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THE SOLUBILITY OF SULPHONILAMIDE DRUGS IN WATER.

by

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CONTENTS.

INTRODUCTION.

Sulphonilamide or para-amino benzene sulphonamide $NH_2-C_6H_4-SO_2NH_2$ was first synthesised by Gelmo[1] in 1909. In 1935, Domagk[2] showed that when a sulphonilamide nucleus was contained in an azo dye it prevented the development of streptococcal septicaemia in mice. This dye, used originally in pharmacy under the name Prontosil, later as Prontosil Rubrum or sulphamido-chrysoidin, was very efficacious, but had the disadvantage of low solubility, with some toxicity. It was later shown that it was the sulphonamide nucleus that was responsible for the activity and that it was less toxic than the azo dye. Sulphonilamide given by the mouth is absorbed very rapidly, concentration in the blood reaching a maximum in four hours. Excretion begins very shortly after administration.

Sulphonilamide when administered by oral methods was found to produce certain toxic conditions, such as nausea, vomiting and cyanosis, despite its success as a chemotherapeutic agent. It was to eliminate or lessen these undesirable side effects which prompted the production of derivatives formed by substitution of the $-NH_2$ or $-SO_2NH_2$ groupings. Earlier derivatives all had the substituent in the $-SO_2NH_2$ group, and these have been much more freely used in medicine than those derivatives

in which substitution is in the $-NH_2$ group. Some derivatives, for example, sulphaguanidine, have been found of use in specific cases; while others are useful in a variety of infections.

It is now considered that the absolute bacteriological efficacies of all the sulphonilamides are very similar and that the large difference in medicinal efficacy between the various derivatives is due to differences in solubility, rate of absorption into the blood stream and rate of excretion in the urine. The necessity from the pharmaceutical side for a comprehensive list of solubilities at varying temperatures is therefore obvious.

The solubility of most sulphonilamide derivatives is much lower than that of the parent substance. Thus, although the compound may be absorbed very rapidly and completely from the intestinal tract into the blood stream it is excreted rapidly by way of the kidneys and a high concentration is established in the urinary tract. This tends to lead to crystallisation in the tract and constitutes a danger to the patient. Since medication is often in tablet form or as a suspension, the intake of fluid sufficient to avoid crystallisation in the urine can be calculated if the solubility is known. Sulphonilamide, sulphathiazole and sulphamezathine are also employed as dusting powders incorporating Penicillin,

and absorption by the skin may lead to poisoning, especially in the case of burns.

In the case of some derivatives, sodium compounds, which are readily soluble, can be prepared. However, the solutions are highly alkaline, due to hydrolysis, and administration by intravenous injection is painful. When this type of injection is necessary the solubilities are important to determine the minimum quantity of solution to be given.

Since 1939-1940, there have been some measurements made on the solubility of sulphonilamide and some of its derivatives in various solvents, but no complete investigation of comparative solubilities has been made.

Kiele and Sayward[3] determined the concentration of aqueous saturated solutions of sulphonilamide and its two isomers, ortho- and metanilamide at fifteen temperatures between 23° and 50° C. Sapozhikova and Postovskii[4] measured the solubility of sulphonilamide, sulphaguanidine, sulphapyridine, sulphathiazole and sulphethylthiazole and their acetyl derivatives between 20° and 30° C. The N' heterocyclic derivatives had the lowest solubility. Both pairs of workers calculated the heats of solubility. Using a photoelectric colourimeter to measure the amount dissolved, Clark, Strakosch and Levitan[5] determined the solubilities at 25° and 37° C. of sulphonilamide,

sulphathiazole, sulphapyridine, sulphadiazine and their sodium salts.

The influence of pH on the solubility of the sulphonilamides has been investigated by a number of workers. Kiele and Sayward[3] found that there was a minimum in the solubility versus pH curve in aqueous solutions at 37° C. between pH 4-7. Hug[6] obtained a similar result at the same temperature using sulphapyridine and the acetyl derivative. He found that the solubility in urine was slightly greater. Rose, Martin and Bevan,[7] Gilligan and Plummer,[8] and later, Frisk, Haggerman, Helander and Sjorgen[9] found that in citrate or phosphate buffers at 37° C., the solubility of sulphamerazine and sulphamezathine, sulphadiazine, sulphathiazole and their N-4 acetyl derivatives increased very rapidly above pH 6. The same phenomenon occurs in urine solution with sulphathiazole[10] and sulphadiazine.[11] Sulphapyridine, however, shows no increase in solubility up to pH 8.[7] The change in solubility with pH has been discussed from a physico-chemical point of view.[12] Also, the solubility of some sulphonilamide derivatives has been measured in phosphate buffers and urine,[13] and water, 0.9 per cent. sodium chloride solution and blood serum,[14] at different pHs. The addition of pectin has been found to increase the solubility of sulphonilamide, sulphathiazole and

sulphaguanidine in water.[15]

The solubilities of some sulphonilamides have been determined in aqueous solutions of diethylamine,[16] in acetone[17] and in isopropyl alcohol.[18]

The manufacturers of sulphonilamides have also put out literature which includes figures of solubility. No details, however, are given in the pamphlets, and very often expressions such as "very slightly soluble" are used.

