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PREPARATION AND ANTIBACTERIAL PROPERTIES OF CERTAIN DERIVATIVES OF ISOMERIC HYDROXYPHENYLACETIC ACIDS *

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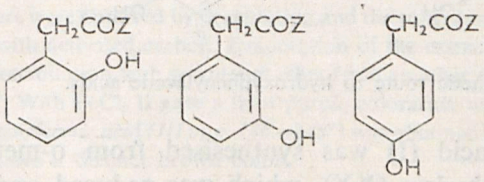
Continuing our research [8, 9] on new antibacterial, mostly antituberculotic agents in the group of amides, hydrazides and hydroxamic acids derived from organic carboxylic acids, we have prepared now and submitted for bacteriological screening certain derivatives of the three isomeric hydroxyphenylacetic acids.



Z=OH , OR , NH_2 , $NHNH_2$, $NHN{=}CHC_6H_5$, NHOH

Fig. 1.

Our interest in those acids was stimulated first and foremost by the known fact of the natural occurrence of p-hydroxyphenylacetic acid, which was identified as a metabolite of tyrosine [1] and isolated from the roots of dandelion *(Taraxacum officinale)* [12], a commonly used officinal plant; the same acid is a constituent of hydroxybenzylpenicillin. On the other hand, promising antibacterial properties of certain derivatives of salicylic acid encouraged our research on its closest homologue, o-hydroxyphenylacetic acid. In all the compounds prepared the phenolic group was expected to decrease toxicity according to the hypothesis advanced by McIsaac and Williams [11].

Amides and hydrazides of m- and p-hydroxyphenylacetic acids were pre-

* Paper XLII in the series „Research on new antitubercular compounds".

pared by the routine method involving ammonolysis and hydrazinolysis of the corresponding esters. In the ortho series this method yielded complex mixtures of unidentified products, whose separation and purification failed. Products of satisfactory purity were obtained, however, when o-hydroxyphenylacetolactone (IV) was used in the place of the ester.

The hydroxamic acids were synthesised by treating the corresponding esters with hydroxylamine in ethanol. The conversion of the sodium salts into free acids by simple acidification was successful only with the para isomer. The other two hydroxamic acids were prepared by precipitating copper chelates and subsequently decomposing them with hydrogen sulphide *.

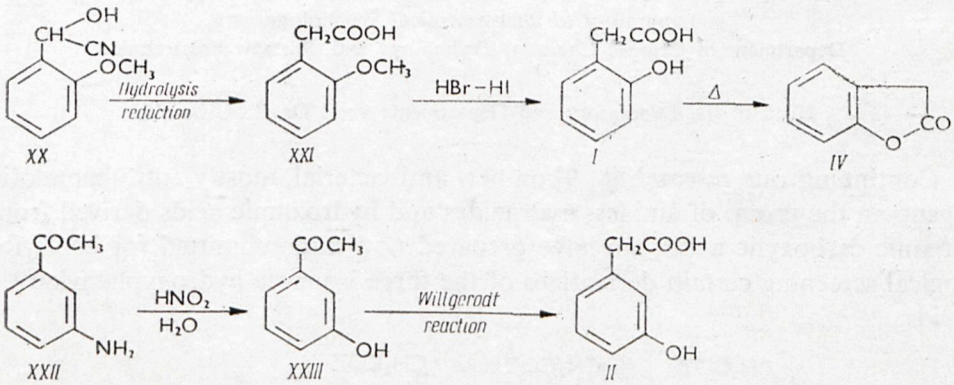


Fig. 2. Synthetic route to hydroxyphenylacetic acids.

o-Hydroxyphenylacetic acid (I) was synthesised from o-methoxybenzaldehyde through the cyanohydrin (XX), which was reduced and hydrolysed in one operation ($SnCl_2$ and HCl) to give o-methoxyphenylacetic acid (XXI), subsequently demethylated in the usual way [10].

m-Hydroxyphenylacetic acid (II) was prepared in the yield of 40% by the Willgerodt reaction. The starting material was m-nitroacetophenone, which was first reduced to m-aminoacetophenone (XXII). The reduction with ammonium sulphide was in many respects more convenient than that with iron filings in acetic acid [17]. The Willgerodt reaction with XXII [7] gave very poor yields. The indirect method, in which XXII was first converted into the hydroxy derivative (XXIII) [6] and the latter subject to the Willgerodt reaction with sulphur and morpholine, was evidently superior.

p-Hydroxyphenylacetic acid (III) was prepared by diazotisation of p-aminophenylacetic acid [13] and subsequent replacement of the diazonium group by hydroxyl [4].

