SUBSTITUTED 5- AND 6-QUINOXALINECARBOXYLIC ACIDS AND THEIR TUBERCULOSTATIC ACTIVITY

František Roubínek, Viktor Bydžovský and Zdeněk Budějínský

Research Institute for Pharmacy and Biochemistry, 130 00 Prague 3

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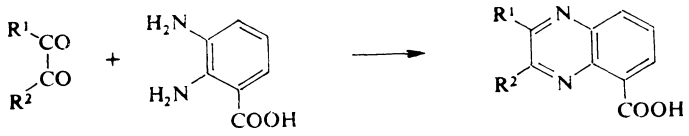
Condensation of aliphatic and aliphatic-aromatic α-diketones, and of substituted benzils with 2,3- and 3,4-diaminobenzoic acids and with 4,5-diamino-2-hydroxybenzoic acid gave 74 5- and 6-quinoxalinecarboxylic acids, with the same or different alkyls and aryls as substituents at positions 2 and 3. The compounds with different substituents at positions 2 and 3 were resolved into positional isomers. Their structures were determined by means of the dipole moments. The compounds were tested for tuberculostatic activity. Some exhibited it *in vitro* (*LI*, *LVII*), but failed *in vivo*.

A significant tuberculostatic activity was demonstrated with some derivatives of quinoxaline and benzo[*b*]quinoxaline[1-3]. The *in vivo* tests also showed a high activity, but their side effects and too firm binding to tissues[3] make them clinically unsuitable. Since the introduction of a carboxyl group into an organic compound usually suppresses its affinity to tissues and speeds up its secretion, we have prepared variously substituted 5- and 6-quinoxalinecarboxylic acids. Some of them have been described before, but were not tested bacteriologically.

To synthetize them we used the general reaction of α-diketones with aromatic *o*-diamines. The latter were 2,3 and 3,4-diaminobenzoic acids and 4,5-diamino-2-hydroxybenzoic acid. These were condensed with aliphatic, cycloaliphatic and aliphatic-aromatic α-diketones, as well as with variously substituted benzils. These reactions proceeded smoothly and largely gave good yields. In most cases we used to advantage the method of van der Stellt and coworkers[4], who heated an equimolar mixture of an α-diketone and an *o*-diamino compound in acetic acid (method *A*). However, in using this method we sometimes obtained blackish products. In such cases it proved rewarding to replace acetic acid by ethanol (method *B*). If the starting α-diketone was at least partially soluble in water it was possible to use water acidified with hydrochloric acid (method *C*), as described by Perelló and coworkers[5].

In the condensation of non-symmetrical α-diketones (different R's) mixtures of positional isomers were formed. With only one exception, these were resolved by crystallization or column chromatography. However, demonstration of their structures was a problem. First we tried the synthetic method, attempting condensation of 1-methyl-2-phenylethanedione with 4-nitro-5-aminosalicyclic acid and/or

with 4-acetamido-5-aminosalicylic acid. We had supposed that the more reactive keto group (here carbonyl bound to methyl) would react with the free amino group, and the product, after reduction or deacetylation, would cyclize to 7-hydroxy-3-methyl-2-phenyl-6-quinoxalinecarboxylic acid. As, however, these experiments ended in failure, we attacked the problem by measuring the dipole moments. Since the isomeric 2-methyl-3-phenyl- and 3-methyl-2-phenyl-6-quinoxalinecarboxylic acids would be expected to differ very little in their dipole moments we chose the corresponding *p*-bromophenyl derivatives. Condensation of 1-(4-bromophenyl)-1,2-pro-



I– *XXIV*

I, $R^1 = R^2 = CH_3$
II, $R^1—R^2 = —(CH_2)_4$
III, $R^1—R^2 = —(CH_2)_5$
IV, $R^1 = R^2 = C_6H_5$
V, $R^1 = R^2 = 2\text{-}CH_3C_6H_4$
VI, $R^1 = R^2 = 4\text{-}CH_3C_6H_4$
VII, $R^1 = R^2 = 2\text{-}ClC_6H_4$
VIII, $R^1 = R^2 = 4\text{-}ClC_6H_4$
IX, $R^1 = R^2 = 2\text{-}HOC_6H_4$
X, $R^1 = R^2 = 3\text{-}HOC_6H_4$
XI, $R^1 = R^2 = 4\text{-}HOC_6H_4$
XII, $R^1 = R^2 = 2\text{-}CH_3OC_6H_4$

