SYNTHESIS OF XANTHENE AND THIOXANTHENE DERIVATIVES AND STUDY OF THEIR ANTIMICROBIAL ACTIVITY

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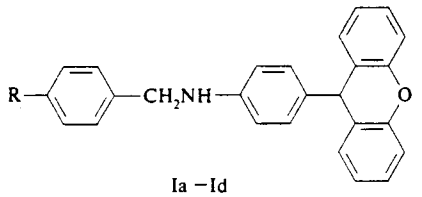
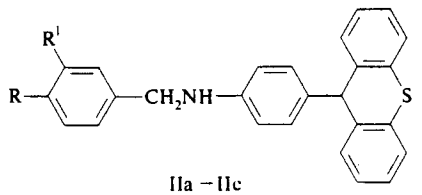
It has been reported that some of the thioxanthene derivatives are biologically active. For example, 1,4-aminoalkyl amino-9H-thioxanthen-9-ones showed antimicrobial, fungicide, and antitumor activity [1].

We have studied the antimicrobial activity of a series of the secondary aromatic amines, including N-arylmethyl-4-(xanthen-9-yl)anilines (Ia – Id) and N-arylmethyl-4-(thioxanthen-9-yl)anilines (IIa – IIc), and a group of structurally related imines, N-arylmethylene-4-(xanthen-9-yl)anilines (IIIa – IIId) and N-arylmethylene-4-(thioxanthen-9-yl)anilines (IVa – IVc). Imines IIIa, IIIc and IVa, IVb can be obtained by dehydrogenation of the corresponding amines by Schiff bases [2, 3].



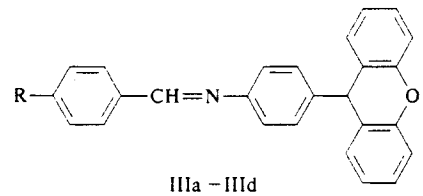
Ia – Id

R = H (Ia), Cl (Ib), NMe_2 (Ic), OMe (Id)



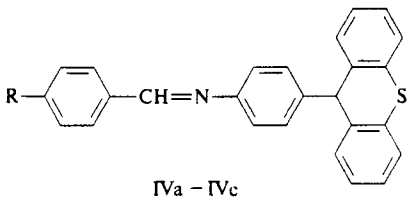
IIa – IIc

R = H, R^1 = H (IIa);
R = Cl, R^1 = H (IIb);
R = OMe, R^1 = OMe (IIc)



IIIa – IIId

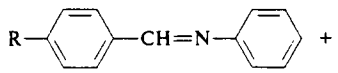
R = H (IIIa), Cl (IIIb), NMe_2 (IIIc), OMe (IIId)



IVa – IVc

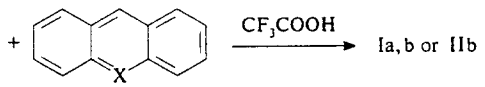
R = H (IVa), Cl (IVb), NO_2 (IVc)

Amines Ia, Ib and IIb were obtained by reductive hetarylation of imines Va, Vb by xanthene VI [4] or thioxanthene VII [3]. Note that this method is inapplicable to Schiff bases possessing electron-donor substituents R. For this reason, amines Ic, Id, IIa, and IIc were synthesized by a different scheme [5].



Va, b

R = H (Va), Cl (Vb)



VI, VII

X = O (VI), S (VII)

The results of our investigations showed that compounds IIa, IIb, IIIc, and IVc at a concentration of 500 μg / ml exhibit a bacteriostatic affect with respect to *Staphylococcus aureus*, which is comparable to the activity of ethacridine lactate, a drug that is widely used in medical practice.

At the same time, the compounds showed virtually no activity with respect to bacteria of the *Escherichia coli* group even at a concentration of 1000 μg / ml.

EXPERIMENTAL CHEMICAL PART

The ^{1}H NMR spectra were measured on a Bruker WP-80GU (80 MHz) spectrometer using $CDCl_3$ as the solvent and HMDS as the internal standard. The IR spectra were recorded on a Specord M-80 spectrophotometer using samples

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pelletized with KBr. The results of elemental analyses agreed with the calculations.

