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p-Toluenesulphonyl Derivatives of N,N'-bis-(4-quinolino-4-quinaldino/4-quinazolino and 9-acridino) Polymethylene Diamines as Hypoglycemic Agents*

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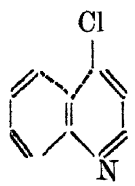
In view of the encouraging results shown by a number of bis-benzimidazole-2-sulphonamido derivatives as hypoglycemic agents (under communication), a series of compounds namely *p*-toluenesulphonyl derivatives of N,N'-bis-(4-quinolino/4-quinaldino/4-quinazolino and 9-acridino) polymethylene diamines have been prepared and screened for their hypoglycemic activity. Some of the compounds showed significant blood sugar lowering activity in rats.

ONE of the reasons for hypoglycemic activity in 'Carbutamide'[1] and 'Tolbutamide'[1] may be that they contain sulphonamido group. Further the hypoglycemic activity of 'Synthalin'[2] may be partly attributed to the presence of a long chain of carbon atoms (methylene groups). Hence it was considered of sufficient interest to synthesise a new series of compounds, hitherto unknown, containing sulphonamido group, a varying long chain carbon linkage and different heterocyclic nuclei in the same molecule as represented by the general structure,

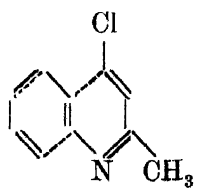
$$CH_3\text{-}C_6H_4\text{-}SO_2\text{-}N(R)\text{-}(CH_2)_n\text{-}N(R)\text{-}O_2S\text{-}C_6H_4\text{-}CH_3 \quad (I)$$

where R = 4-quinoline/4-quinaldine/4-quinazoline and 9-acridine and $n = 2$ to 12. We have obeserved earlier that a combination of the same above factors in bis-benzimidazole-2-sulphonamido derivatives (under communication) gives rise to promising potent antidiabetic compounds. The synthesis, screening of the compounds and their structure-activity relationship are reported in this paper.

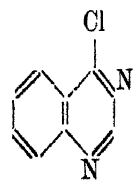
The synthesis of the proposed derivatives (I) was achieved by condensation of 4-chloroquinoline[3,4], 4-chloroquinaldine[5-7], 4-chloroquinazoline[8,9] and 9-chloroacridine[10,11] with different diamines, $H_2N\text{-}(CH_2)_n\text{-}NH_2$, $n = 1$ to 12, in the usual manner to give dihydrochlorides of bis amino compounds and then the free bases derived from them were condensed with *p*-toluene sulphonyl chloride in dry pyridine to give (I).



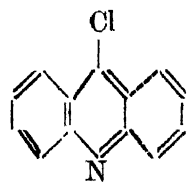
4-chloroquinoline



4-chloroquinalidine



4-chloroquinazoline



9-chloroacridine

The above chloro compounds were prepared by the standard procedures given in literature.

Preparation of compounds mentioned in Table 1 (*General Procedure*) :

The diamines used in the reactions were of Fulka variety. Freshly distilled phenol was used in the reactions.

A mixture of 0.01 mole of the diamine, 0.02 mole of the chloro compound with 10 g of phenol was refluxed in an oil bath maintained at 130°–135° for 14–16 hr. The mixture was cooled to room temperature and diluted with 40 ml. of ether. On scratching the dihydrochlorides were precipitated (vide Table 1). These were filtered and washed several times with ether and recrystallised from solvents mentioned against each.

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TABLE 1—N,N'-BIS-(4-QUINOLINO/4-QUINALDINO/4-QUINAZOLINO AND 9-ACRIDINO) POLYMETHYLRENE DIAMINE DIHYDROCHLORIDES