XIII, $R^1 = R^2 = 3\text{-}CH_3OC_6H_4$
XIV, $R^1 = R^2 = 4\text{-}CH_3OC_6H_4$
XV, $R^1 = R^2 = 3,4\text{-}(CH_3O)_2C_6H_3$
XVI, $R^1 = R^2 = 3,4\text{-}(OCH_2O)C_6H_3$
XVII, $R^1 = R^2 = 4\text{-}(CH_3)_2NC_6H_4$
XVIII, $R^1 = R^2 =$ 2-furyl
XIX, $R^1 = CH_3$; $R^2 = n\text{-}C_8H_{17}$
XX, $R^1 = n\text{-}C_6H_{17}$; $R^2 = CH_3$
XXI, $R^1 = CH_3$; $R^2 = C_6H_5$
XXII, $R^1 = C_6H_5$; $R^2 = CH_3$
XXIII, $R^1 = CH_3$; $R^2 = 2\text{-}HOC_6H_4$
XXIV, $R^1 = 2\text{-}HOC_6H_4$; $R^2 = CH_3$

SCHEME 1

panedione with 3,4-diaminobenzoic acid gave a mixture of two compounds, which were separated by successive crystallization from water, ethanol, acetic acid and dioxan. Their elemental compositions and IR spectra proved identical. One had a m.p. of 233–235°C and a dipole moment of 4·67 ± 0·04 D, the other 258–260°C and 4·04 ± 0·05 D; the ratio of yields was 1 : 3. From these data we concluded that the former, having a lower m.p. and a higher μ, was 3-(4-bromophenyl)-2-methyl-6-quinoxalinecarboxylic acid (*LXIX*, the bonding moment of the carboxyl was parallel to that of the carboxyl), whereas the latter (a higher m.p. and a lower μ; the moments of the bonds had opposite directions) consequently was 2-(4-bromophenyl)-3-methyl-6-quinoxalinecarboxylic acid (*LXX*). This finding accords with the assumed mechanism of the reaction. The condensation of the amino group with the keto group proceeds by a nucleophilic attack of the free electron pair of the amino nitrogen on the positively charged carbon atom of the carbonyl group. Judging by the

