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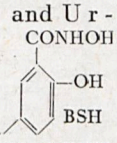
Lowering of Cholesterol Level in the Blood Serum of Rabbits by Halogen Substituted Salicylhydroxamic Acids

By A. Czyżyk, A. Ostaszyński, H. Plenkiewicz, Z. Szczepanik, and T. Urbański

Introduction

It has formerly been shown by Czyżyk and Urbański [4] that 5-bromosalicylhydroxamic acid (BSH) in some clinical cases significantly reduced the cholesterol-level in blood serum. The choice of BSH for these experiments was based on the fact observed by Johnson, Mankiewicz *et al.* [8] that BSH was proved to be (in clinical experiments) an effective inhibitor of isoniazide inactivation, which in turn is the result of N-acetylation of isoniazide [7], and on the other hand it is well known that acetic acid is the precursor of cholesterol in the rat [2], and the biosynthesis of cholesterol can start from acetate [1, 16].



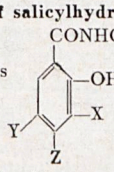
BSH

Subsequently Czyżyk and Urbański [4] expected that BSH might inhibit the formation of cholesterol in the blood serum. This proved to be correct and the next step was to examine the activity in rabbits of a number of different halogeno-substituted derivatives of salicylhydroxamic acid. All of them showed a significant effect of lowering the cholesterol level. On the contrary, salicylhydroxamic acid was practically deviod of this activity.

Materials

Halogen derivatives of salicylhydroxamic acid

All derivatives



Y = H, F, Cl, Br,
X = H, Br, J,
Z = H, F,

described already in the literature were prepared according to the methods previously given by acting with alcoholic hydroxylamine on methyl esters of the corresponding derivatives of salicylic acid [3, 5, 6, 10, 11, 15].

Methyl ester of 3,5-dibromo-4-fluorosalicylic acid

Methyl ester of 4-fluorosalicylic acid (0.2 mol, 34 g) was dissolved in 100 ml anhydrous acetic acid and conc. (40%) aqueous hydrobromic acid (80 g) was added. The mixture was warmed to 60° and sodium chlorate (7 g) aqueous solution was added at 60—65° under vigorous stirring. After that the temperature of 65° was kept for one hour. The solution was cooled, poured into water, the precipitate was collected and crystallised from methanol. The yield was 64 g (97%), m.p. 144—145.

3,5-dibromo-4-fluorosalicylhydroxamic acid (X = Y = Br, Z = F)

A solution of hydroxylamine in aqueous ethanol was prepared by dissolving hydroxylamine hydrochloride (9 g) in a solution of sodium hydroxide (9 g) in water (50 ml) and ethanol (100 ml).

To the solution of hydroxylamine, methyl ester of 3,5-dibromo-4-fluorsalicylic acid (0.1 mol, 32.8 g) dissolved in ethanol (150 ml) was added under vigorous stirring. The solution was warmed to 70° and kept at this temperature for 2 h. The reaction solution was left overnight. Ethanol was evaporated under reduced pressure. Water (200 ml) was added to the residue and acidified (to Congo-red) with 10% hydrochloric acid. The precipitate was crystallised from dilute ethanol. The yield was 28 g (85%), m.p. 185—186°.

Analysis. $C_7H_4Br_2FNO_3$ requires:
C 25.6; H 1.2; Br 48.8; N 4.3%.
Found: C 25.8; H 1.35; Br 49.6; N 4.6%

Methods

Male rabbits (weighing 2—3 kg) were dosed with the hydroxamic acids suspended in an aqueous solution of gum arabic. The suspension was introduced into the stomach by means of a stomach tube in doses of 100 mg/kg.

The animals were kept on the standard diet*) during at least a fortnight before the experiments and in the course of experiments.

The acute oral toxicity of compounds H I — H VIII (see Table 2) was investigated using male mice of the Porton strain. A dose of 1125 mg/kg was used for each compound and no toxic effects were observed at this dose indicating that the LD_{50} s of these compounds lie above this level confirming previous findings [14].

