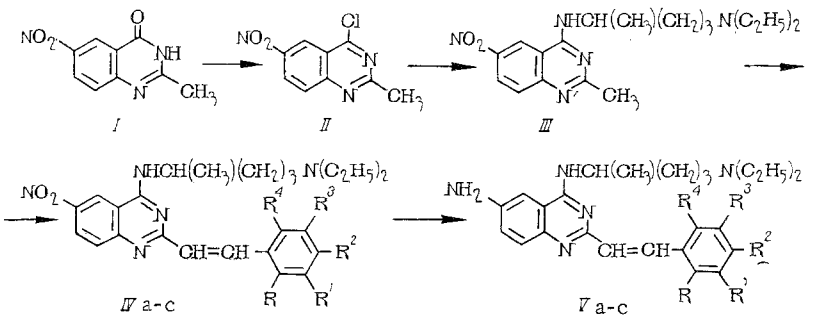
Systematic studies carried out at the All-Union Scientific-Research Pharmaceutical Chemistry Institute to find physiologically active compounds in the styrylquinazoline series have revealed anti-inflammatory activity in several compounds synthesized earlier [1, 2]. Here we report the results of a study of the anti-inflammatory properties of a new group of 4-amino-2-styrylquinazolines.

The starting compounds for the synthesis of the substituted 2-styryl-4-(δ-diethylamino-α-methylbutylamino)-6-nitro- (IV) and 2-styryl-4-(δ-diethylamino-α-methylbutylamino)-6-aminoquinazolines (V) was 2-methyl-6-nitro-4-quinazolone (I), prepared by nitration of 2-methyl-4-quinazolone by the literature method [3] in 62% yield after recrystallization from 50% acetic acid



a: $R = R^2 = R^4 = Cl$, $R' = R^3 = H$; b: $R = R^1 = R^2 = R^3 = R^4 = F$; c: $R = R^2 = R^4 = Br$, $R' = R^3 = H$.

Reaction of nitroquinazoline I with phosphorus oxychloride in the presence of dimethylaniline formed, by analogy with the reactions of other substituted quinazolones carried out in our earlier work [1], 2-methyl-4-chloro-6-nitroquinazoline (II). Because the 4-chloro atom of compound II is highly labile the substituted 2-methyl-4-amino-6-nitroquinazoline (III) could be prepared in 76% yield by refluxing the chloro derivative II with δ-diethylamino-α-methylbutylamine in benzene. Condensation of the substituted 2-methylquinazoline III with various aldehydes under conditions like those described earlier for the synthesis of other styrylquinazolines [4, 5] gave compounds IV. We carried out the selective reduction of the nitro group in position 6 of the quinazoline nucleus of styrylquinazolines IV by two methods — heating with sodium sulfide in aqueous alcohol and reaction with hydrazine hydrate in the presence of a nickel catalyst. Compounds V were formed quite smoothly and selectively in yields of about 60% by the first route. The second method was less selective and required additional purification of the products V.

In addition to compounds IV and V we also examined several other substituted 2-styryl-4-aminoquinazolines (VI, VII).

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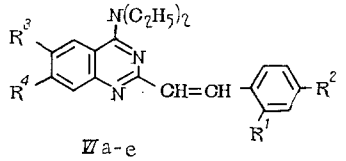
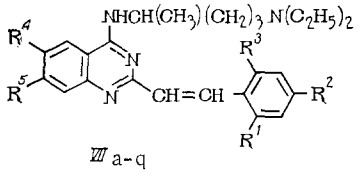


VIIa-e

a: $R^1 = R^3 = H$, $R^2 = R^4 = Cl$; b: $R^2 = R^3 = H$, $R^1 = R^4 = Cl$; c: $R^2 = R^4 = H$; $R^1 = Cl$; $R^3 = CH_3O$: d: $R^1 = R^3 = H$: $R^2 = NO_2$, $R^4 = Cl$: e: $R^1 = R^4 = H$, $R^2 = NO_2$, $R^3 = CH_3O$.