XXV–LXXIV

XXV, $R^1 = R^2 = CH_3$; $R^3 = H$
XXVI, $R^1 = R^2 = CH_3$; $R^3 = OH$
XXVII, $R^1—R^2 = (CH_2)_4$; $R^3 = H$
XXVIII, $R^1—R^2 = (CH_2)_4$; $R^3 = OH$
XXIX, $R^1—R^2 = (CH_2)_5$; $R^3 = H$
XXX, $R^1—R^2 = (CH_2)_5$; $R^3 = OH$
XXXI, $R^1 = R^2 = C_6H_5$; $R^3 = H$
XXXII, $R^1 = R^2 = C_6H_5$; $R^3 = OH$
XXXIII, $R^1 = R^2 = 2\text{-}CH_3C_6H_4$; $R^3 = H$
XXXIV, $R^1 = R^2 = 2\text{-}CH_3C_6H_4$; $R^3 = OH$
XXXV, $R^1 = R^2 = 4\text{-}CH_3C_6H_4$; $R^3 = H$
XXXVI, $R^1 = R^2 = 4\text{-}CH_3C_6H_4$; $R^3 = OH$
XXXVII, $R^1 = R^2 = 2\text{-}ClC_6H_4$; $R^3 = H$
XXXVIII, $R^1 = R^2 = 2\text{-}ClC_6H_4$; $R^3 = OH$
XXXIX, $R^1 = R^2 = 4\text{-}ClC_6H_4$; $R^3 = H$
XL, $R^1 = R^2 = 4\text{-}ClC_6H_4$; $R^3 = OH$
XLI, $R^1 = R^2 = 2\text{-}HOC_6H_4$; $R^3 = H$
XLII, $R^1 = R^2 = 2\text{-}HOC_6H_4$; $R^3 = OH$
XLIII, $R^1 = R^2 = 3\text{-}HOC_6H_4$; $R^3 = H$
XLIV, $R^1 = R^2 = 3\text{-}HOC_6H_4$; $R^3 = OH$
XLV, $R^1 = R^2 = 4\text{-}HOC_6H_4$; $R^3 = H$
XLVI, $R^1 = R^2 = 4\text{-}HOC_6H_4$; $R^3 = OH$
XLVII, $R^1 = R^2 = 2\text{-}CH_3OC_6H_4$; $R^3 = H$
XLVIII, $R^1 = R^2 = 2\text{-}CH_3OC_6H_4$; $R^3 = OH$
XLIV, $R^1 = R^3 = 3\text{-}CH_3OC_6H_4$; $R^3 = H$
L, $R^1 = R^2 = 3\text{-}CH_3OC_6H_4$; $R^3 = OH$
LI, $R^1 = R^2 = 4\text{-}CH_3OC_6H_4$; $R^3 = H$
LII, $R^1 = R^2 = 4\text{-}CH_3OC_6H_4$; $R^3 = OH$
LIII, $R^1 = R^2 = 3,4\text{-}(CH_3O)_3C_6H_3$; $R^3 = H$
LIV, $R^1 = R^2 = 3,4\text{-}(CH_3O)_2C_6H_3$; $R^3 = OH$
LV, $R^1 = R^2 = 3,4\text{-}OCH_2OC_6H_3$; $R^3 = H$
LVI, $R^1 = R^2 = 3,4\text{-}CCH_2OC_6H_3$; $R^3 = OH$
LVII, $R^1 = R^2 = 4\text{-}(CH_3)_2NC_6H_4$; $R^3 = H$
LVIII, $R^1 = R^2 = 4\text{-}(CH_3)_2NC_6H_4$; $R^3 = OH$
LIX, $R^1 = R^2 = 2\text{-furyl}$; $R^3 = H$
LX, $R^1 = R^2 = 2\text{-furyl}$; $R^3 = OH$
LXI, $R^1 = CH_3$; $R^2 = n\text{-}C_8H_{17}$; $R^3 = H$
LXII, $R^1 = n\text{-}C_8H_{17}$; $R^2 = CH_3$; $R^3 = H$
LXIII, $R^1 = CH_3$; $R^2 = n\text{-}C_8H_{17}$; $R^3 = OH$
LXIV, $R^1 = n\text{-}C_8H_{17}$; $R^2 = CH_3$; $R^3 = OH$
LXV, $R^1 = CH_3$; $R^2 = C_6H_5$; $R^3 = H$
LXVI, $R^1 = C_6H_5$; $R^2 = CH_3$; $R^2 = H$
LXVII, $R^1 = CH_3$; $R^2 = C_6H_5$; $R^3 = OH$
LXVIII, $R^1 = C_6H_5$; $R^2 = CH_3$; $R^3 = OH$
LXIX, $R^1 = CH_3$; $R^2 = 4\text{-}BrC_6H_4$; $R^3 = H$
LXX, $R^1 = 4\text{-}BrC_6H_4$; $R^2 = CH_3$; $R^3 = H$
LXXI, $R^1 = CH_3$; $R^2 = 2\text{-}HOC_6H_4$; $R^3 = H$
LXXII, $R^1 = 2\text{-}HOC_6H_4$; $R^2 = CH_3$; $R^3 = H$
XLVIII, $R^1 = CH_3$; $R^2 = 2\text{-}HOC_6H_4$; $R^3 = OH$
LXXIV, $R^1 = 2\text{-}HOC_6H_4$; $R^2 = CH_3$; $R^3 = OH$

SCHEME 2

delocalization of a free electron pair on the amino group at the 4-position, and by the K_B constants of 2-, 3- and 4-aminobenzoic acids, the amino group at position 3