The solubilities of very large numbers of organic compounds are known, but from the physico-chemical point of view the data have been mainly correlated with regard to the solubilities of the same solute in different solvents (e.g. Hildebrand[19]).

Very little direct work appears to have been done on the complementary problem of the solubilities of groups of related compounds in the same solvent. It has, of course, long been known that similarity appears to favour solubility - for example, that naphthalene is very soluble in benzene, but much less so in acetic acid or alcohols. In connection with this Prins[20] concluded that the solubility of organic compounds in hydrocarbons does not depend directly on the polar or active groups, but upon the saturated carbon group. Pastak[21] investigated the relative solubilities of substituted benzene derivatives, biphenyls and α and β naphthalenes from the point of

view of the crystal structure of the solid. He found that the most soluble isomers possessed the greatest degree of crystal symmetry.

The dependence of the solubility of pyranase sugars on their structure [22] and the effect of addition of $-SO_3H$ or -COOH groups on the solubility of drugs [23] have also been studied.

Some work has been done of the comparative solubilities of aliphatic compounds. Dorough, Glass, Gresham, Malone and Reid [24] measured the solubilities of twenty four isomeric octanols in water, while Hoerr, Ralston and their co-workers have given data in a series of papers on the solubilities of normal paraffins,[25] normal aliphatic alcohols,[26] ketones,[27] saturated fatty acids,[28] amides, anilides and N, N phenylanilides,[29] and amines,[30] in numbers of organic solvents. The solubility decreases in any solvent with increasing chain length, as might be expected, and the solubility curves show breaks and a characteristic deviation from a smooth relationship between solubility and temperature.

The sulphonilamide drugs form an interesting series of compounds for the study of comparative solubility, since they all contain the same aromatic nucleus.

with different organic groups at either or both ends. The

importance in pharmaceutical work of a knowledge of their solubilities has been stressed earlier.

Earlier in this introduction previous work on the solubilities of some of these substances was summarised. There is considerable discrepancy between values found by different workers, due to different methods and conditions of measurement used. The solubilities in water of sulphonilamide, a number of its derivatives and their sodium salts were measured, therefore, by the same method at different temperatures.

EXPERIMENTAL.

Procedure. A quantity of each compound was weighed and placed in 100 mils of distilled water in a glass boiling tube, which was fitted with a rubber cork, through which a calibrated Centigrade thermometer, reading in degrees, and a stirrer passed. The boiling tube was placed in an outer glass tube and the whole apparatus was heated in a water or glycerin bath, the temperature of which was slowly raised, until the powder in the inner tube dissolved. The apparatus was then cooled, with vigorous stirring, until the substance began to crystallise. The reading of the thermometer was taken to the nearest degree the instant the crystals began to form, and was accurate to approximately $\pm$ 0.5° C. The experiment was repeated until several readings for the crystallisation temperature consistent to 1 - 2° C. were recorded. Several weights of each sulphonilamide were taken.

Materials. The sulphonilamide and all the derivatives, except N-4 succinyl-sulphonilamide, were commercial products for direct pharmaceutical use. The purity is given in the British Pharmacopoeia as 99 per cent., and thus they were not further purified. Four of the derivatives contained water of crystallisation.

Preparation of N-4 Succinyl-sulphonilamide.

The method of Miller, Rock and Moore [34] was used.

Ten grammes of succinic anhydride and 17.2 grammes of sulphonilamide with 100 mils of absolute alcohol were refluxed for 10 minutes, when a crystalline solid was deposited. The refluxing was continued for five minutes and the mixture then filtered whilst hot. The filtrate was cooled and the N-4 succinyl-sulphonilamide crystallised out. It was filtered off and recrystallised from water.

RESULTS.

Table I shows the solubilities of sulphonilamide and its derivatives, in approximate order of increasing solubility.