* The hydroxamic acid could not be obtained crystalline unless the copper chelate was thoroughly dried in vacuo over P_2O_5.

The synthetic routes used in the preparation of hydroxyphenylacetic acids are presented in Fig. 2.

The amides, hydrazides and hydroxamic acids prepared showed moderate or weak activity against several Gram-positive and Gram-negative bacteria strains (Table 2) *.

EXPERIMENTAL **

o-Hydroxyphenylacetic acid (I). o-Methoxybenzaldehyde [2] was converted in the yield of 85% into the cyanohydrin (XX), which was subsequently hydrolyzed and reduced with $SnCl_2$ in a hydrochloric acid-acetic acid medium with some hydriodic acid added to yield 70% of o-methoxyphenylacetic acid (XXI) (mp 121—123°). Demethylation with a mixture of hydrobromic and hydriodic acids in acetic acid yielded 57% of I, mp 144—146°. The procedure used was an adaptation of that reported by Levine, et al. [10].

m-Hydroxyphenylacetic acid (II). A) m-Aminoacetophenone (XXII). A solution of 38 g (0·23 mole) of m-nitroacetophenone [5] in 145 ml of methanol was alkalised with 25 ml of concd. aq. ammonia and saturated with H_2S until completely homogeneous. The mixture was refluxed 2 hrs, filtered to remove precipitated sulphur, the filtrate concentrated in vacuo and the residue acidified with acetic acid to yield 21 g (67·7%) of XXII, mp 90—92° (dil. ethanol). According to [17] mp 92—92·5°.

B) m-Hydroxycetophenone (XXIII). The procedure of King and McMillan [7] (diazotisation and replacement of the diazonium group by hydroxyl) gave 73·5% of XXIII, mp 94—96°.

C) m-Hydroxyphenylacetic acid (II). A mixture of 56 g (0·41 mole) of XXIII, 20·5 g (0·64 mole) of sulphur and 70 g of morpholine was refluxed 6 hrs, treated with 400 ml of 10% NaOH in ethanol, refluxed again 6 hrs, diluted with water, distilled to remove ethanol and the residue acidified with 50% H_2SO_4. Tars were removed by decantation and the supernatant was extracted with ether after decolorisation with activated carbon. Evaporation of the extract gave 22 g (35·1%) of II, purified by repeated reprecipitation with petroleum ether from an ether solution; mp 121—124°. According to [15] mp 129°. With $FeCl_3$ II gave a faint purple coloration which abruptly turned light-brown.

p-Hydroxyphenylacetic acid (III m.p. 146—148°) was obtained according [4] in the yield of 55·8%. With $FeCl_3$ it gave a distinct brown color.

Esters of hydroxyphenylacetic acids (V, VI and VII) were prepared by the routine method with a considerable excess of alcohol (10 ml of ethanol or methanol/g of acid) and with H_2SO_4 (1 ml/g of acid) as catalyst. The products were purified by vacuum distillation.

o-Hydroxyphenylacetolactone (IV). I (15 g, 0·1 mole) was heated at 200—210° until evolution of water ceased and the residue was distilled in vacuo to yield 81·7% of IV, b_{14} 129—133°; according to [16] bp 240—243°. The distillate slowly solidified on standing; mp 45—48°.

o-Hydroxyphenylacetamide (VIII). A mixture of 7·2 g (0·054 mole) of IV and 50 ml of concd. aq. ammonia was left standing 48 hrs and evaporated in vacuo to give 6·8 g (83·3%) of crude VIII, subsequently purified by reprecipitation with petroleum ether from ether solution. Yield 3·8 g.