TABLE I

5-Quinoxalinecarboxylic acids and their tuberculostatic activity

Compound Method Yield, %	M.p., °C solvent	Formula (mol.mass)	Calculated/Found			Activity[a]
			% C	% H	% N	
I	127—128	$C_{11}H_{10}N_2O_2$	65·33	4·99	13·86	—
A, 94·0	water	(202·2)	65·11	5·12	13·58	
II	227—229	$C_{13}H_{12}N_2O_2$	68·36	5·29	12·27	—
A, 61·3	ethanol	(228·2)	68·08	5·60	12·31	
III	205—208	$C_{14}H_{14}N_2O_2$	69·40	5·83	11·57	—
A, 82·4	ethanol	(242·3)	69·29	5·86	11·42	
IV	214—215	$C_{21}H_{14}N_2O_2$	77·29	4·33	9·59	100
A, *C*, 89·4	ethanol	(326·3)	76·87	4·67	8·45	
V	236—238	$C_{23}H_{18}N_2O_2$	77·94	5·09	7·91	—
C, 36·8	ethanol	(354·4)	78·17	5·50	7·82	
VI	311—312	$C_{23}H_{18}N_2O_2$	77·94	5·09	7·91	12·5
C, 31·0	acetic acid	(354·4)	78·07	5·28	7·95	
VII[b]	218—220	$C_{21}H_{12}Cl_2N_2O_2$	63·81	3·06	7·09	100
C,	ethanol	(395·2)	63·84	3·15	6·89	
VIII[c]	273—276	$C_{21}H_{12}Cl_2N_2O_2$	63·81	3·06	7·09	100
C, 32·4	ethanol	(395·2)	63·84	3·24	7·14	
IX	254—256	$C_{21}H_{14}N_2O_4$	70·38	3·94	7·82	100
C, 53·0	50% ethanol	(358·3)	70·51	3·92	7·83	
X	295—300	$C_{21}H_{14}N_2O_4$	70·38	3·94	8·82	100
A	ethanol	(358·3)	69·94	4·30	7·78	
XI	336—338	$C_{21}H_{14}N_2O_4$	70·38	3·94	7·82	—
C, 53·0	ethanol	(358·3)	70·33	4·32	7·87	
XII	236—238	$C_{23}H_{18}N_2O_4$	71·49	4·70	7·25	—
C, 36·2	ethanol	(386·4)	71·67	4·50	7·28	
XIII	126—127	$C_{23}H_{18}N_2O_4$	71·49	4·70	7·25	—
C,	ethanol	(386·4)	71·41	4·52	7·29	
XIV	149—150	$C_{23}H_{18}N_2O_4$	71·49	4·70	7·25	100
C, 91·9	acetic acid	(386·4)	71·28	4·80	7·33	7
XV	185—186	$C_{25}H_{22}N_2O_6$	67·24	4·97	6·28	—
C	ethanol	)446·4)	66·86	5·23	6·27	
XVI	246—247	$C_{23}H_{14}N_2O_6$	66·67	3·41	6·76	100
C, 48·3	ethanol	(414·4)	66·79	3·54	6·84	
XVII	197—200	$C_{25}H_{24}N_4O_2$	72·79	5·88	13·58	6·25
C	ethanol	(412·5)	72·73	5·94	13·65	

TABLE I
(*Continued*)

Compound Method Yield, %	M.p., °C solvent	Formula (mol.mass)	Calculated/Found % C	% H	% N	Activity[a]
XVIII	186–188	$C_{17}H_{10}N_2O_4$	66·66	3·29	9·15	—
C, 99·8	acetic acid, benzene	(036·4)	67·01	3·47	9·35	
XIX, *XX*[d]	109–111	$C_{18}H_{24}N_2O_2$	71·97	8·05	9·33	12·5
B, 72·3	ethanol	(300·4)	71·40	8·06	9·37	
XXI[e]	165–166	$C_{16}G_{12}N_2O_2$	72·71	4·58	10·60	—
A, *B*,	ethanol	(264·3)	72·61	4·54	10·60	
XXII[e]	196–199	$C_{16}H_{12}N_2O_3$	72·71	4·58	10·60	—
A, *B*	ethanol	(264·3)	72·50	4·44	10·26	
XXIII[f]	241–243	$C_{16}H_{12}N_2O_2$	68·56	4·32	10·00	—
A	methanol, ethanol	(280·3)	68·26	4·32	10·01	
XXIV[f]	245–247	$C_{16}H_{12}N_2O_3$	68·56	4·32	10·00	—
A	methanol, ethanol	(280·3)	68·34	4·58	9·93	