The fasting serum cholesterol level was determined by the method of Zlatkis *et al.* [17] modified by Searcy and Berquist [15] daily for three days preceding the treatment with the hydroxamic acids. In the course of the following seven days the animals were dosed with hydroxamic acids. After that the cholesterol level was determined for three consecutive days.

Results

Table 1 gives as an example the results obtained in ten rabbits before and after seven days treatment with 3,5-dibromosalicylhydroxamic acid (H IV).

Table 1: Treatment of rabbits with 3,5-dibromosalicylhydroxamic acid (H IV) through a stomach tube.

No. of the rabbit	Cholesterol level in blood serum in mg%					
	before the treatment days			after the treatment days		
	1st	2nd	3rd	1st	2nd	3rd
1	40	40	43	30	30	30
2	60	73	60	40	43	40
3	40	60	43	40	43	30
4	83	73	83	43	43	40
5	110	120	120	60	40	43
6	120	110	120	43	43	43
7	43	60	60	60	43	40
8	32	73	83	43	40	30
9	73	60	73	40	43	40
10	80	83	83	60	43	43
Mean value	68,1	75.2	76.8	45.9	41.1	37.9
Standard deviation	±30.57	±24.09	±27.31	±10.43	± 4.09	± 5.61
Standard error	± 9.67	± 7.62	± 8.63	± 3.30	± 1.29	± 1.77

The mean reduction of the serum cholesterol level varied from 3.7 to 39.3% *versus* the serum cholesterol concentration before the treatment.

The mean values obtained for different derivatives of salicylhydroxamic acids (SH) and gum arabic suspension in water alone are collected in Table 2.

Here mean values of the cholesterol level in serum are given. They were calculated from three consecutive days before and after the administration of hy-

*) The diet „LSK" produced by the food factory Łowicz, Poland, was composed of:

wheat bran	15%
barley cake	20%
malt germs	10%
peanut cake solvent extracted	20%
fish meal	8%
greenstuff food meal	26%
mixed vitamin additive "Mokro DK"	1%

It was guaranteed that "LSK" food contains:

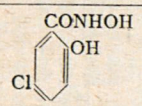
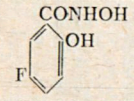
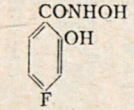
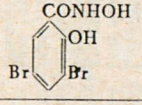
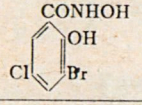
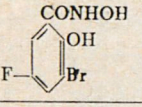
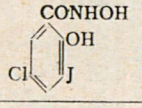
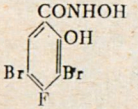
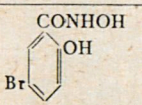
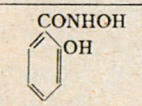
total proteins	24%
raw fat	2.7%
crude fibres	9.5%
calcium	1.2%
phosphorus	0.9%
salts of Na, Mg, K, Fe, Cu, Mn, Co.	

One kg of the food contains:

vitamin A	5000 units
vitamin D_3	1000 units
vitamin E	2.5 mg
nicotinamide	10 mg
riboflavin	2.5 mg
pyridoxin	0.5 mg
calcium DL-pantothenate	10 mg

The food was completed by fresh greenstuff in summer and hey or root crops in winter.

Table 2: Mean cholesterol level in the serum of rabbits with the mean errors in mg%, under action of different compounds.