TABLE I

Substance	Solubility Grammes in 100 mils water	Temperature o C.
Sulphathalidine	0·01	50
(Phthalyl-sulpha-thiazole)	0.02	65
	0.04	80
	0.08	98
Sulphadiazine	0.025	63
[2(p-amino benzene	0.035	68
Sulphamido)-pyrimidine]	0.075	80
Sulphamerazine	0.075	55
[2(p-amino benzene -	0.10	60
Sulphonamido) - 4 methyl	0.15	70
Pyrimidine]	0.175	76
	0.20	80
Sulphapyridine	0.062	40
[2(p-amino benzene	0.093	45
Sulphonilamido)-pyridine]	0.129	50

TABLE I (continued)

Substance	Solubility Grammes in 100 mils water	Temperature oC.
Sulphamezathine	0.175	48
[Sulphadimethyl	0.225	60
pyrimidine or	0.275	70
2(p - amino benzene	0.325	80
Sulphonamido) - 4:6		
dimethyl pyrimidine]		
Sulphathiazole	0.25	40
[2(p - amino benzene -	0.375	49
Sulphonamido) thiazole]	0.50	59
Succinyl-sulpha-	0.20	50
thiazole mono- hydrate	0.30	60
[2(p - succinyl -	0.40	66
amino-benzene-	0.50	74
Sulphonamido) thiazole]		
N - 4 Succinyl -	0.75	58
Sulphonilamide	1.25	68
	1.75	75

TABLE I (continued)

Substance	Solubility Grammes in 100 mils water	Temperature o C.
Sulphaguanidine	1.00	46
Monohydrate	1.25	57
[p-amino benzene-	1.75	68
Sulphonyl-guanidine]	2.25	73
Sulphacetamide	1.25	35.5
[p-amino-benzene-	1.875	57
Sulphonacetamide]	2.50	73
Sulphonilamide	1.25	25
[p-amino-benzene-	1.875	38
Sulphonamide]	2.50	47

Table II shows the solubilities of the sodium salts of some sulphonilamide derivatives.

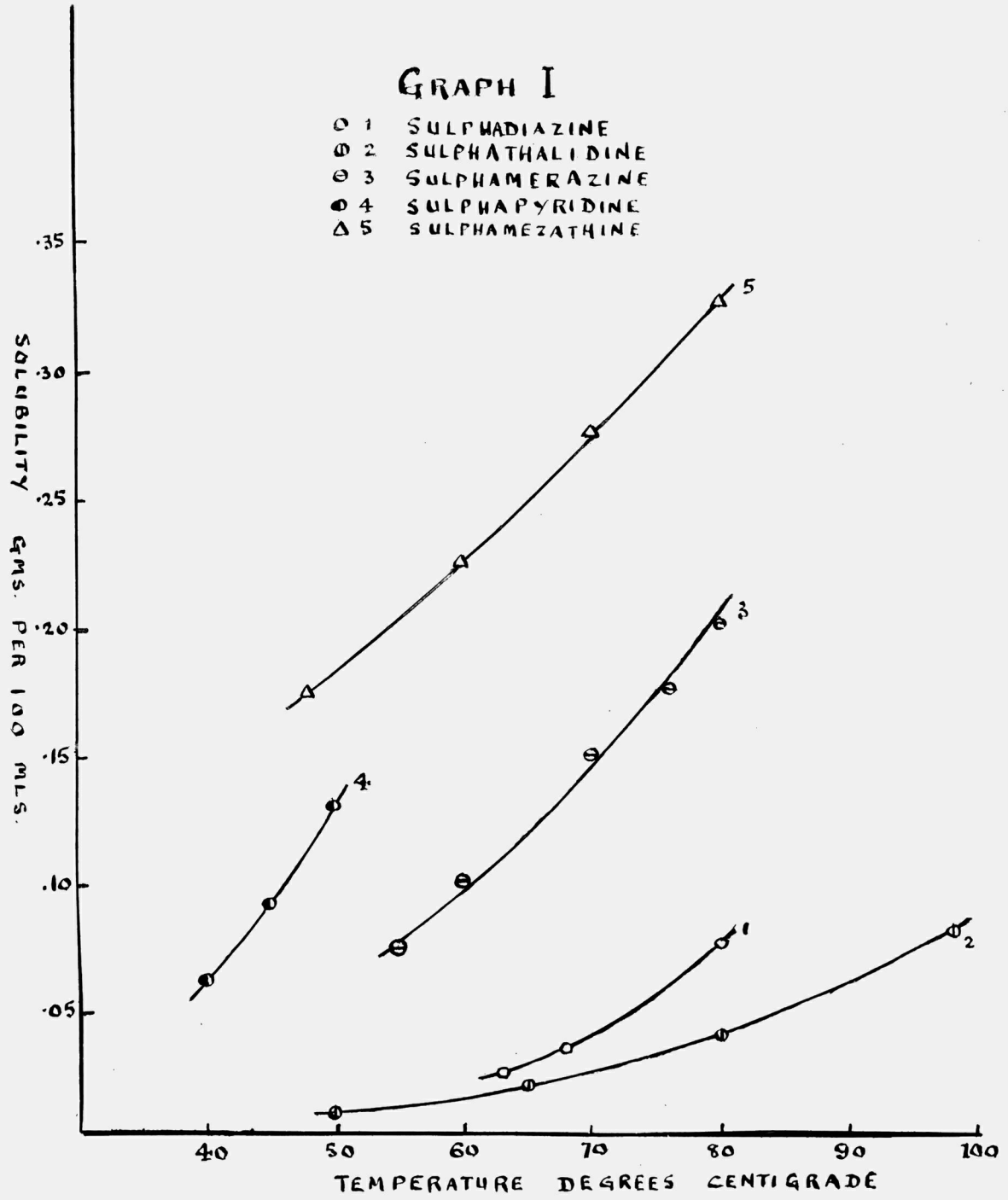
TABLE II.