[a] The smallest concentration, in μg/ml, completely inhibiting the growth of the turbecle bacillus H37Rv in Proskauer and Beck's medium. [b] Calculated: 18·94% Cl; found: 17·93% Cl. [c] Calculated: 17·94% Cl; found: 17·87% Cl. [d] Separation of isomers by crystallization was unsuccessful. [e] The ratio of isolated amounts of *XXI* and *XXII* was 1 : 3. [f] The ratio of isolated amounts of *XXIII* and *XXIV* was 1 : 3.

of 3,4-diaminobenzoic acid is probably the more basic, and thus more reactive than the 4-amino group. Out of the two carbonyls of 1-(4-bromophenyl)-1,2-propanedione, the one adjacent to the aromatic ring is not so polarized (owing to the effect of delocalized π-electrons of the aromatic ring), and consequently not so reactive, as the other, which is bound to the methyl group. Therefore, the nucleophilic addition should be directed mainly to this carbonyl, with the formation of the acid *LXX*. Hence we infer that the condensation of methyl phenyl diketones with 2,3-and 3,4-diaminobenzoic acids and with 4,5-diaminosalicylic acid produces higher yield of the isomers having the methyl group at position 3.

Nearly all the compounds prepared in this study were tested *in vitro* in Proskauer–Beck's medium for tuberculostatic activity against *Mycobacterium tuberculosis* H 37 Rv. The results are given in the last columns of Tables I and II. The following correlation of structure and biological activity can be drawn from them: 5- and 6-quino-

TABLE II

6-Quinoxalinecarboxylic acids

Compound Method Yield, %	M.p., °C solvent	Formula (mol.mass)	Calculated/Found % C	 % H	 % N	Antitbc. activity[a]
XXV[a] *C*, 81·6	262 ethanol	—	—	—	—	—
XXVI[b] *A*, *B*, 64·3	312 ethanol	$C_{11}H_{10}N_2O_3$ (218·2)	60·54 59·39	4·62 4·72	12·84 12·73	—
XXVII *A*, 52·6	250—252 ethanol	$C_{13}H_{12}N_2O_2$ (228·2)	68·36 68·28	5·29 5·91	12·27 12·37	—
XXVIII[c] *A*, *B*, 41·0	245—246	$C_{13}H_{12}N_2O_3$ (244·2)	63·92 64·09	4·95 4·70	11·47 10·88	—
XXIX *A*	226—230 ethanol	$C_{14}H_{14}N_2O_2$ (242·3)	69·40 69·11	5·83 5·91	11·57 11·39	—
XXX *A*, 19·4	266—267 dioxan, ethanol	$C_{14}H_{14}N_2O_3$ (258·3)	65·10 64·83	5·46 5·61	10·85 11·09	100
XXXI[d] *C*, 98·5	291 acetic acid	—	—	—	—	—
XXXII[e] *B*, *C*, 98·7	257—258 ethanol	—	—	—	—	—
XXXIII *C*	239—242 ethanol	$C_{23}H_{18}N_2O_2$ (354·4)	77·94 77·81	5·09 5·29	7·91 7·77	—
XXXIV *C*	302 ethanol	$C_{23}H_{18}N_2O_3$ (370·4)	74·58 74·38	4·90 5·02	7·56 7·35	—
XXXV *C*, 42·3	314—315 acetic acid	$C_{23}H_{18}N_2O_2$ (354·4)	77·94 78·09	5·37 5·37	7·91 7·92	3·1
XXXVI *C*, 30·9	160 (decomp.) acetic acid	$C_{23}H_{18}N_2O_3.H_2O$ (388·4)	71·12 71·34	5·19 5·46	7·21 7·46	3·1
XXXVII[f] *C*,	236—238 50% ethanol	$C_{21}H_{12}Cl_2N_2O_2$ (395·2)	63·81 64·00	3·06 3·36	7·06 5·97	—
XXXVIII[g] *C*	298—299 acetic acid	$C_{21}H_{12}Cl_2N_2O_3$ (411·2)	61·33 61·37	2·94 3·11	6·81 6·93	—
XXXIX[h] *C*, 38·0	273—276 acetic acid	$C_{21}H_{12}Cl_2N_2O_2$ (395·2)	63·81 63·11	3·06 3·28	7·09 7·11	12·5
XL[i] *C*	264—264 acetic acid	$C_{21}H_{12}Cl_2N_2O_3$ (411·2)	61·33 60·75	2·94 3·16	6·81 6·80	3·1
XLI *C*, 61·9	238—240 50% ethanol	$C_{21}H_{14}N_2O_4$ (358·3)	70·38 70·64	3·94 3·66	7·82 8·08	—