VIIIa-q

a: $R^1 = R^5 = Cl$, $R^2 = R^3 = R^4 = H$; b: $R^1 = Cl$, $R^4 = CH_3O$, $R^2 = R^3 = R^4 = H$; c: $R^1 = R^2 = R^5 = Cl$, $R^3 = R^4 = H$; d: $R^1 = R^2 = Cl$, $R^4 = CH_3O$, $R^3 = R^5 = H$; e: $R^1 = R^2 = R^5 = R^3 = Cl$, $R^4 = H$; f: $R^2 = Br$, $R^5 = Cl$, $R^1 = R^3 = R^4 = H$; g: R^2=Br; $R^4 = CH_3O$, $R^1 = R^3 = R^5 = H$; h: $R^1 = R^2 = Br$, $R^5 = Cl$, $R^3 = R^4$=H; j: R^2=R^1=Br, R^4=CH_3O, R^3=R^5=H; k: R^2=R^1=R^3=Br, R^4=H, R^5=Cl; m: R^2=NO_2, R^1=R^3=R^4= =R^5=H; n: $R^2 = NO_2$, $R^5 = Cl$, $R^1 = R^3 = R^4 = H$; p: $R^2 = NO_2$, $R^1 = R^3 = R^5 = H$, $R^4 = CH_3O$; q: $R^4 = H$, $R^5 = Cl$; 5-notrofuryl instead of the substituted aryl group.

The syntheses of some of these compounds have been described in previous publications: compounds VIa and VIb in [1]; VIIm in [2]; VIc, VIIa, VIIb, VIIc, VIIf, VIIg, VIIj, and VIIk, in [6]: VId, VIe, VIId, VIIe, VIIh, VIIn, VIIp, and VIIq in [7].

EXPERIMENTAL CHEMISTRY

2-Methyl-4-chloro-6-nitroquinazoline (II). A mixture of I (7 g, 34.1 mmole), freshly distilled phosphorus oxychloride (3.55 g, 23.0 mmole), dimethylaniline (10.94 g, 84.2 mmole), and anhydrous benzene (140 ml) was refluxed with stirring for 8 h until the starting quinazolone I had disappeared (TLC on Silufol in ethyl acetate). The mixture was cooled. The benzene solution was decanted from the resinous precipitate, washed with water, 10% sodium hydroxide solution, and water, dried over calcined potassium carbonate, and evaporated. The dimethylaniline was stripped off under vacuum.

The residue was triturated with hexane and crude II (4.5 g) was filtered off, mp 119-120°C. Two recrystallizations from benzene—hexane gave II (3.91 g, 51%), mp 136-137°C. The light orange crystals were soluble in alcohol, ethyl acetate, ether, acetone, chloroform, and benzene, less so in heptane and hexane, and insoluble in water. Found, %: C 48.62; H 2.61, N 18.77, Cl 15.77. $C_9H_6ClN_3O_2$. Calculated, %: C 48.34, H 2.70, N 18.79, Cl 15.86.

2-Methyl-4-(δ-diethylamino-α-methylbutylamino)-6-nitroquinazoline (III). A solution of II (10 g, 44.7 mmole) and δ-diethylamino-α-methylbutylamine (14.1 g, 89.4 mmole) in anhydrous benzene (200 ml) was refluxed for 3 h until the starting quinazoline II had disappeared (TLC on Silufol in benzene). The cooled reaction mixture was treated with 10% sodium hydroxide solution (30 ml). The benzene solution was washed with water and dried over potassium carbonate. Evaporation of the benzene and vacuum distillation of the residual δ-diethylamino-α-methylbutylamine gave crude aminoquinazoline III (13.7 g). The product was recrystallized from heptane with carbon, yield 11.7 g (76%), mp 114-115°C. The yellow crystals were soluble in alcohol, ethyl acetate, ether, acetone, chloroform, and benzene, less so in heptane and hexane, and insoluble in water. Found, %: C 62.26, H 7.79, N 20.31. $C_{18}H_{27}N_5O_2$. Calculated, %: C 62.58, H 7.86, N 20.30.

