# SYNTHESIS AND BIOLOGICAL ACTIVITY OF ACRIDINYL-9-THIOACETIC ACIDS AND THEIR DERIVATIVES

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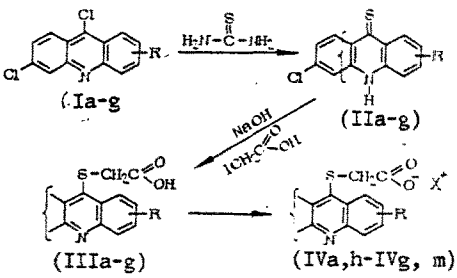
UDC 615.211+615.276]:547.835].012.1

Among the 9-substituted compounds of 9-acridine that have been little studied with respect to their biolgoical and chemical properties, some have been noted to exhibit anti-inflammatory, analgesic, and antihypoxic acitvity [7, 10].

As a continuation of our research on pharmacologically active comounds in the acridine series, we have synthesized derivatives of 6-chloro-9-thioacridine starting with 6,9-dichloroacridine (Ia) and its 2- and 4-methoxy (Ib, Ic), methyl (Id, Ie), chloro (If) as well as 2,3-dimethyl derivatives (Ig). By reacting the latter with thiourea in a dioxane medium [8] we obtained 6-chloro-9-thioacridone and its methoxy-, methyl-, chloro-, and dimethyl derivatives (IIa-g).

Upon the action of NaOH the compounds IIa-g, like 9-thioacridone, are converted to the tautomer (thiol) derivatives, i.e., the corresponding 6-chloro-9-thioacridines, which react readily with monoiodoacetic acid to form 6-chloroacridinyl-9-thioacetic acid (IIIa) and its derivatives (IIIb-g).

The salts of the acridinyl-9-thioacetic acids (IVa,h-IVg, m) were obtained from the acids IIIa-g and equimolecular quantities of inorganic and organic type bases.




a: R = H; b: R = MeO-2; c: R = MeO-4; d: R = Me-2; e: R = Me-4; f: R = Cl-4; g: R = Me-2,3; $X^+$ — cations: h - morpholine; i - piperidine; j - diethylaminoethanol, k - dimethylaminoethanol, l - potassium.

The structure of the resultant compounds was confirmed by IR and UV spectral data. The IR spectra of compounds IIa-g are characterized by the presence of absorption bands in the range of 3350-2910 $cm^{-1}$ which should be grouped with $\nu_{NH}$. The intensive absorption band at 1570-1380 $cm^{-1}$ is the result of $\nu_{C=S}$ vibrations. The compounds IIb-g can be identified by the absorption bands that are characteristic of substituents in the aromatic system of thioacridones: $\nu_{OCH_3}$ 1550-1540 $cm^{-1}$, $\nu_{CH_3}$ 1570-1560 $cm^{-1}$.

Three absorption bands with maxima of 480, 397, and 258 nm were identified in the UV spectrum of IIa in ethanol. A significant change in the spectral characteristics of IIa was observed in a solution of 1 M sodium ethanolate, i.e., the appearance of a new intensive astructural band with $\lambda_{max}$ 286 and 243 nm. A similar situation was characteristic of compounds IIb-g. The described changes indicate that the compounds under study, like 9-thioacridone, are converted in the presence of NaOH to the thiol tautomer form [2, 9].

In the IR spectra of compounds IIIa-g the bands corresponding to $\nu_{C=O}$ are manifested at 1725-1700 $cm^{-1}$, the band corresponding to $\nu_{S-CH_2}$ at 670 $cm^{-1}$, and those corresponding to $\nu_{OCH_3}$ at 1560 $cm^{-1}$. It is worth noting that the absorption bands for the compounds IIIa-g

Khar'kov Pharmaceutical Institute. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 21, No. 9, pp. 1067-1070, September, 1987. Original article submitted April 7, 1986.