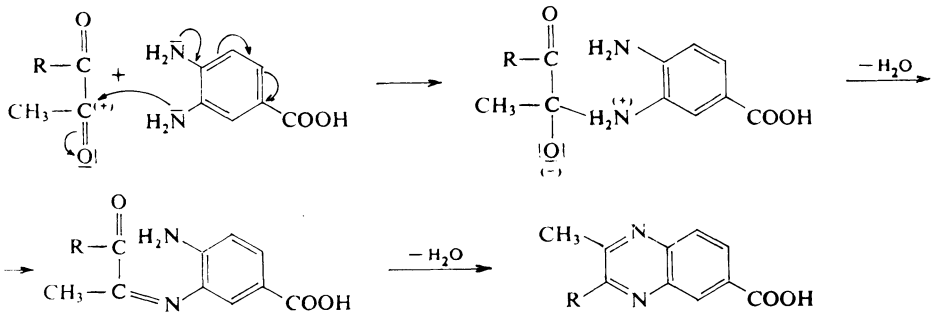
TABLE II

6-Quinoxalinecarboxylic acids

Compound Method Yield, %	M.p., °C solvent	Formula (mol.mass)	Calculated/Found			Antitbc. activity[a]
			% C	% H	% N	
XLII	288–290	$C_{21}H_{14}N_2O_5$	67·38	3·77	7·48	50
C, 73·0	50% ethanol	(374·3)	67·49	3·60	7·53	
XLIII	176–178	$C_{21}H_{14}N_2O_4$	70·38	3·94	7·82	—
A	ethanol	(358·3)	69·91	4·15	7·92	
XLIV	192	$C_{21}H_{14}N_2O_5$	67·38	3·77	7·48	—
A	50% ethanol	(374·3)	67·11	3·93	7·39	
XLV	320–322	$C_{21}H_{14}N_2O_4$	70·38	3·94	7·82	—
C, 53·0	80% acetic acid	(358·4)	70·43	4·39	7·56	
XLVI	277	$C_{21}H_{14}N_2O_5$	67·38	3·77	7·48	—
C, 82·8	50% methanol	(374·3)	67·20	3·92	7·41	
XLVII	200	$C_{23}H_{18}N_2O_4$	71·49	4·70	7·25	—
C, 20·7	50% ethanol	(386·4)	71·32	4·76	7·29	
XLVIII[j]	163	$C_{23}H_{18}N_2O_5$	68·64	4·51	6·96	—
C, 39·8		(402·4)	68·55	4·48	6·89	
XLIX	179–180	$C_{23}H_{18}N_2O_4$	71·49	4·70	7·25	—
C	ethanol	(386·4)	71·28	4·79	7·24	
L	190	$C_{23}H_{18}N_2O_5$	68·64	4·53	6·96	50
C	ethanol	(402·4)	68·34	4·93	7·01	
LI[k]	293–294	$C_{23}H_{18}N_2O_4$	71·49	4·70	7·25	0·75
C, 97·8	acetic acid	(386·4)	71·23	4·82	7·29	
LII	195–196	$C_{23}H_{18}N_2O_5$	68·64	4·51	6·96	3·1
C, 79·5	acetic acid	(402·4)	68·21	4·61	7·05	
LIII	225	$C_{25}H_{22}N_2O_6$	67·24	4·97	6·28	—
C	ethanol	(446·4)	66·97	5·17	6·29	
LIV	165–172	$C_{25}H_{22}N_2O_7$	64·93	4·79	6·06	—
C	ethanol	(462·4)	64·77	5·26	6·08	
LV	253–255	$C_{23}H_{14}N_2O_6$	66·67	3·41	6·76	—
C, 36·2	acetic acid	(414·4)	66·38	3·37	6·73	
LVI	127–130	$C_{23}H_{14}N_2O_7$	64·19	3·28	6·51	25
C, 32·5	butanol	(430·4)	64·12	3·51	6·51	
LVII	311–312	$C_{25}H_{24}N_4O_2$	72·79	5·88	13·58	1·5
C	ethanol	(412·5)	72·67	5·91	13·40	
LVIII	167–170	$C_{25}H_{24}N_4O_3$	70·07	5·65	13·08	3·1
C	ethanol	(428·5)	69·91	5·92	13·29	