Substance	Solubility Grammes in 100 mils water	Temperature o C.
Sulphapyridine-sodium	40	22
	50	35
	60	46
	70	60
	80	68
Marfenil [4-amino-methyl-benzene-sulphon-amido hydrochloride]	30	55
	40	58
	50	60
Sulphamerazine-sodium	33.3	22
	50	53
	75	83
Sulphadiazine-sodium	50	55
	66.6	75
	83	90
Sulphathiazole-sodium pentahydrate	60	21
	70	25
	80	28
	90	32
	100	36

TABLE II (continued)

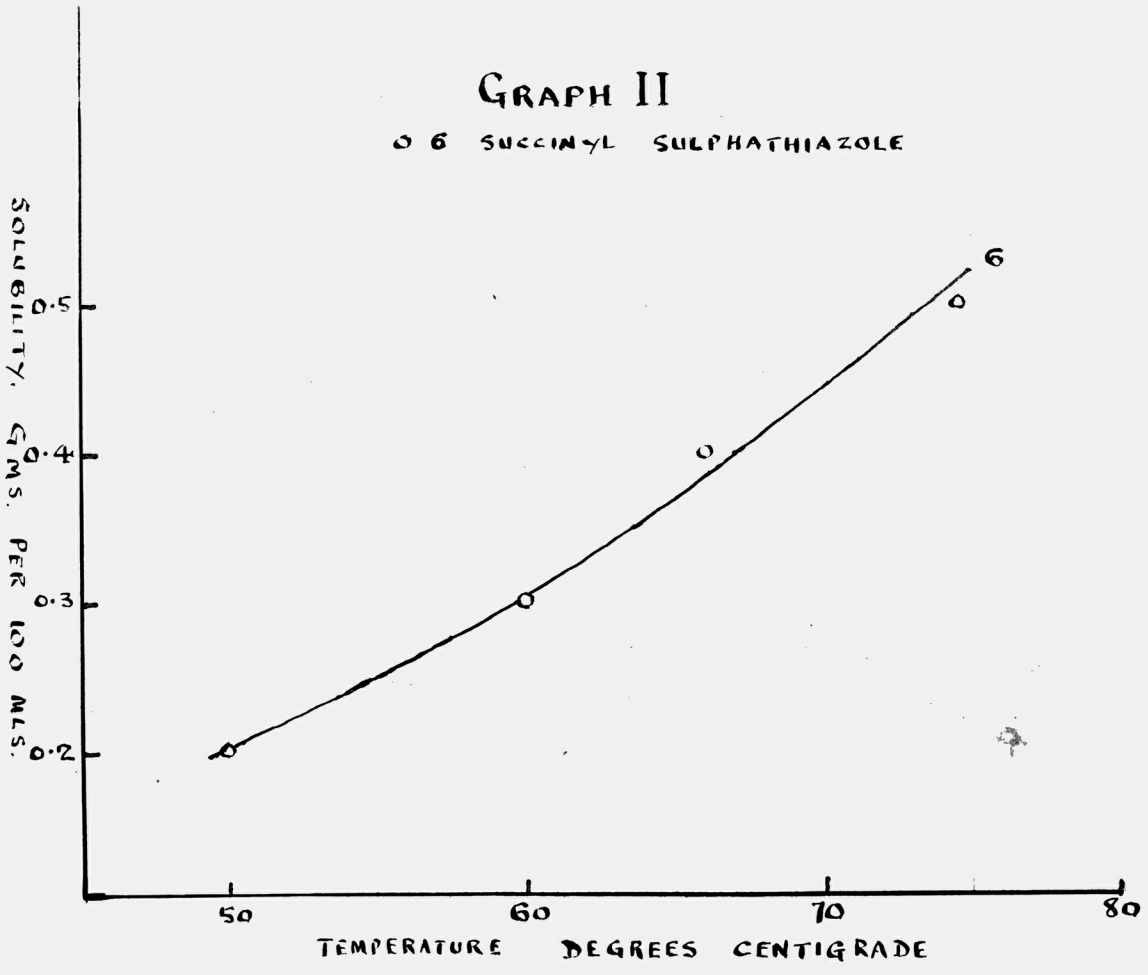
Substance	Solubility Grammes in 100 mils water	Temperature o C.
E.O.S.	62.5	34
p-ethyl, a-sodium	87.5	50
Sulphonate - amino-	112.5	65
benzene sulphonamide		
Sulphacetamide-	100	35
sodium	120	53
Monohydrate	130	65
	140	72
	150	80
Sulphamezathine-	62.5	50
sodium	75	58
	100	70
Succinyl-	100	21
Sulphathiazole	150	38
sodium	200	58