Symbol of compound	Formula	Number of rabbits n*)	Before the treatment								After the treatment							
			1st day		2nd day		3rd day		Total mean values mg%	Total standard error	1st day		2nd day		3rd day		Total mean values mg%	Total standard error
			mean value mg%	standard error	mean value mg%	standard error	mean value mg%	standard error			mean value mg%	standard error	mean value mg%	standard error	mean value mg%	standard error		
H I		10	71.1	±8.05	85.5	±8.71	88.1	±7.64	81.6	±4.75	75.0	±7.00	57.4	±3.55	48.6	±3.18	60.3	±3.40
H II		10	92.7	±4.93	91.5	±3.90	92.3	±3.84	92.2	±2.37	84.5	±4.11	78.4	±3.37	72.7	±2.77	78.5	±2.12
H III		10	109.5	±3.68	109.8	±3.88	114.1	±3.44	111.1	±2.08	90.8	±2.57	85.5	±1.60	76.7	±1.98	84.3	±1.59
H IV		10	68.1	±9.67	75.2	±7.62	76.8	±8.63	73.3	±4.89	45.9	±3.30	41.1	±1.29	37.9	±1.77	41.6	±1.41
H V		10	84.5	±7.41	101.6	±7.54	105.8	±5.57	97.3	±4.21	76.0	±5.28	71.8	±4.87	68.3	±4.90	72.0	±2.86
H VI		10	92.8	±8.42	89.7	±7.91	90.0	±7.12	90.8	±4.37	60.9	±9.95	56.2	±8.95	54.7	±6.44	57.3	±4.80
H VII		9	80.8	±8.67	85.4	±7.88	86.1	±7.70	84.1	±4.53	67.2	±6.92	48.8	±6.01	52.2	±4.66	56.1	±3.65
H VIII		8	119.0	±5.76	124.0	±6.40	119.5	±4.74	120.8	±3.19	110.0	±4.91	98.1	±5.74	95.6	±6.58	101.3	±3.45
BSH		11	89.0	±7.54	92.7	±4.26	89.6	±4.10	90.5	±3.05	73.6	±6.94	65.1	±7.16	69.9	±6.36	69.5	±3.90
SH		10	105.6	±2.98	108.5	±3.39	109.6	±3.42	107.9	±1.85	104.6	±3.01	98.2	±3.10	94.4	±3.42	99.0	±1.94
Aqueous suspension of gum arabic	H_2O	10	75.7	±6.52	96.7	±5.41	99.2	±6.45	90.5	±3.94	75.4	±6.50	92.5	±6.80	90.1	±7.12	85.9	±4.05

*) Number of rabbits before the treatment.

Table 3: Mean lowering of the cholesterol level in the blood serum of rabbits (n in each group), absolute value in mg% and relative values in % with standard errors after the treatment through a stomach tube.

Number of the rabbit of each group	Compounds																					
	H I		H II		H III		H IV		H V		H VI		H VII		H VIII		BSH		SH		Water + gum arabic	
	mg%	%	mg%	%	mg%	%	mg%	%	mg%	%	mg%	%	mg%	%	mg%	%	mg%	%	mg%	%	mg%	%
1	19.3	26.1	17.3	15.6	28.6	24.0	11.0	26.8	25.4	25.0	45.0	53.0	15.0	17.6	—	—	38.8	48.9	1.7	1.7	8.6	10.6
2	12.0	17.2	7.6	9.0	10.4	10.3	23.3	36.2	13.0	17.6	37.7	31.7	25.3	24.8	25.0	25.0	7.3	9.6	14.4	12.0	24.0	24.3
3	11.3	18.2	20.7	21.9	35.3	31.0	10.0	21.0	8.7	15.0	29.3	44.4	—	—	20.0	18.2	51.3	42.1	4.0	4.1	2.0	2.9
4	0.6	1.3	19.6	19.0	20.7	20.5	37.7	47.3	38.0	40.4	55.0	54.1	14.0	25.9	—	—	45.4	43.7	7.0	7.8	3.3	5.0
5	26.4	35.8	8.3	8.8	29.4	26.8	69.0	59.1	19.3	25.7	32.0	51.6	47.3	40.4	13.3	11.5	—	—	16.4	14.2	—0.3	—0.4
6	11.3	19.5	1.7	2.4	47.0	38.3	73.7	63.2	40.7	38.4	29.3	24.6	26.0	39.4	11.6	9.4	—	—	2.6	2.3	5.5	5.5
7	14.0	18.8	15.6	18.7	42.3	32.0	6.6	12.2	23.3	20.1	31.0	39.9	22.7	34.4	10.0	10.0	24.7	34.9	18.0	15.9	3.4	3.3
8	25.7	24.8	19.7	18.1	34.0	30.4	25.0	39.9	32.3	27.8	19.7	22.0	12.0	18.2	—	—	6.0	7.3	10.4	10.5	—0.3	—0.3
9	42.3	37.8	14.0	15.2	15.7	15.2	27.7	40.3	26.7	25.2	20.6	16.9	26.4	37.9	38.3	25.5	27.0	33.6	5.0	4.2	—3.0	—2.7
10	45.3	38.1	12.4	16.0	4.7	4.9	32.3	39.9	25.3	21.1	36.0	54.6	22.6	27.8	20.0	14.6	4.0	4.5	9.0	8.3	0.7	0.9
11	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	15.7	11.7	—	—	—	—
12	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	46.3	50.2	—	—	—	—
13	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	24.0	30.4	—	—	—	—
Mean value	20.8	23.8	13.7	14.5	26.8	23.3	31.6	38.6	25.3	25.4	33.6	39.3	23.5	29.6	19.7	16.3	26.4	28.8	8.8	8.1	4.4	4.9
Standard error ±	4.51	3.61	1.97	1.88	4.35	3.34	7.34	5.01	3.19	2.62	3.36	4.59	3.50	2.93	3.70	2.57	5.17	5.25	1.84	1.58	2.37	2.45
n	10	10	10	10	10	10	10	10	10	10	10	10	9	9	7	7	11	11	10	10	10	10