TABLE II
(*Continued*)

Compound Method Yield, %	M.p., °C solvent	Formula (mol.mass)	Calculated/Found			Antitbc. activity[a]
			% C	% H	% N	
LIX[l] *B*, 68·6	245 ethanol	—	—	—	—	—
LX	220—222	$C_{17}H_{10}N_2O_5 \cdot 1{\cdot}5\ H_2O$	Z8·46	3·75	8·02	—
B, 97·0	ethanol, acetic acid	(322·3)	58·28	4·20	8·07	
LXI[m] *A*	122—124 ethanol	$C_{18}H_{24}N_2O_2$ (300·4)	71·97 71·45	8·05 8·00	9·33 9·53	6·25
LXII[m] *A*	126—128 ethanol	$C_{18}H_{24}N_2O_2$ (300·4)	71·97 71·34	8·05 8·25	9·33 8·73	6·25
LXIII[n] *B*	264 ethanol	$C_{18}H_{24}N_2O_3$ (316·4)	68·33 68·29	7·65 7·86	8·86 8·79	6·25
LXIV[n] *B*	268 ethanol	$C_{18}H_{24}N_2O_3$ (316·4)	68·33 68·28	7·65 7·78	8·86 8·65	6·25
LXV[o] *A*	219 ethanol	$C_{16}H_{12}N_2O_2$ (264·3)	72·71 72·55	4·58 4·47	10·60 10·69	—
LXVI[o] *A*	232 ethanol	$C_{16}H_{12}N_2O_2$ (264·3)	72·71 72·76	4·58 5·07	10·60 10·41	—
LXVII[p] *A*	249 dioxan	$Cl_6H_{12}N_2O_3$ (280·3)	68·56 68·38	4·32 4·41	10·00 10·54	—
LXVIII[p] *A*	318 dioxan	$C_{16}H_{12}N_2O_3$ (280·3)	68·56 68·38	4·32 4·38	10·00 10·25	—
LXIX[q] *B*	233—235 dioxan	$C_{16}H_{11}BrN_2O_3$ (343·2)	55·99 56·23	3·23 3·51	8·16 8·27	—
LXX[q] *B*	258—260 dioxan	$C_{16}H_{11}BrN_2O_3$ (343·2)	55·99 55·87	3·23 3·55	8·15 8·15	—
LXXI[r] *A*	240—245 acetic acid	$C_{16}H_{12}N_2O_3$ (280·3)	68·56 68·15	4·32 3·55	10·00 9·59	—
LXXIL[r] *A*	261—264 acetic acid	$C_{16}H_{12}N_2O_3$ (280·3)	68·56 68·15	4·32 4·60	10·00 9·69	—
LXXIII[s] *B*	215—217 acetic acid	$C_{16}H_{12}N_2O_4$ (296·3)	64·86 64·54	4·08 4·53	9·46 9·07	—
LXXIV[s] *B*	297—298 acetic acid	$C_{16}H_{12}N_2O_4$ (296·3)	64·86 64·95	4·08 4·37	9·46 9·50	—



R = aryl

SCHEME 3

xaline carboxylic acids substituted at positions 2 and 3 with methyl, tetramethylene pentamethylene and 2-furyl groups, or with one methyl and one phenyl group, are all inactive. 2- and 3-methyl-5-quinoxalinecarboxylic acids, and 3- and 2-n-octyl--5-quinoxalinecarboxylic a acids, as well as the 6-isomers. exhibited significant effects, but quite failed *in vivo*. Activity was observed with the 2,3-diphenyl compounds, especially those substituted at the *para* position of the phenyl rings with a methyl, methoxy or dimethylamino group, whereas their *ortho* isomers were inactive. The highest tuberculostatic activity was observed with 2,3-bis(4-methoxyphenyl)- and 2,3-bis(4-dimethylaminophenyl)-6-quinoxalinecarboxylic acids (*LI*, *LVII*). *In vivo*, however, these compounds failed also. The presence of a hydroxyl group at position 7 of the quinoxaline skeleton seemed to play no role.