2-(2,4,6-Trichlorostyryl)-4-(δ-diethylamino-α-methylbutylamino)-6-nitroquinazoline (IVa). A mixture of III (8 g, 23.2 mmole), 2,4,6-trichlorobenzaldehyde (13.5 g, 69.8 mmole), sodium acetate (2.86 g, 3.5 mmole), and acetic anhydride (40 ml) was heated at 114-116°C with stirring for 4 h. It was then poured into 50% hydrochloric acid (100 ml) previously heated to 80°C. After cooling the solution was made alkaline with 50% aqueous potassium carbonate and extracted with ether (6 × 100 ml). The ethereal extract was dried over potassium carbonate and evaporated. The residue was dissolved in anhydrous acetone (600 ml) and 20% alcoholic hydrogen chloride (about 15 ml) was added. The precipitate was filtered off and transferred to a separating funnel and, after addition of water (250 ml), made alkaline with 50% aqueous

potassium carbonate and extracted with ether (6 × 100 ml). The extract was dried over potassium carbonate and evaporated. The residue (10.3 g) was crystallized from methanol (800 ml) with carbon to give styrylquinazoline IVa (9.26 g, 74.5%), mp 181-183°C. The yellow powder was highly soluble in hot alcohols and other common organic solvents but insoluble in water. Found, %: C 55.85, H 5.22, Cl 20.02, N 13.01. $C_{25}H_{28}Cl_3N_5O_2$. Calculated, %: C 55.92, H 5.26, Cl 19.81, N 13.05.

Dihydrochloride of IVa. This was a yellowish-green powder, soluble in water and alcohols on warming but insoluble in acetone, ethyl acetate, benzene, chloroform, and ether, mp 260-262°C. Found, %: Cl 28.82, N 11.72. $C_{25}H_{28}Cl_3N_5O_2 \cdot 2HCl$. Calculated, %: Cl 29.07, N 11.49.

2-(2,4,6-Trichlorostyryl)-4-(δ-diethylamino-α-methylbutylamino)-6-aminoquinazoline (Va). A. To a solution of IVa (4 g, 7.44 mmole) in a mixture of alcohol (100 ml) and water (100 ml) was added a solution of sodium sulfide (40 g, 167 mmole) in water (100 ml). The mixture was heated under reflux until the precipitate had completely dissolved. The mixture was left overnight. The alcohol was stripped off and the residue was extracted with ether (6 × 50 ml). The ethereal extract was dried over potassium carbonate and evaporated. The residue (3.04 g) was crystallized from heptane (500 ml) with carbon to give Va (2.28 g, 60.1%) as a light brown powder, mp 156-157°C, insoluble in water, soluble in heptane and hexane on warming, and highly soluble in other common organic solvents. Found, %: C 58.95, H 5.63, Cl 20.77, N 13.64. $C_{25}H_{30}Cl_3N_5$. Calculated, %: C 59.23, H 5.97, Cl 20.98, N 13.82.

Trihydrochloride of Va. This was a brown powder, mp 181-184°C. The compound was soluble in water, alcohols, chloroform, poorly soluble in acetone, and insoluble in ethyl acetate, benzene, and heptane. Found, %: C 48.49, H 5.38, N 11.52. $C_{25}H_{30}Cl_3N_5 \cdot 3HCl$. Calculated, %: C 48.72, H 5.40, N 11.37.

B. To a solution of IVa (1 g, 1.86 mmole) in methyl alcohol (40 ml) were added Raney nickel (0.5 g) in methyl alcohol (2 ml) and then, dropwise over 45 min, hydrazine hydrate (40 ml). The mixture was left overnight. The nickel was filtered off and the solution was evaporated. The residue was made alkaline with 50% aqueous potassium carbonate and extracted with ether. The ethereal extract was dried over potassium carbonate and evaporated. The residue (0.87 g) was dissolved in anhydrous acetone (20 ml) and alcoholic hydrogen chloride was added until acid to Congo Red. The precipitate of the crude trihydrochloride Va (0.66 g) was filtered off and treated with aqueous sodium hydroxide. The base was extracted with ether. The ether was stripped off and the residue was recrystallized twice from heptane to give Va with mp 156-157°C, which did not depress the melting point of a mixture with the sample prepared by method A.