0091/150X/87/2109-0633$12.50  

TABLE 1. Derivatives of 6-Chloro-9-thioacridone and 6-Chloro-9-thioacridine

| Compound | Yield (%) | mp, °C | Found, % | | Empirical formula | Calculated, % | | $R_f$ |
|---|---|---|---|---|---|---|---|---|
| | | | N | Cl | | N | Cl | |
| IIa | 90 | 249—50 | 5,9 | 14,4 | $C_{13}H_8ClNS$ | 5,7 | 14,4 | 0,58 |
| IIb | 84 | 278—9 | 4,9 | 12,7 | $C_{14}H_{10}ClNOS$ | 5,1 | 12,8 | 0,59 |
| IIc | 87 | 208—9 | 5,2 | 13,0 | $C_{14}H_{10}ClNOS$ | 5,1 | 12,8 | 0,56 |
| IId | 85 | 265—6 | 5,2 | 13,4 | $C_{14}H_{10}ClNS$ | 5,4 | 13,6 | 0,61 |
| IIe | 82 | 185—6 | 5,4 | 13,8 | $C_{14}H_{10}ClNS$ | 5,4 | 13,6 | 0,62 |
| IIf | 81 | 235—6 | 5,1 | 25,4 | $C_{13}H_7Cl_2NS$ | 5,0 | 25,3 | 0,70 |
| IIg | 86 | 225—6 | 5,2 | 13,1 | $C_{15}H_{12}ClNS$ | 5,1 | 12,9 | 0,64 |
| IIIa | 54 | 252—3 | 4,7 | 11,7 | $C_{15}H_{10}ClNO_2S$ | 4,6 | 11,7 | 0,48 |
| IIIb | 49 | 258—9 | 4,2 | 10,7 | $C_{16}H_{12}ClNO_3S$ | 4,2 | 10,6 | 0,51 |
| IIIc | 56 | 205—6 | 4,0 | 10,5 | $C_{16}H_{12}ClNO_3S$ | 4,2 | 10,6 | 0,50 |
| IIId | 52 | 255—6 | 4,6 | 11,3 | $C_{16}H_{12}ClNO_2S$ | 4,4 | 11,2 | 0,57 |
| IIIe | 45 | 243—4 | 4,3 | 11,0 | $C_{16}H_{12}ClNO_2S$ | 4,4 | 11,2 | 0,53 |
| IIIf | 43 | 223—4 | 4,5 | 21,6 | $C_{15}H_9Cl_2NO_2S$ | 4,2 | 21,3 | 0,63 |
| IIIg | 48 | 215—6 | 4,2 | 10,6 | $C_{17}H_{14}ClNO_2S$ | 4,2 | 10,7 | 0,56 |
| IVa, h | 61 | 247—8 | 7,2 | 9,2 | $C_{19}H_{19}ClN_2O_3S$ | 7,2 | 9,1 | 0,62 |
| IVb, h | 57 | 273—4 | 6,8 | 8,5 | $C_{20}H_{21}ClN_2O_4S$ | 6,6 | 8,4 | 0,60 |
| IVc, h | 59 | 209—11 | 6,4 | 8,3 | $C_{20}H_{21}ClN_2O_4S$ | 6,6 | 8,4 | 0,56 |
| IVd, h | 60 | 269—70 | 6,7 | 8,5 | $C_{20}H_{21}ClN_2O_3S$ | 6,9 | 8,8 | 0,62 |
| IVe, h | 63 | 210—1 | 7,0 | 8,9 | $C_{20}H_{21}ClN_2O_3S$ | 6,9 | 8,8 | 0,57 |
| IVf, h | 55 | 229—30 | 6,5 | 16,5 | $C_{19}H_{19}Cl_2N_2O_3S$ | 6,6 | 16,7 | 0,69 |
| IFg, h | 58 | 212—3 | 6,9 | 8,6 | $C_{21}H_{23}ClN_2O_3S$ | 6,7 | 8,5 | 0,54 |
| IVa, i | 52 | 254—5 | 7,2 | 9,2 | $C_{20}H_{21}ClN_2O_2S$ | 7,2 | 9,1 | 0,58 |
| IVb, i | 51 | 285—6 | 6,9 | 8,8 | $C_{21}H_{23}ClN_2O_3S$ | 6,7 | 8,5 | 0,56 |