[a] Ref.[6]: m.p. 257–260°C. [b] Ref.[5]: The authors prepared dihydrochloride m.p. 194–197°C. [c] Purified by precipitation from its Na-salt. [d] Ref.[6]: m.p. 280–288°C. [e] Ref.[4]: m.p. 252–254°C. [f] Calculated: 17·94% Cl; found: 18·11% Cl. [g] Calculated: 17·24% Cl; found: 16·98% Cl. [h] Calculated: ed: 17·94% Cl; found: 17·78% Cl. [i] Calculated: 17·14% Cl; found: 17·24% Cl. [j] Purified by precipitation from its Na-salt. [k] The compound is mentioned in ref.[7] without description of the preparation and m.p. [l] Ref.[6]: m.p. 235–245°C. [m] The isomers were separated by recrystallization from ethanol. [n] The isomers were separated by recrystallization from ethanol. The ratio of isolated amounts of *LXIII* and *LXIV* was 1 : 6. [o] The isomers were separated by fractional precipitation from the Na-salt of the crude product. [p] The isomers were separated by fractional crystallization of the crude product. The ratio of the isolated amounts of *LXVII* and *LXVIII* was 3 : 5. [q] The isomers were separated by recrystallization from water, ethanol, acetic acid and dioxan. The ratio of *LXIX* to *LXX* was 1 : 3. For *LXIX* calculated: 23·29% Br; found: 23·33% Br. For *LXX* found: 23·34% Br. [r] The isomers were separated by recrystallization from methanol, ethanol and acetic acid. The ratio of isolated amounts of *LXXI* and *LXXII* was 3 : 4. [s] The isomers were separated by chromatography of 4% aqueous solution of Na-salts on cellulose and then by recrystallization from acetic acid. The ratio of isolated amounts of *LXXIII* and *LXXIV* was 1 : 8.

EXPERIMENTAL

The melting points were determined on the Kofler stage.

Method A (ref.[4]): A mixture of 0·01 mol of 2,3- or 3,4-diaminobenzoic acid, or 3,4-diamino--2-hydroxybenzoic acid and 0·01 mol of a diketone in 25 to 30 ml of glacial acetic acid was boiled for 2 h under a reflux condenser. While still hot it was then poured into 150 ml of water and allowed to cool down. The product was collected on a filter, dissolved in aqueous sodium hydroxide and precipitated again by bringing the solution to pH 3 with hydrochloric acid. It was further purified by crystallization from a suitable solvent (Tables I and II).

Method B: The only difference from method *A* was that ethanol was used instead of acetic acid and that the mixture was refluxed for 2—12 h. After cooling, the separated product was collected on a filter and crystallized from a suitable solvent; in some cases it was first reprecipitated as in method *A*.

Method C (ref.[5]): 0·01 mol of a substituted acid was dissolved in a mixture of 100 ml of water and 4 ml of concentrated hydrochloric acid. The solution was discoloured with activated carbon, then 0·01 mol of a diketone was added. The mixture was heated 1 h on a boiling water bath. After cooling, the separated product was collected on a filter and crystallized from a suitable solvent (Tables I and II).

The dipole moments were measured by Dr V. Jehlička, Department of Physical Chemistry, Institute of Chemical Technology, Prague. The elemental analyses were performed at the Analytical Department of our Institute (head: Dr J. Körbl).

REFERENCES

1. Sorkin E., Roth W.: Helv. Chim. Acta *34*, 427 (1951).
2. Barry V. C., Belton J. G., Sullivan J. F. O., Twomey Dermont: J. Chem. Soc. *1956*, 893, 896.
3. Barry V. C., Conalty M. L.: Amer. Rev. Tuberc. *78*, 62 (1958).
4. Stellt van der C., Zwart-Voorspuij A. J., Nauta W. Th.: Arzneim.-Forsch. *4*, 544 (1954).
5. Perelló J., Bartulin J., Urrutia H.: Nol. Soc. Chilena Quim. *9*, 22 (1959); Chem. Abstr. *54*, 14 262 (1960).
6. Zehra A.: Ber. *23*, 3625 (1890).
7. Sikova H., Fress W. (Kalle Co).: Ger. Offen. 2 064 380; Chem. Abstr. *78*, 65 232 (1973).

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