2-(Pentafluorostyryl)-4-(δ-diethylamino-α-methylbutylamino)-6-nitroquinazoline (IVb). A mixture of III (5 g, 14.5 mmole), pentafluorobenzaldehyde (8.6 g, 43.9 mmole), sodium acetate (1.77 g, 2.14 mmole), and acetic anhydride (30 ml) was heated at 162-164°C with stirring for 10 h. The mixture was then poured into 5% hydrochloric acid (100 ml) previously heated to 80°C. After cooling it was made alkaline with 50% aqueous potassium carbonate and extracted with chloroform (8 × 50 ml). The extract was dried over potassium carbonate and evaporated; the residue was dissolved in anhydrous acetone (3.5 ml) and alcoholic hydrogen chloride was added until the solution was acid to Congo Red. The resulting precipitate was filtered off to give the dihydrochloride of IVb (2.90 g, 33.6%). The yellow powder had mp 244-245°C. The compound was soluble in water and alcohols on warming and insoluble in other common organic solvents. Found, %: C 50.33, H 4.69, N 11.66. $C_{25}H_{26}F_5N_5O_2 \cdot 2HCl$. Calculated, %: C 50.34, H 4.73, N 11.74. The base formed light brown crystals, mp 168-170°C (from heptane). The compound was insoluble in water, soluble in hot heptane, but less so in other common organic solvents. Found, %: C 57.07, H 5.24, F 17.88, N 13.34. $C_{25}H_{26}F_5N_5O_2$. Calculated, %: C 57.35, H 5.01, F 18.5, N 13.38.

EXPERIMENTAL PHARMACOLOGY

We assayed the anti-inflammatory activity in mongrel male rats weighing 130-150 g against paw edema induced by subplanar injection of 1% carrageenan solution (0.1 ml) into the right rear paw [8]. The degree of the edematous response was assessed volumetrically.

We screened the compounds for antipyretic properties against pyrexia induced by subcutaneous administration of 2,4-dinitrophenol [9] in a dose of 20 mg/kg and assessed their analgesic activity from the increase in the pain sensitivity threshold [10].

TABLE 1. Anti-inflammatory Activity and Toxicity of Styrylquinazoline Derivatives

Compound	LD_{50}, mg/kg	Reduction in carrageenan paw edema, % of original	Depression of 2,4-dinitrophenol-induced pyrexia, % of original	Increase in the pain sensitivity threshold, % of original
VI a	>1000	—*	—	—
VI b	>1000	—	—	—
VI c	>1000	—	—	—
VII a	1000	—	60	12
VII b	>1000	—	—	—
VII c	>1000	44	—	42
VII d	>1000	—	—	—
IV a	>1000	54	—	35
VII e	>1000	35	—	61
V a	1000	23	67	—
VII f	>1000	19†	—	—
VII g	1000	27†	—	—
VII h	>1000	—	—	—
VII j	>1000	—	—	—
VII k	~1000	—	23†	—
IVc	1000	—	23†	—
V c	>1000	22†	—	—
VI d	>1000	40	—	26
VI e	~1000	—	—	—
VII m	~1000	—	—	—
VII n	>1000	68	—	47
VII p	~1000	—	47	32
VII q	650	—	—	—
IV b	>1000	35†	—	—
amidopyrine	—	52	80	14
brufen	740	78	25	35

*No effect in a dose of 100 mg/kg.
†Differences with control were unreliable at P = 0.05.

In all the tests the compounds were administered in a dose of 100 mg/kg as suspensions in 1% starch slurry by gastric gavage 1 h before the administration of carrageenan or 2,4-dinitrophenol and the measurement of the pain sensitivity threshold. We compared the activity of the compounds with that of amidopyrine and brufen given in the same dose, in terms of these indices.

We determined the acute toxicity of the compounds on gastric administration in male mice weighing 18-20 g.

Our tests revealed that these new styrylquinazoline derivatives have anti-inflammatory activity (Table 1). This applies in general to those that contain the di- or trichlorostyryl radical in position 2 of the (VIIc, IVa, VIIe, and Va). Replacement of chlorine by other halogens — bromine or fluorine — removes the anti-inflammatory activity, in compounds VIIh, VIIj, VIIk, IVc, Vc, and IVb. We also confirmed that the nitrostyrylquinazolines VIIn and VId examined earlier [1, 2] have anti-inflammatory properties.

In addition to anti-inflammatory activity the majority of the active compounds have analgesic properties, while several, such as Va, also possess antipyretic activity. The most active of these compounds approach brufen and amidopyrine in anti-inflammatory, analgesic, and antipyretic potency.

Despite this extra information on the biological properties of styrylquinazolines, our results do not reveal any general correlation between chemical structure and anti-inflammatory activity in this series of compounds. Since the test preparations are relatively nontoxic on internal administration ($LD_{50} \geq 1000$ mg/kg), while some possess comparatively high anti-inflammatory activity, further work on quinazoline derivatives in this respect seems advisable.