Graphs I to VI are plots of solubility against temperature.


GRAPH I
1 SULPHADIAZINE
2 SULPHATHALIDINE
3 SULPHAMERAZINE
4 SULPHAPYRIDINE
5 SULPHAMEZATHINE
SOLUBILITY GMS. PER 100 MLS.
·35
·30
·25
·20
·15
·10
·05
40
50
60
70
80
90
100
TEMPERATURE DEGREES CENTIGRADE

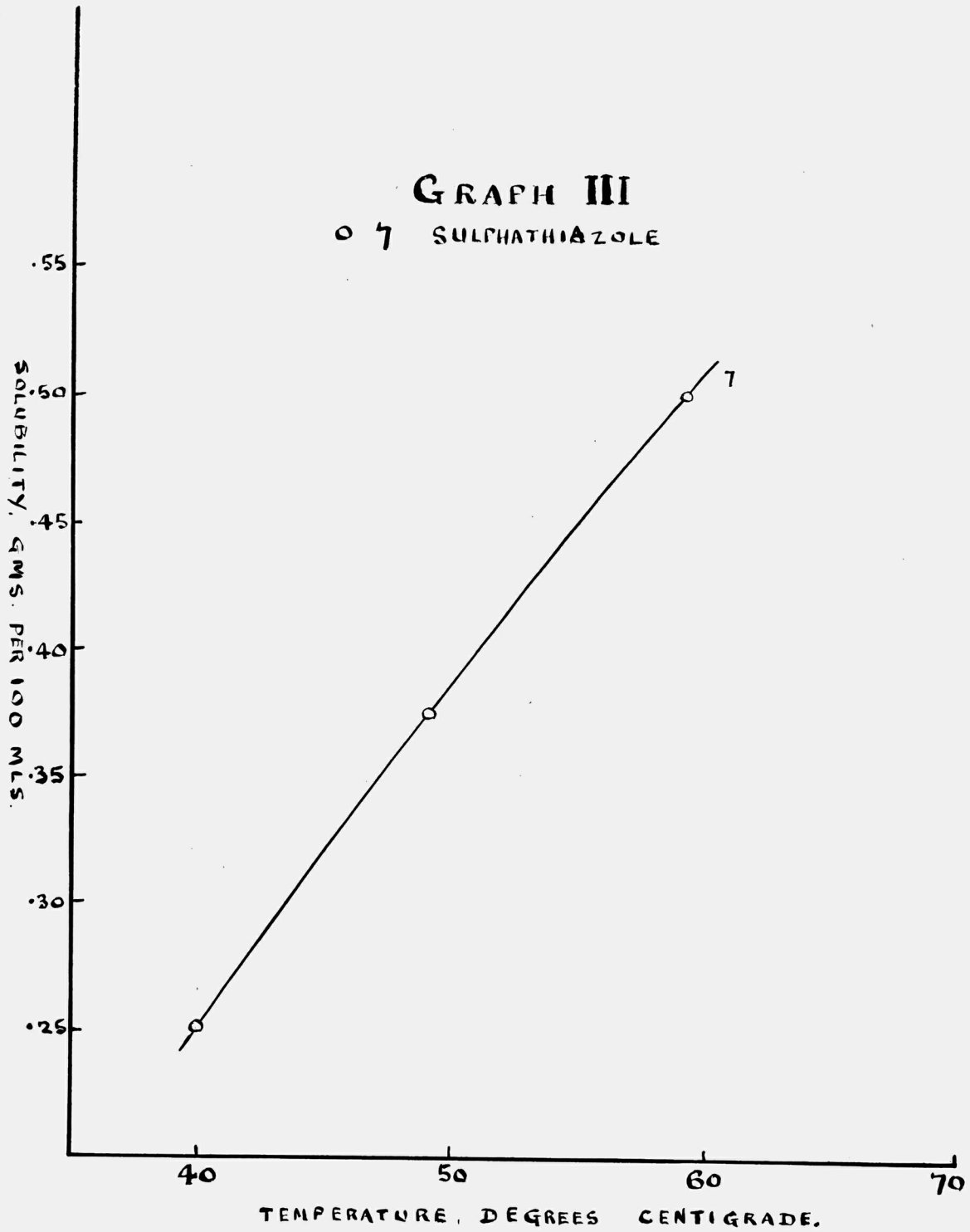
GRAPH II

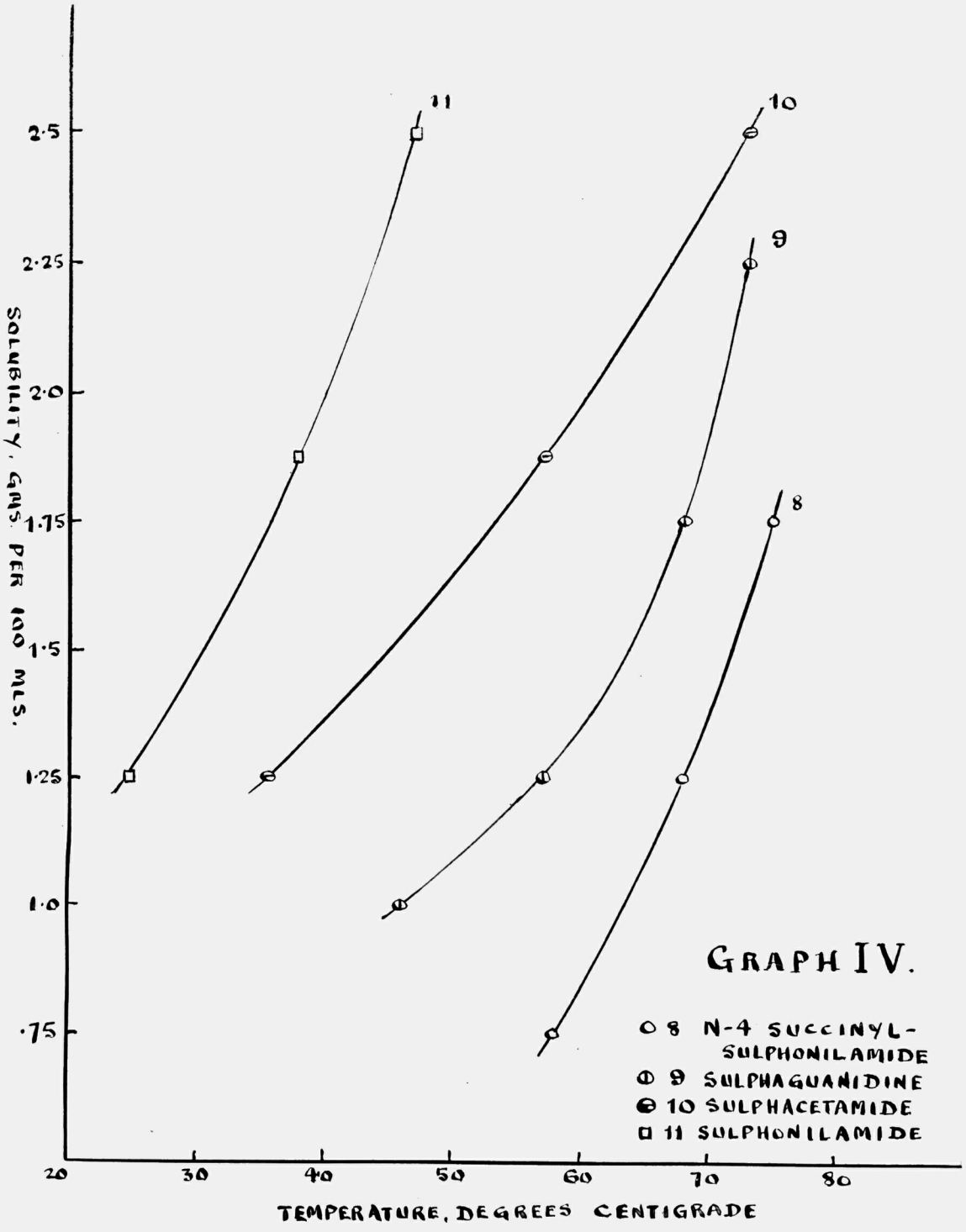
O 6 SUCCINYL SULPHATHIAZOLE

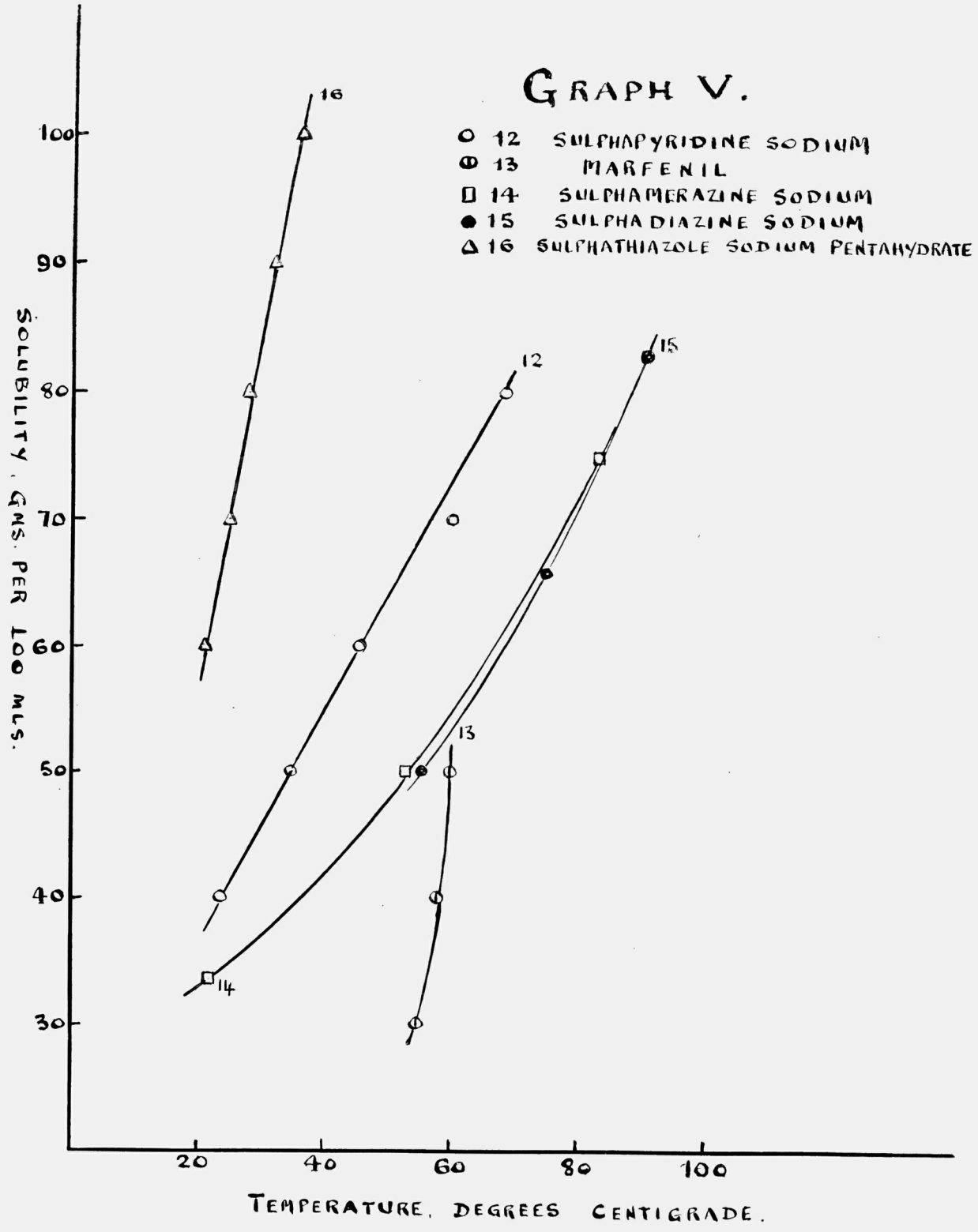