droxamic acids. From these figures a lowering of cholesterol level was calculated.

In Table 3 the lowering of cholesterol level in serum is given for each rabbit of eleven groups of animals. The figures were calculated as follows:

1. by comparing mean values of three consecutive days before and after the administration of hydroxamic acids,

2. the data thus obtained were used to calculate the mean values for the lowering of cholesterol level in the whole group of experimental animals.

The strongest activity is shown by 3,5-dibromosalicylhydroxamic acid (H IV), 3-bromo-5-fluoro- and 3-iodo-5-chlorosalicylhydroxamic acids (H VI and H VII respectively). Less active is the 3-bromo-5-chloro derivative (H V). 5-Chlorosalicylhydroxamic acid (H I) is the strongest among the monosubstituted derivatives and the weakest is the 5-fluoro derivative (H II). The fluoro derivative with a fluorine atom in position 4 is more active. The trihalogeno-substituted derivative (H VIII) is much less active than mono- and diderivatives with the same substituents Br and F (BSH and H II respectively).

Salicylhydroxamic acid without halogen substituents shows a very low activity. No significant change of the weight of rabbits was noticed.

The lowering of cholesterol level after the administration of hydroxamic acids was compared with that of control experiments when aqueous suspension of gum arabic was given to the rabbits. When unsubstituted salicylhydroxamic acid was administered, the lowering of cholesterol level was found to be small and non-significant as compared with the effect of aqueous gum arabic. On the contrary, when halogenated derivatives of salicylhydroxamic acid were given, the lowering was statistically highly significant as compared with cholesterol level after the administration of aqueous suspension of gum arabic or unsubstituted sailcylhydroxamic acid. The only two exceptions found were with 5-fluoro- and with 3,5-dibromo-4-fluorosalicylhydroxamic acids. They lowered the cholesterol level in serum to a lesser extent, but significantly stronger than aqueous gum arabic or unsubstituted salicylhydroxamic acid. (Table 4).

Discussion

Halogen substituted salicylhydroxamic acids lower significantly the serum cholesterol level in the blood serum of rabbits, but the unsubstituted salicylhydroxamic acid has practically no effect upon the cholesterol level. The presence of halogen atoms as substituents appears to be essential in the anticholesterol activity of salicylhydroxamic acid derivatives.

Table 4: Statistical evaluation of the lowering of serum cholesterol level by hydrogen-substituted salicylhydroxamic acids in rabbits.

Compound	Comparison with salicylhydroxamid acid (SH)		Comparison with an aqueous suspension of gum arabic	
	t	p	t	p
H I	3.984	0.0005	3.334	0.0005
H II	2.602	0.01	3.117	0.005
H III	4.119	0.0005	4.444	0.0005
H IV	1.836	0.05	6.050	0.0005
H V	5.653	0.0005	5.726	0.0005
H VI	2.034	0.05	6.364	0.0005
H VII	6.633	0.0005	6.517	0.0005
H VIII	2.877	0.01	3.140	0.005
BSH	3.612	0.005	3.989	0.0005
SH	—	—	1.099	0.2
Water	1.099	0.2	—	—

The degree of the lowering depends on the nature of the halogen and the number of substituents.