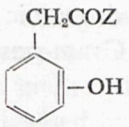
o-Hydroxyphenylacetylhydrazine (XI). A procedure similar to that used in the preparation of VIII (7·2 g, 0·054 mole of IV in 20 ml of ethanol and 50 ml, 0·43 mole of 50% hydrazine hydrate) yielded 6·6 g (74%) of crude XI. After purification the yield was 4·0 g.

o-Hydroxyphenylacetohydroxamic acid (XVII). Methanolic hydroxylamine (0·065 mole of NH_2OH in roughly 140 ml of methanol) was mixed with 8·3 g (0·05 mole) of V and then with sodium methoxide (1·2 g, 0·053 mole of Na in 20 ml of methanol), the mixture left standing overnight, evapo-

* Bacteriological tests were carried out in the Pharmacology Department, Institute of Drugs, Warsaw, under the supervision of Doc. Dr. J. Venulet, whose kind co-operation is hereby gratefully acknowledged.

** Taken in part from the graduation thesis by D. Sałbut.

Table 1. Hydroxyphenylacetic acid derivatives



Compound	OH group position	Z	Mp °C [a] (solvent) [b] or Bp/mm	Formula (mol. wt.)	Color reaction with $FeCl_3$	Analysis calcd. %	Analysis found %
V	o-	OCH_3	71—72 c) (EE—PE)	$C_9H_{10}O_3$ (166·2)	—	—	—
VI	m-	OC_2H_5	177—179°/12	$C_{10}H_{12}O_3$ (180·2)	—	C 66·65 H 6·7	C 66·8 H 6·6
VII	p-	OC_2H_5	187—189 /20 d)	$C_{10}H_{12}O_3$ (180·2)	—	—	—
VIII	o-	NH_2	113—114·5 e) (EE—PE)	$C_8H_9NO_2$ (151·2)	purple	—	—
IX	m-	NH_2	122—123·5 (EE—PE)	$C_8H_9NO_2$ (151·2)	purple	N 9·3	N 9·5
X	p-	NH_2	174—175 f) (W)	$C_8H_9NO_2$ (151·2)	red-purple	—	—
XI	o-	$NHNH_2$	154—155 g) (W)	$C_8H_{10}N_2O_2$ (166·2)	dark purple	—	—
XII	m-	$NHNH_2$	169·5—171 (W)	$C_8H_{10}N_2O_2$ (166·2)	light brown	N 16·9	N 17·0
XIII	p-	$NHNH_2$	199—200 (W)	$C_8H_{10}N_2O_2$ (166·2)	faint pink-purple	N 16·9	N 16·8
XIV	o-	NHN=Bz [h]	184—185 (dil. E)	$C_{15}H_{14}N_2O_2$ (254·3)	—	C 70·85 H 5·55 N 11·0	C 71·0 H 5·25 N 11·1
XV	m-	NHN=Bz [h]	189—190 (dil. E)	$C_{15}H_{14}N_2O_2$ (254·3)		C 70·85 H 5·55 N 11·0	C 71·1 H 5·5 N 11·0
XVI	p-	NHN=Bz [h]	248—251 (dil. E)	$C_{15}H_{14}N_2O_2$ (254·3)	—	C 70·85 H 5·55 N 11·0	C 71·25 H 5·55 N 11·3
XVII	o-	NHOH	95—96·5 (EE—PE)	$C_8H_9NO_3$ (167·2)	deep red	N 8·4	N 8·5
XVIII	m-	NHOH	132·5—134 (EE—PE)	$C_8H_9NO_3$ (167·2)	deep red	N 8·4	N 8·2
XIX	p-	NHOH	176 (dec.) i) (W)	$C_8H_9NO_3$ (167·2)	deep red	N 8·4	N 8·4

a) All melting and boiling points are uncorrected; b) solvents: W — water, E — ethanol, EE — ethyl ether, PE — petroleum ether; c) the same mp was given by [10]; d) according to [14] bp 314°; e) according to [16] mp 116—117°; f) according to [14] mp 175°; g) according to [16] mp 153—154°; h) Bz stands for $C_6H_5CH=$; i) according to [3] mp 161—163° (decompn.).