LITERATURE CITED

1. L. N. Yakhontov, G. P. Zhikhareva, E. V. Pronina, et al., Khim. Farm. Zh., No. 11, 12 (1975).
2. G. P. Zhikhareva, E. A. Berlyand, S. S. Liberman, et al., Khim. Farm. Zh., No. 10, 58 (1977).

3. A. J. Tomisek and B. E. Christensen, J. Am. Chem. Soc., 70, 2423 (1948).
4. L. N. Yakhontov, E. V. Pronina, and G. P. Zhikhareva, Inventor's Certificate No. 466233; Otkrytiya, No. 13, 55 (1975).
5. L. N. Yakhontov, E. V. Pronina, and G. P. Zhikhareva, Inventor's Certificate No. 641621; Otkrytiya, No. 43, 190 (1975).
6. G. P. Zhikhareva, E. V. Pronina, E. A. Golovanova, et al., Khim. Farm. Zh., No. 4, 62 (1976).
7. G. P. Zhikhareva, L. I. Mastafanova, N. S. Bogdanova, et al., Khim. Farm. Zh., No. 11, 44 (1978).
8. C. A. Winter, E. A. Risley, and G. W. Nuss, Proc. Soc. Exp. Biol. Med., 111, 544 (1962).
9. N. A. Shtakel'berg, "The mechanism of fever," Candidate's Dissertation, Leningrad (1950).
10. J. Jusziekiewicz-Dousbach and G. Levy, J. Pharm. Sci., 51, 185 (1962).

SYNTHESIS AND PROPERTIES OF PYRIDINE- AND s-TRIAZOLO[4,3-a]PYRIDINESULFONAMIDES

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Pyridinesulfonamides are known to have a broad spectrum of biological activity [1-4]. Many compounds of this series display anti-inflammatory, antibacterial, antipyretic, and diuretic activity.

Here we report a continuation of our earlier work on the synthesis of biologically active pyrido-annelated heterocycles based on 2-chloro-3-pyridinesulfonyl chloride [5]. We have developed [6] a convenient route to 2-chloro-3-pyridinesulfonyl chloride (II) involving the diazotization of 2-nitro-3-aminopyridine (I) with simultaneous substitution of the diazo group by sulfonyl chloride and of the nitro group by chlorine, which makes possible the extensive use of 2-chloro-3-pyridinesulfonyl chloride as a starting compound. On the basis of this compound we prepared a series of 2-hydrazino(α-methylhydrazino)-3-aminosulfonylpyridines and cyclized them to s-triazolo[4,3-a]pyridines.

Reaction of compound II with various amines — ammonia, morpholine, isopropylamine — gave the corresponding 2-chloro-3-aminosulfonylpyridines (III). The 2-chloro atom is highly reactive and can readily be substituted by nucleophiles. Thus, compounds III were converted to the 2-hydrazino-3-aminosulfonylpyridines (IV) by refluxing with alcoholic hydrazine hydrate or α-methylhydrazine. When refluxed with excess carbon disulfide in the presence of triethylamine the 2-(α-methylhydrazino)-3-aminosulfonylpyridines (IV, R' = CH_3) generated the 1-methyl-3-thioxo-8-aminosulfonyl-s-triazolo[4,3-a]pyridin-1-ium inner salts (V) in 30-40% yield. The reason for the low yield of the cyclization products is that the reaction is accompanied by partial destruction of the hydrazine group to form 2-methylamino-3-aminosulfonylpyridines. Cyclization of 2-hydrazino-3-aminosulfonylpyridines (IV, R' = H) with carbon disulfide in the presence of triethylamine formed 3-thioxo-8-aminosulfonyl-s-triazolo-[4,3-a]pyridines (VI) in 60-80% yield. Methylation of zwitterions V in neutral solution gave quantitative yields of the quaternary salts — 1-methyl-3-methylthio-8-aminosulfonyl-s-triazolo[4,3-a]pyridin-1-ium iodides (VII). Methylation of compounds VI with a 1.5-fold excess of methyl iodide in aqueous alcoholic alkali formed 3-methylthio-8-aminosulfonyl-s-triazolo-[4,3-a]pyridines (VIII).

We verified the structures of the methylation products VIII by oxidizing compound VIIIb to the corresponding methylsulfonyl derivative IXb with hydrogen peroxide or potassium permanganate in acetic acid.

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