| IVc, i | 49 | 272—2 | 6,7 | 8,5 | $C_{21}H_{23}ClN_2O_3S$ | 6,7 | 8,5 | 0,61 |
| IVd, i | 53 | 212—3 | 6,9 | 8,6 | $C_{21}H_{23}ClN_2O_3S$ | 7,0 | 8,8 | 0,55 |
| IVe, i | 50 | 289—90 | 7,0 | 9,1 | $C_{21}H_{23}ClN_2O_3S$ | 7,0 | 8,8 | 0,60 |
| IVf, i | 45 | 228—9 | 6,5 | 16,7 | $C_{20}H_{20}Cl_2N_2O_2S$ | 6,6 | 16,7 | 0,70 |
| IVg, i | 48 | 142—3 | 7,0 | 8,7 | $C_{22}H_{25}ClN_2O_2S$ | 6,7 | 8,5 | 0,54 |
| IVa, j | 61 | >300 | 6,8 | 8,8 | $C_{21}H_{25}ClN_2O_3S$ | 6,7 | 8,4 | 0,52 |
| IVb, j | 57 | 266—7 | 6,6 | 8,0 | $C_{22}H_{27}ClN_2O_4S$ | 6,2 | 7,9 | 0,53 |
| IVc, j | 59 | 190—1 | 6,5 | 8,0 | $C_{22}H_{27}ClN_2O_4S$ | 6,2 | 7,9 | 0,51 |
| IVd, j | 54 | 250—1 | 6,2 | 7,9 | $C_{22}H_{27}ClN_2O_3S$ | 6,4 | 8,1 | 0,58 |
| IVe, j | 52 | 242—3 | 6,5 | 8,3 | $C_{22}H_{27}ClN_2O_3S$ | 6,4 | 8,1 | 0,61 |
| IVf, j | 47 | >300 | 6,2 | 15,8 | $C_{21}H_{24}Cl_2N_2O_3S$ | 6,1 | 15,6 | 0,72 |
| IVg, j | 50 | 219—20 | 6,5 | 8,0 | $C_{23}H_{29}ClN_2O_3S$ | 6,2 | 7,9 | 0,62 |
| IVa, k | 62 | 245—6 | 7,0 | 8,9 | $C_{19}H_{21}ClN_2O_3S$ | 7,1 | 9,0 | 0,52 |
| IVb, k | 61 | 269—9 | 6,3 | 8,0 | $C_{20}H_{23}ClN_2O_4S$ | 6,6 | 8,4 | 0,59 |
| IVc, k | 58 | 197—8 | 6,4 | 8,1 | $C_{20}H_{23}ClN_2O_4S$ | 6,6 | 8,4 | 0,51 |
| IVd, k | 62 | 270—1 | 6,5 | 8,5 | $C_{20}H_{23}ClN_2O_3S$ | 6,9 | 8,7 | 0,56 |
| IVe, k | 65 | 256—7 | 6,5 | 8,6 | $C_{20}H_{23}ClN_2O_3S$ | 6,9 | 8,7 | 0,62 |
| IVf, k | 59 | 225—6 | 7,7 | 19,6 | $C_{19}H_{20}Cl_2N_2O_3S$ | 7,8 | 19,9 | 0,72 |
| IVg, k | 66 | 244—5 | 6,5 | 8,2 | $C_{21}H_{25}ClN_2O_2S$ | 6,7 | 8,4 | 0,63 |
| IVa, ℓ | 74 | >300 | 4,3 | 10,6 | $C_{15}H_9ClNO_2SK$ | 4,1 | 10,4 | 0,54 |
| IVb, ℓ | 71 | >300 | 3,7 | 9,6 | $C_{16}H_{11}ClNO_3SK$ | 3,7 | 9,5 | 0,53 |
| IVc, ℓ | 76 | >300 | 4,0 | 9,6 | $C_{16}H_{11}ClNO_3SK$ | 3,7 | 9,5 | 0,52 |
| IVd, ℓ | 80 | >300 | 3,6 | 9,7 | $C_{16}H_{11}ClNO_2SK$ | 3,9 | 10,0 | 0,48 |
| IVe, ℓ | 78 | >300 | 3,8 | 9,8 | $C_{16}H_{11}ClNO_2SK$ | 3,9 | 10,0 | 0,47 |
| IVf, ℓ | 69 | >300 | 4,0 | 19,0 | $C_{15}H_8Cl_2NO_2SK$ | 3,7 | 18,8 | 0,64 |
| IVg, ℓ | 72 | >300 | 3,6 | 9,3 | $C_{17}H_{13}ClNO_2SK$ | 3,8 | 9,6 | 0,38 |