$R-NH-(CH_2)_n-NH-R.2HCl$

Sl. No.	R.	*n*	M.P.* °C	Crystallised from	Yield %	Molecular formula	Analyses % Element	Found	Reqd.
1.	4-quinolino	6	112	Ethanol	94.8	$C_{24}H_{28}N_4Cl_2$	C	64.85	65.01
							H	6.01	6.33
							N	12.84	12.64
2.	4-quinolino	8	267–268	Ethanol	80.6	$C_{26}H_{32}N_4Cl_2$	C	65.67	66.24
							H	6.67	6.79
							N	11.53	11.88
3.	4-quinolino	9	265–266	Ethanol	80.4	$C_{27}H_{34}N_4Cl_2$	C	66.31	66.80
							H	6.87	7.01
							N	11.30	11.54
4.	4-quinolino	12	249–250	Ethanol	91.0	$C_{30}H_{40}N_4Cl_2$	C	68.60	68.51
							H	7.70	7.59
							N	10.23	10.62
5.	4-quinaldino	7	115(d)	Ethanol	78.3	$C_{27}H_{36}N_4OCl_2$	C	63.98	64.41
							H	6.88	7.15
							N	10.95	11.11
6.	4-quinaldino	8	310(d)	Ethanol	86.2	$C_{28}H_{34}N_4Cl_2$	C	67.56	67.33
							H	6.81	7.21
							N	11.40	11.22
7.	4-quinaldino	9	73(d)	Ethanol	89.6	$C_{28}H_{42}N_4OCl_2$	C	63.51	63.38
							H	7.55	7.65
							N	9.78	10.20
8.	4-quinaldino	10	75(d)	Ethanol	89.1	$C_{30}H_{44}N_4OCl_2$	C	64.05	63.94
							H	7.90	7.81
							N	9.62	9.94
9.	4-quanaldino	12	70(d)	Ethanol	93.6	$C_{32}H_{46}N_4OCl_2$	C	66.85	67.01
							H	7.70	8.02
							N	9.28	9.77
10.	4-quinazolino	10	193–194	Ethanol	79.8	$C_{26}H_{34}N_6Cl_2$	C	61.87	62.27
							H	6.96	6.66
							N	16.55	16.76
11.	9-acridino	8	154–155	Ethanol+ Ether.	91.0	$C_{34}H_{38}N_4OCl_2$	C	68.79	69.26
							H	6.88	6.45
							N	9.07	9.50

* All melting points are uncorrected. (d) = decomposed.

Preparation of free bases from the dihydrochlorides (General Procedure) :

The dihydrochlorides prepared (mentioned in Table 1) were dissolved in 15% NaOH solution with careful cooling and the liberated free bases were extracted with chloroform. The chloroform extract was dried over anhydrous K_2CO_3, filtered, and the free bases were obtained by evaporating the solvents.

Preparation of p-toluenesulphonyl derivatives (General Procedure) :

In a 50 ml R.B. flask fitted with a reflux condenser and a $CaCl_2$ guard tube 0.000625 mole of the above free base, freshly distilled dry pyridine (10 ml) and *p*-toluenesulphonyl chloride (0.00125 mole) were refluxed together for 2–3 hr in an oil bath maintained at 130°–135°. When the reaction was complete, the solvent was removed under reduced pressure and the solid remaining was recrystallised from water (vide Table 2).

Pharmacology and the structure action relationship :

The compounds were studied for their hypoglycemic action in albino rats of either sex weighing 150–200 g, fasted for 18 hr (water was allowed ad.lib.).

The blood sugar was determined by collecting blood (0.1 ml) from the tail of the rats and determined by the method of Folin and Wu[12].

A suspension of 250 mg/kg of the test compounds in gum accacia was administered orally to 11 groups

TABLE 2—*p*-TOLUENESULPHONYL DERIVATIVES OF N,N'-BIS- (4-QUINOLINO/4-QUINALDINO/4-QUINAZOLINO AND 9-ACRIDINO) POLYMETHYLENE DIAMINES

$$H_3C-C_6H_4-SO_2-\underset{\displaystyle R}{\underset{|}{N}}-(CH_2)_n-\underset{\displaystyle R}{\underset{|}{N}}-SO_2-C_6H_4-CH_3$$

Sl. No.	R	*n*	M.P.* °C	Crystallised from	Yield %	Molecular formula	Analyses % Element	Found	Reqd.
1.	4-quinolino	6	182	water	71.4	$C_{36}H_{36}N_4O_4S_2$	N	8.23	8.25
2.	4-quinolino	8	185–186	water	90.7	$C_{40}H_{42}N_4O_4S_2$	N	7.80	7.93
3.	4-quinolino	9	72–73	water	88.0	$C_{41}H_{44}N_4O_4S_2$	N	7.56	7.77
4.	4-quinolino	12	210–211	water	73.5	$C_{44}H_{50}N_4O_4S_2$	N	7.38	7.34
5.	4-quinaldino	7	139–140	water	75.0	$C_{42}H_{44}N_4O_4S_2$	N	7.47	7.77
6.	4-quinaldino	8	125–126	water	76.5	$C_{42}H_{46}N_4O_4S_2$	N	7.20	7.62
7.	4-quinaldino	9	101–102	water	86.0	$C_{43}H_{48}N_4O_4S_2$	N	7.54	7.48
8.	4-quinaldino	10	175–176	water	84.0	$C_{44}H_{50}N_4O_4S_2$	N	7.56	7.36
9.	4-quinaldino	12	208–209	water	91.2	$C_{46}H_{54}N_4O_4S_2$	N	6.72	7.08
10.	4-quinazolino	10	229–230	water	75.9	$C_{40}H_{44}N_6O_4S_2$	N	11.88	11.65
11.	9-acridino	8	220–221	water	80.0	$C_{48}H_{46}N_4O_4S_2$	N	6.60	6.94

* All melting points are uncorrected.

of rats. The blood sugar was determined after 1 hr and 3 hr. The reference drug, tolbutamide, was administered at 250 mg/kg. The results are tabulated in Table 3.