Imines IIIb, IIId, and IVc were obtained from the corresponding aldehydes and amines by a conventional scheme described in [6]. Imines IIIa, IIIc and amines Ia – Ic, IIa, IIb were reported previously [2 – 4].

N-(4-Methoxybenzyl)-4-(xanthen-9-yl)aniline (Id). Yield 66%; m.p., 114 – 115°C (cryst. from benzene); ^{1}H NMR spectrum, $CDCl_3$ (δ, ppm): 1.45 (s, 1H, NH), 3.70 (s, 3H, CH_3), 4.11 (s, 2NH, CH_2), 5.05 (s, 1H, C^9H), 6.41 – 8.32 (m, 16H, $2C_6H_4$, $C_{13}H_8O$); $C_{27}H_{23}NO_2$.

N-(3,4-Dimethoxybenzyl)-4-(thioxanthen-9-yl)aniline (IIc). Yield 72%; m.p., 150 – 151°C (cryst. from acetone); ^{1}H NMR spectrum, C_6D_6 (δ, ppm): 1.35 (s, 1H, NH), 3.27 (s, 3H, 3-OCH_3), 3.30 (s, 3H, 4-OCH_3), 3.77 (s, 2H, CH_2), 4.98 (s, 1H, C^9H), 6.18 – 7.25 (m, 15H, C_6H_3, C_6H_5, $C_{13}H_7S$); IR spectrum (ν_{max}, cm^{-1}): 3368 (NH); $C_{28}H_{25}NO_2$.

N-(4-Chlorobenzylidene)-4-(xanthen-9-yl)aniline (IIIb). Yield 92%; m.p., 169 – 170°C (cryst. from benzene); ^{1}H NMR spectrum, $CDCl_3$ (δ, ppm): 5.21 (s, 1H, C^9H), 8.30 (s, 1H, CH=N), 6.92 – 7.81 (m, 16H, $2C_6H_4$, $C_{13}H_8O$); $C_{28}H_{18}NOCl$.

N-(4-Methoxybenzylidene)-4-(xanthen-9-yl)aniline (IIId). Yield 84%; m.p., 175 – 176°C (cryst. from benzene); ^{1}H NMR spectrum, $CDCl_3$ (δ, ppm): 3.77 (s, 3H, OCH_3), 5.19 (s, 1H, C^9H), 8.26 (s, 1H, CH=N), 6.80 – 7.85 (m, 16H, $2C_6H_4$, $C_{13}H_8O$); $C_{27}H_{21}NO_2$.

N-(4-Nitrobenzylidene)-4-(thioxanthen-9-yl)aniline (IVc). Yield 68%; m.p., 166 – 167°C; ^{1}H NMR spectrum, C_6D_6 (δ, ppm): 5.05 (s, 1H, C^9H), 7.72 (s, 1H, CH=N), 6.70 – 7.64 (m, 16H, $2C_6H_4$, $C_{13}H_8S$); $C_{26}H_{18}N_2O_2S$.

EXPERIMENTAL BIOLOGICAL PART

The antimicrobial activity was determined with respect to *St. aureus* and *E. coli* by the conventional method of serial dilutions in a beef-infusion broth [7]. The stock solution of a bacterial culture contained 5×10^6 microbial cells per ml. An aliquot (0.1 ml) of the stock solution was introduced into 2 ml of the beef-infusion broth containing the test substances diluted to the necessary level. The bacterial load was 250,000 microbial cells per ml solution. The results of the experiments were assessed after a 18 – 20 h incubation of the control and test tubes in a thermostat at 36 – 37°C, judging by the growth of bacterial cultures or its suppression as a result of the bacteriostatic action of the drugs. The active dose was determined as the minimum inhibiting concentration (MIC, μg / ml) of the compound ensuring complete suppression of the growth of test microbes.

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