The strongest lowering of the cholesterol level was shown by dihalogeno-substituted derivatives of salicylhydroxamic acids.

It should be pointed out that the lowering of the cholesterol level in rabbits was found in all animals examined, whereas in human patients the activity of salicylbromohydroxamic acid was found only in 45% of patients (Czyżyk and Urbański [4]).

All examined halogeno derivatives of salicylhydroxamic acid show a very low toxicity. This is in agreement with findings of Williams and McIsaac [9] that both salicylhydroxamic acid and bromosalicylhydroxamic acid are detoxicated in the animal and human organism through the formation of glucuronides. It is likely that the same detoxication mechanism characterises the examined salicylhydroxamic derivatives.

Although the mechanism of the action of the compounds remains unknown, it is probably connected with the inhibition of the metabolic path leading from acetate through squalene to cholesterol. It should be pointed out that salicylhydroxamic acid and its halogen derivatives can readily be acetylated *in vitro* [12]. It seems that halogen-substituted salicylhydroxamic acid derivatives can bind acetate ions and their activity is (at least partly) connected with the increase of the acidity of salicylhydroxamic acid by the substitution. The acidity might increase the activity towards metabolic processes in the living organism.

The determination of the acidity of the examined acids will be reported in one of our future papers.

Summary

The lowering of serum cholesterol level in rabbits by oral administration of salicylhydroxamic acid and its halogen derivatives has been examined. Most of the halogen-substituted derivatives gave statistically highly significant lowering effects, dihalogeno-substituted derivatives, such as 3,5-dibromo and 3-bromo-5-fluoro-salicylhydroxamic acids were found to be particularly effective. The effect produced by unsubstituted salicylhydroxamic acid was significantly lower than that of all halogen derivatives. A small effect was obtained with 5-fluoro- and 3,5-dibromo-4-fluorosalicylhydroxamic acid.

A number of known mono- and dihalogen derivatives of salicylhydroxamic acid were prepared for that respect and also 3,5-dibromo-4-fluorosalicylhydroxamic acid, so far unknown to the literature.

Zusammenfassung

Senkung des Cholesterinspiegels im Blutserum von Kaninchen durch Halogen-substituierte Salicylhydroxamsäuren

Die Senkung des Cholesterinspiegels im Serum von Kaninchen durch orale Verabreichung von Salicylhydroxamsäure und ihren Halogen-Derivaten wurde untersucht. Die meisten der Halogen-substituierten Derivate erzielten eine statistisch hoch signifikante Senkung, Dihalogen-substituierte Derivate wie 3,5-Dibrom- und 3-Brom-5-fluorsalicylhydroxamsäure erwiesen sich als besonders wirksam. Der Effekt von unsubstituierter Salicylhydroxamsäure war signifikant schwächer als der aller Halogen-Derivate. Eine geringe Wirkung wurde mit 5-Fluor- und 3,5-Dibrom-4-fluorsalicyloxamsäure erreicht.

Im Hinblick auf diese Befunde wurde eine Reihe von bekannten Mono- und Dihalogen-Derivaten der Salicylhydroxamsäure synthetisiert, desgleichen 3,5-Dibrom-4-fluorsalicylhydroxamsäure, die bisher in der Literatur noch nicht beschrieben wurde.

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Entwicklungstendenzen in der Naturwissenschaft während der letzten 50 Jahre und ihre Auswirkungen auf die Arzneimittelkunde

Von H. Haas

Noch vor 50 Jahren war die Therapie der schwächste Punkt der Medizin. Seitdem hat sich die Situation der Arzneimittelkunde, insbesondere in den beiden letzten Jahrzehnten erheblich geändert. 90% der heute üblichen Verordnungen konnten vor 20 Jahren nicht ausgeführt werden, weil das Angebot an Arzneimitteln damals sehr viel kleiner war.