Table 2. Bacteriological screening data

Strain / Compound No.	Minimum concentration (in mg%) inhibiting the growth of								
	Mycobacterium smegmatis	*Mycobacterium tuberculosis* strain 279	*Mycobacterium tuberculosis* strain 607	*Mycobacterium tuberculosis* strain 209P	*Mycobacterium tuberculosis* strain H37Rv	*Escherichia coli*	*Klebsiella pneumoniae*	*Salmonella typhi murium*	*Shigella flexneri*
VIII	500	500	500	500	—	500	500	500	500
IX	500	500	500	500	—	500	500	500	500
X	500	500	500	250	—	500	500	500	500
XI	250	125	250	500	62·5	500	500	500	500
XII	15·6	15·6	15·6	500	15·6	500	500	500	500
XIII	31·2	31·2	15·6	125	31·2	500	500	500	250
XVII	62·5	62·5	62·5	250	—	250	250	250	250
XVIII	62·5	62·5	125	500	—	250	250	250	250
XIX	62·5	62·5	125	250	62·5	500	500	500	500

Liquid medium according to Youmans was used in all test. The compounds tested were applied in aqueous or aqueous-alcoholic solutions.

rated in vacuo to dryness, the residue dissolved in 20 ml of water, the solution acidified with 40 ml of 25% acetic acid and treated with an excess of aqueous copper acetate. The chelate was filtered off and thoroughly dried (12·7 g), powdered, suspended in 50 ml of methanol and decomposed with H_2S. Coagulation of CuS was accelerated by gently heating the mixture towards the end of the saturation operation. The filtrate was treated with activated carbon, evaporated in vacuo, the remaining orange oil was dissolved in ether, the solution decanted from a small amount of undissolved red tars and finally treated with petroleum ether until a faint cloudiness appeared. Prolonged cooling gave 6 g (72%) of pink crystals; repetition of the purification procedure yielded finally 3·5 g of a colorless product.

m-Hydroxyphenylacetamide (IX). A mixture of 5 g (0·028 mole) of VI and 30 ml of concd. aq. ammonia was made homogeneous with a little of ethanol and refluxed 3 hrs, gaseous ammonia being continuously bubbled through the boiling solution. Vacuum concentration yielded a mass of tan crystals (2 g, 42%), filtered off and washed with ethanol-ether. Pure IX was obtained on reprecipitation with petroleum ether from a solution in ethyl ether and acetone; the final yield was 0·6 g.

m-Hydroxyphenylacetylhydrazine (XII). A mixture of 9 g (0·05 mole) of VI and 50 ml (0·43 mole) of 50% hydrazine hydrate was refluxed 2·5 hrs, cooled, filtered, the filtrate concentrated in vacuo and filtered to yield (in 2 crops) 6 g (72·3%) of XII.

m-Hydroxyphenylacetohydroxamic acid (XVIII). The procedure was similar to that used in preparing XVII. Decomposition of the Cu chelate yielded 5 g (60%) of XVIII in the form of pink

crystals. Purification by dissolving in ethyl ether containing a little methanol and reprecipitating with petroleum ether yielded finally 2·3 g.

p-Hydroxyphenylacetamide (X). A mixture of 9 g (0·05 mole) of VII and 50 ml of concd. aq. ammonia was refluxed 6 hrs, filtered upon cooling and the filtrate concentrated in vacuo to deposit the second crop of X. The total yield was 7 g (92·7%).

p-Hydroxyphenylacetylhydrazine (XIII). The procedure was identical with that used in preparing XII. The yield was 6·4 g (77%).

p-Hydroxyphenylacetohydroxamic acid (XIX). Starting with 9 g (0·05 mole) of VII a solution of sodium hydroxamate was prepared as above. Upon evaporation of methanol the residue was dissolved in a small amount of water and acidified with 25% acetic acid to yield 7 g (83·8%) of XIX.