The introduction of *p*-toluenesulphonamido group in such compounds (Table 2) akin to the one in tolbutamide was specially made in order to see whether this has any additional advantage in the

TABLE 3—BLOOD SUGAR DETERMINATION

$$H_3C-C_6H_4-SO_2-\underset{\displaystyle R}{\underset{|}{N}}-(CH_2)_n-\underset{\displaystyle R}{\underset{|}{N}}-SO_2-C_6H_4-CH_3$$

Sl. No.	Test compound	No. of animals	Initial Blood sugar	Blood sugar (mg/100 ml) level after 1 hr	3 hr
1.	Control	5	101.94± 5.2*	99.65± 5.4	98.68± 5.2
2.	*n* = 6 R = 4-quinolino	5	89.72± 0.85	87.93± 1.60	84.24± 0.96
3.	*n* = 8 R = 4-quinolino	5	99.17± 0.98	79.17± 1.10	77.39± 3.25
4.	*n* = 9 R = 4-quinolino	5	70.23± 4.27	79.53± 4.63	82.91± 1.52
5.	*n* = 12 R = 4-quinolino	5	115.10± 3.84	82.12± 1.56	79.43± 1.54
6.	*n* = 7 R = 4-quinaldino	5	86.03± 2.42	71.25± 1.70	101.60± 5.15
7.	*n* = 8 R = 4-quinaldino	5	81.22± 0.89	69.87± 0.83	69.02± 1.46
8.	*n* = 9 R = 4-quinaldino	5	88.74± 5.32	72.45± 2.26	70.72± 2.28
9.	*n* = 10 R = 4-quinaldino	5	86.78± 1.72	78.07± 0.80	78.34± 0.75
10.	*n* = 12 R = 4-quinaldino	5	100.40± 7.59	99.77± 1.11	87.87± 1.79
11.	*n* = 10 R = 4-quinazolino	5	93.03± 9.32	87.24± 7.63	92.07± 5.57
12.	*n* = 8 R = 9-acridino	5	72.65± 3.49	84.27±15.83	82.69± 4.34
13.	Tolbutamide	5	87.12±14.00	69.95±13.12	52.36±15.90

* Mean±SE.

production of active hypoglycemic agents. It may be observed from Table 3 that two compounds bearing R = 4-quinolino group and $n = 8$ and 12 show substantial reduction in blood sugar value viz., 21.78 (Compound No. 3) and 35.67 (Compound No. 5) units respectively. The last one with $n = 12$ (Compound No. 5) possesses maximum activity (35.67 units) which is even greater than that of tolbutamide and is therefore much promising. Corresponding 4-quinaldino and 4-quinazolino derivatives are however active only to a very small extent. 9-Acridino compound (Compound No. 12) shows hyperglycemic effect. Hence it may be concluded that Compound No. 5 possesses a fair chance of competing with tolbutamide and may be expected to have a superior edge over the standard substance.

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References

1. I. Simon, *Bull. Soc. ital. biol. sper.*, 1956, **32**, 1329.
2. E. Frank, *Naturwiss.*, 1927, **15**, 213.
3. C. J. Albisette, Jr., G. R. Lappin and R. H. Baker, *J. Amer. Chem. Soc.*, 1946, **68**, 2685.
4. I. Heilborn and H. M. Bunbury, "Dictionary of Organic Compounds", Vol. I, Eyre and Spottiswoode, London, 1953, p. 560.
5. G. A. Reynolds and C. A. Hauser, "Organic Syntheses", Col. Vol. III, John Wiley & Sons, Inc., New York, 1955, p. 374.
6. G. A. Reynolds and C. A. Hauser, "Organic Syntheses", Col. Vol. III, John Wiley & Sons, Inc., New York, 1955, p. 593.
7. I. Heilborn and H. M. Bunbury, "Dictionary of Organic Compounds", Vol. I, Eyre and Spottiswoode, London, 1953, p. 559.
8. M. T. Bogert and C. E. May, *J. Amer. Chem. Soc.*, 1909, **31**, 509.
9. A. J. Tomisek and B. E. Charistensen, *J. Amer. Chem. Soc.*, 1945, **67**, 2112.
10. A. Albert, "The Acridines", Edward Arnold & Co., London, 1951, p. 54.
11. A. Albert, "The Acridines", Edward Arnold & Co., London, 1951, p. 38.
12. O. Folin and H. Wu, *J. Boil. Chem.*, 1920, **41**, 367.