in the region of 3310-2910 $cm^{-1}$ that corresponds to the vibrations of the NH-group which is not observed in the compounds IVa, h-IVg, ℓ, might be attributed to the existence of 6-chloroacridinyl-9-thioacetic acids in the form of zwitterions that result from the protonization of the nitrogen ring.

The constants of the resultant compounds are given in Table 1.

## EXPERIMENTAL CHEMICAL

IR spectra of the compounds were read on a Specord 75-IR spectrophotometer (GDR) in KBr pellets (substance concentration 1%). UV spectra were recorded on a Specord UV-Vis spectrophotometer (GDR). $R_f$ of the compounds were determined on Silufol UV-254 plates (Czechoslovakia) in an ethylacetate–chloroform (4:1) system.

6-Chloro-9-thioacridone (IIa). A 0.1-g (0.01-mole) portion of thiourea dissolved in 10 ml of dioxane was added to a solution of 2.5 g (0.01 mole) of 6,9-dichloroacridine in 50 ml of dioxane. The mixture was heated for 10 to 15 min on a boiling water bath. The mixture was then cooled and the resultant precipitate was filtered off, dissolved in 200 ml of 2% NaOH, and filtered. The filtrate was acidified with AcOH to pH 6.0 and the resultant

precipitate of IIa was filtered off, washed with water, dried, and crystallized from dioxane. Compounds IIb-g were obtianed in a similar manner.

6-Chloroacridinyl-9-thioacetic Acid (IIIa). A 5-ml portion of 4.5 M NaOH was added to a solution of 2.5 g (0.01 mole) of 6-chloro-9-thioacridone in 100 ml of DMPA. Then 2.43 g (0.01 mole) of monoiodoacetic acid was added to the reaction mixture which was then heated for 15 to 20 min on a boiling water bath. After the mixture was cooled and diluted with water the resultant precipitate was filtered off, dissolved in 200 ml of a 10% $NaHCO_3$ solution, boiled with activated charcoal, and filtered. The filtrate was acidified to pH 2.0. The precipitate IIIa was then washed with water, dried, and crystallized from dioxane. Compounds IIIb-g were obtained in a similar manner.

Potassium 6-Chloroacridinyl-9-thioacetate (IVa, ℓ). A 3-g (0.01-mole) portion of 6-chloroacridinyl-9-thioacetic acid was added to an aq. solution of 0.56 g (0.01 mole) of KOH. The mixture was heated on a boiling water bath for 20 min. Then it was boiled with activated charcoal and filtered. The filtrate was boiled down to a dry precipitate at 50°C. Compounds IVa, j-IVg, k were obtained in a similar manner.

Morpholine 6-Chloroacridinyl-9-thioacetate (IVa, h). A 1.21-ml (0.014-mole) portion of morpholine in 20 ml of dioxane was added to a solution of 4.25 g (0.014 mole) of 6-chloroacridinyl-9-thioacetic acid in 50 ml of dioxane. The mixture was then heated for 15 min on a water bath and cooled. The resultant precipitate IVa, h was filtered and dried. Compounds IVb, h-IVg, i were obtained in the same manner.

## EXPERIMENTAL PHARMACOLOGICAL

6-Chloroacridinyl-9-thioacetic acids and their salts IIIa-IVg, ℓ were tested for antiinflammatory, analgesic, and antihypoxic activity.

The compounds' antiinflammatory activity was evaluated by their antiexudative action which was assayed on mice weighing 18-20 g by applying a 2.5% formalin solution as the inflammatory agent in accordance with the method in [5]. The compounds were administered at doses of from 14 to 17 mg/kg [1]. Comparative parallel tests were performed with indomethacin which was administered at a dose of 15 mg/kg.

Analgesic activity was evaluated in the mice by the changes in the animals' pain sensitivity upon chemical irritation induced by an ip injection of 3% AcOH at a dose rate of 300 mg/kg [6]. The compounds were administered at a dose of 60 mg/kg 1 h before the investigation. The animals' response to the injected AcOH was recorded for the first 20 min after the irritant was administered.

Comparative tests for analgesic activity were made with Dipyrone at the same dosage.