Benzylidene derivatives of the hydrazides (XIV, XV and *XVI).* A solution of 0·83 g (0·005 mole) of the hydrazide in 5 ml of water was shaken a few min with 0·6 g (0·0065 mole) of benzaldehyde, the precipitate filtered off and recrystallised from dilute ethanol.

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OTRZYMYWANIE I WŁASNOŚCI ANTYBAKTERYJNE NIEKTÓRYCH POCHODNYCH IZOMERYCZNYCH KWASÓW HYDROKSYFENYLOOCTOWYCH

Streszczenie

Amidy, hydrazydy i kwasy hydroksamowe pochodne kwasu o-hydroksyfenylooctowego (VIII, XI i XVII), m-hydroksyfenylooctowego (IX, XII i XVIII) oraz p-hydroksyfenylooctowego (X, XIII i XIX) otrzymano drogą aminolizy estrów tych kwasów za pomocą amoniaku, hydratu hydrazyny i hydroksyloaminy. Opracowano szczegółowe metody otrzymywania wyjściowych kwasów karboksylowych (ryc. 1). Badania bakteriologiczne (tab. 2) wykazały umiarkowaną aktywność antybakteryjną otrzymanych pochodnych.

Dla celów identyfikacji sporządzono również pochodne benzylidenowe (XIV, XV i XVI) wszystkich trzech hydrazydów.

Й. Ланге, Т. Урбански

ПОЛУЧЕНИЕ И ПРОТИВОБАКТЕРИЙНЫЕ СВОЙСТВА НЕКОТОРЫХ ПРОИЗВОДНЫХ ИЗОМЕРИЧНЫХ ОКСИЧЕНИЛУКСЫСНЫХ КИСЛОТ

Содержание

Амиды, гидразиды и гидраксамовые кислоты производные о-оксифенилуксусной кислоты (VIII, XI и XVII), м-оксифенилуксусной кислоты (IX, XII и XVIII) и р-оксифенилуксусной кислоты (X, XIII и XIX) были получены путем аминолиза эфиров этих кислот при помощи аммиака, гидразита гидразина и гидроксиламина. Разработаны точные методы получения исходных карбоновых кислот (Черт. 1). Бактериологические исследования (Таб. 2) показали умеренное действие полученных производных.

Для отождествления получены также бензенилиденовые производные (XIV, XV и XVI) всех трех гидразидов.

REFERENCES

1. Baumann E.: Ber. 1880, 13, 280.
2. Buck J. S.: Org. Syntheses, Coll. Vol. II, 619.
3. Buraczewski K., Czerwińska E., Eckstein Z., Grochowski E., Kowalik R., Plenkiewicz J.: Przemysł Chem. 1964, 43, 626.
4. Carter P. R., Hey D. H.: J. Chem. Soc. 1948, 152.
5. Corson B. B., Hazen R. K.: Org. Syntheses, Coll. Vol. II, 434.
6. Fuson R. C., Lewis P. H., Du Puis R. N.: J. Am. Chem. Soc. 1932, 54, 1118.
7. King J. A., McMillan P. H.: J. Am. Chem. Soc. 1946, 68, 2335.
8. Lange J., Urbański T.: Dissert. Pharm. Pharmacol. 1968, 20, 589.
9. Lange J., Urbański T.: Dissert. Pharm. Pharmacol. 1968, 20, 599.
10. Levine J., Eble T. E., Fischbach H.: J. Am. Chem. Soc. 1948, 70, 1933.
11. McIsaac W. M., Williams R. T.: Biochem. J. 1957, 66, 369.
12. Power M., Browning B.: J. Chem. Soc. 1912, 101, 2414.
13. Robertson G. R.: Org. Syntheses, Coll. Vol. I, 52.
14. Salkowski H.: Ber. 1889, 22, 2141.
15. Schwenk E., Papa D.: J. Org. Chem. 1946, 11, 798.
16. Störmer R.: Ann. 1900, 313, 86.
17. Valyashko N. A., Lutskii A. E.: Zhur. Obshchei Khim. 1951, 21, 939.

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