Man darf indes nicht vergessen, daß die bessere Effektivität der heutigen Arzneien auch eine höhere Quote an Nebenwirkungen und damit ein größeres therapeutisches Risiko nach sich zieht. Zudem sind die modernen Medikamente genau wie die Präparate früherer Zeiten nicht gegen menschliche Unzulänglichkeit gefeit. Der Arzt wird durch wirksamere und zweckmäßigere Heilmittel nicht zwangsläufig zum besseren Helfer, es sei denn, daß er mit ihnen sinnvoll umzugehen weiß. Selbst dann noch bleibt sein therapeutisches Handeln problematisch, weil der medikamentöse Eingriff in all seinen Konsequenzen bei einem speziell gelagerten Krankheitsfall schwer zu übersehen, geschweige denn mit absoluter Sicherheit so zu lenken ist, daß nur heilkräftige und keine nachteiligen Folgen für den Patienten entstehen.

Auch die Gegenwartstherapie ist somit nicht etwas absolut Gutes und Ideales. Glücklicherweise überwiegen die positiven Erfahrungen alle etwaigen negativen Praktiken, so daß die modernen Medikamente nicht nur ein Mehr an Angebot, sondern ein echtes Mehr an Qualität und Nutzeffekt bedeuten. Diese verbesserten Behandlungsmöglichkeiten verdankt die Medizin in erster Linie der enormen Fortentwicklung aller naturwissenschaftlichen Disziplinen. Daneben stehen gleichberechtigt die technologischen Fortschritte. Auch die zunehmende Industrialisierung des Arzneimittelwesens ist positiv beteiligt. Heute wird ein erheblicher Anteil der Forschungsarbeiten auf den Gebieten der Pharmakologie, der Toxikologie und der klinischen Pharmakologie von den Laboratorien der Industrie durchgeführt. Der die Lebensgestaltung unserer Zeit beherrschende Einfluß der großen Industrieunternehmungen bestimmt also nicht nur unsere gesellschaftliche und soziologische Entwicklung, er nimmt auch entscheidend Anteil an der Zuwachsrate unserer Naturerkenntnisse.

Gleichgültig von welchen Institutionen und Forschungsstätten der Anstoß für neue Arzneimittel kommt, er ist nicht denkbar ohne die Hilfsmittel, welche zahlreiche andere Wissenschaftsbereiche geliefert haben. Die Wende in der Therapie vollzog sich unter starker Assistenz vieler anderer Fachdisziplinen, und die Leistung der Arzneimittelforschung bestand in vielen Fällen mehr in der Auseinandersetzung mit anderen wichtigen wissenschaftlichen und technologischen Entdeckungen sowie in ihrer Anpassung an die eigenen Probleme und Positionen und deren Verarbeitung als in grundsätzlich neuen naturwissenschaftlichen Entdeckungen.

Wenn eine Wertung der Einzelheiten angestrebt wird, welche die Entwicklung des Arzneimittelwesens bestimmt und gefördert haben, so wird man als erste die Planck'sche Quanten-Theorie (1900) [1] und die Heisenberg'sche Quanten-Mechanik (1925) [2] anführen müssen. Für die Biologie hat sich daraus folgerichtig ergeben, daß wir es bei mikrophysiologischen Objekten genau wie im mikrophysikalischen Bereich mit einem unstetig und sprunghaft ablaufenden Geschehen zu tun haben. Die Vorgänge im organischen Leben verlaufen demnach indeterminiert mit einer statistischen Wahrscheinlichkeit ab. Nach Treffer-theoretischen Überlegungen kann unter günstigen Umständen ein einziges Lichtquant bzw. ein einziges Molekül genügen, um eine Reaktion bei Tier und Mensch auszulösen. Für die Therapie bedeutet dies, daß die Zahl der chemischen Einzelakte, die wir zur Verwirklichung eines therapeutischen Effektes benötigen, um eine krankhafte Schädigung mit wahrnehmbarer Wahrscheinlichkeit zu beeinflussen, sich in einer unwahrscheinlichen