Antihypoxic activity was examined by the L. V. Pastushenkov method on mice of both sexes weighing 20-24 g in a pressure chamber at an elevation of 11,000 meters [3]. The test compounds and sodium oxybutyrate, which was used as the control, were administered at a dose of 100 mg/kg.

Our investigations showed that compounds IIIa, IVe, h, IVb, i, IVb, j, and IVg, ℓ exhibit antiinflammatory activity equivalent to indomethacin. The antiexudative effect of IVd, j, IVc, k, IVd, k, IVd, ℓ, and IVf, ℓ was two to four times less than that of indomethacin. The remaining compounds proved to be inactive.

The analgesic effect of compounds IIIa, IVg, i, and IVb, j was 1.2 to 1.4 times greater than that of Dipyrone. Compounds IIIc, IIIe, IIIf, IVb, i, IVa, ℓ, and IVd, ℓ exhibited an analgesic action that was equal to or near that of Dipyrone while the remaining compounds were 1.3 to 1.9 times less active than Dipyrone.

Compounds IIIa, IIIf, IVe, h, IVc, i, IVa, j, IVd, ℓ, and IVg, ℓ exhibited moderate antihypoxic activity which did not exceed that of sodium oxybutyrate.

The acute toxicity of the tested compounds upon oral administration (over a 24-h observation period) was calculated by method [4] and was found to be in the range of 2,200 to 4,200 mg/kg.

Thus, derivatives of 6-chloroacridinyl-9-thioacetic acid have a comparatively low level of toxicity and are of practical interest in the search for substances with antiinflammatory and analgesic activity.

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# NEUROTROPIC ACTIVITY OF ORGANOGERMANIUM DERIVATIVES OF ADAMANTANE AND NITROGEN-CONTAINING HETEROCYCLES

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UDC 615.214.22:547.246'592.1

We have found organogermanium compounds having neurotropic activity [6, 7]. At the same time, a number of adamantane-containing drugs are known which act primarily on the central nervous system (CNS) [5]. In order to determine the changes in biological activity when these fragmetns are combined into one molecule, we synthesized organosilicon and organogermanium derivatives of adamantane (I-VII) and studied their neurotropic activity. At the same time, the biological properties of organogermanium derivatives of pyrrolidone (VIII-X), pyrazole (XI, XII), benzimidazole (XIII), and pyridine (XIV-XVI) were studied.

1-[β-(trimethylgermyl)ethyl]adamantane (II) was synthesized by alkylation of adamantane (AdH) with vinyltrichlorogermane under conditions of the Friedel–Krafts reaction with subsequent methylation by methylmagnesium iodide [2].

$$AdH + CH_2{=}CHGeCl_3 \longrightarrow 1\text{-}AdCH_2CH_2GeCl_3 \longrightarrow \underset{II}{1\text{-}AdCH_2CH_2GeMe_3}$$

The silicon analog $1\text{-}Ad(CH_2)_2SiMe_3$ (I) was obtained according to the same reaction scheme [8].

1-[γ-(Trimethylgermyl)propyl]adamantane (III) was synthesized by hydrogermylation of 1-allyladamantane by trichlorogermane [8].

$$1\text{-}AdCH_2CH_2{=}CH_2 \longrightarrow 1\text{-}Ad(CH_2)_3GeCl_3 \longrightarrow \underset{III}{1\text{-}Ad(CH_2)_3GeMe_3}$$

The 1-adamantylamide of trimethylgermylpropionic acid (IV) was obtained by acylation of 1-aminoadamantane by trimethylgermylpropionic chloranhydride in dichloroethane.

$$1\text{-}AdNH_2 + Me_3GeCH_2CH_2COCl \longrightarrow \underset{IV}{1\text{-}AdNHCOCH_2CH_2GeMe_3}$$

2-(Adamantyldimethylgermyl)propionic (V) and 3-(adamantyldimethylgermyl)propionhydroxamic (VI) acids were obtained according to the method described in [10], the first stage of which is the hydrogermylation of acrylic acid esters by 1-adamantyldimethylgermane in the presence of $H_2PtCl_6$:

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga; State Scientific Research Institute of Chemistry and Technology of Elemental Organic Compounds, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 21, No. 9, pp. 1070-1074, September, 1987. Original article submitted May 30, 1986.

 0091/150X/87/2109-0636$12.50 