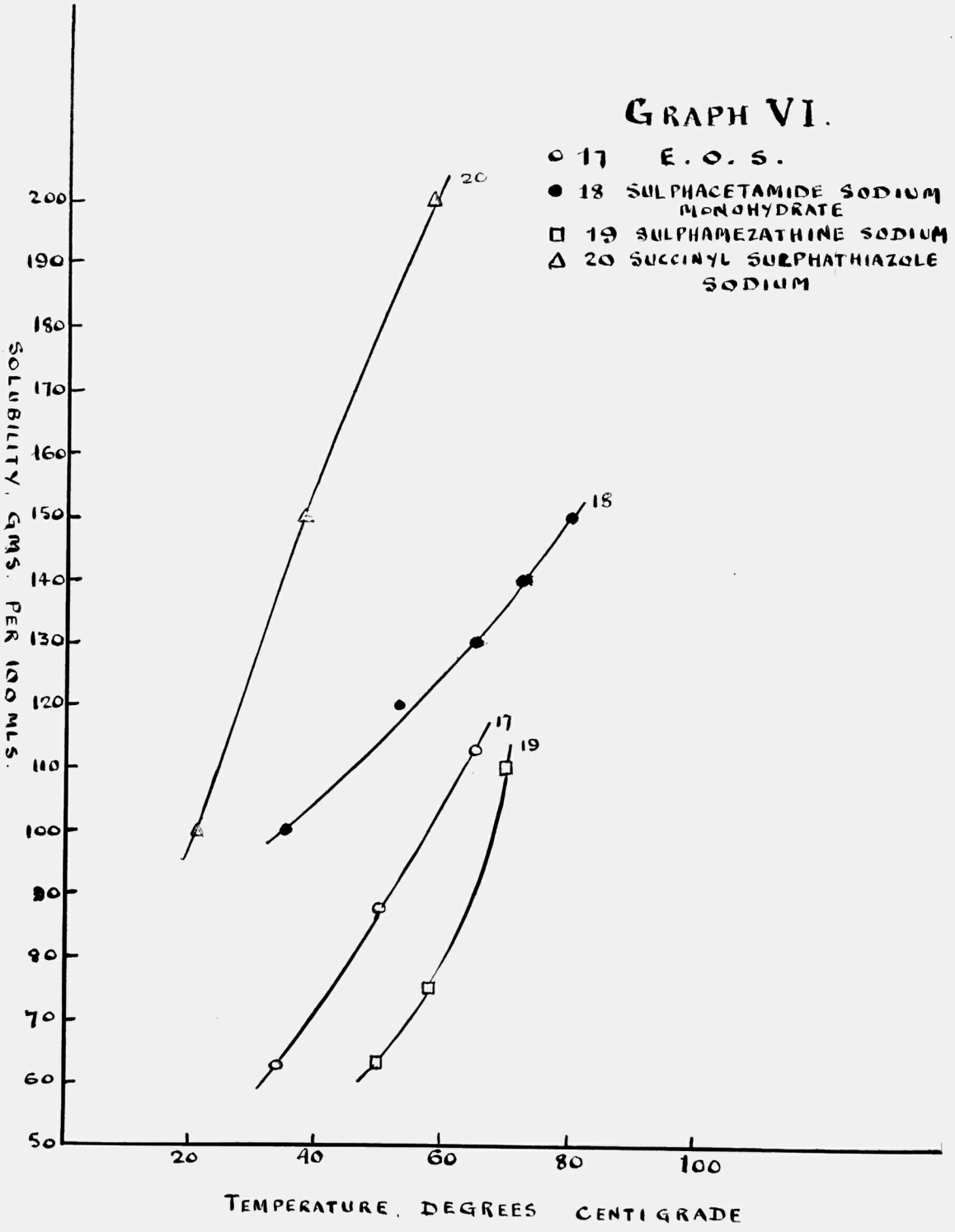
GRAPH III

0 7 SULPHATHIAZOLE




11
10
9
8
2·5
2·25
2·0
1·75
1·5
1·25
1·0
·75
SOLUBILITY, GMS. PER 100 MLS.
20
30
40
50
60
70
80
TEMPERATURE, DEGREES CENTIGRADE
GRAPH IV.
8 N-4 SUCCINYL-SULPHONILAMIDE
9 SULPHAGUANIDINE
10 SULPHACETAMIDE
11 SULPHONILAMIDE


GRAPH V.
○ 12 SULPHAPYRIDINE SODIUM
⊕ 13 MARFENIL
□ 14 SULPHAMERAZINE SODIUM
● 15 SULPHADIAZINE SODIUM
△ 16 SULPHATHIAZOLE SODIUM PENTAHYDRATE
SOLUBILITY. GMS. PER 100 MLS.
100
90
80
70
60
50
40
30
20
40
60
80
100
TEMPERATURE. DEGREES CENTIGRADE.
16
12
15
13
14


GRAPH VI.
○ 17 E. O. S.
● 18 SULPHACETAMIDE SODIUM MONOHYDRATE
□ 19 SULPHAMEZATHINE SODIUM
△ 20 SUCCINYL SULPHATHIAZOLE SODIUM
SOLUBILITY, GMS. PER 100 MLS.
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
20
40
60
80
100
TEMPERATURE, DEGREES CENTIGRADE
20
18
17
19

For any saturated solution of a pure solid in a liquid solvent, the following relationship between solubility and temperature applies

$$\text{①} \quad \left(\frac{\partial \log_e \alpha}{\partial T} \right)_P = \frac{\bar{H} - H_o}{RT^2}$$

where α is the activity of the solute in the saturated solution at temperature T and pressure P. H_o is the molar heat content of the pure solid solute and $\bar{H}$ its partial molar heat content in the saturated solution.

If the solution is dilute, as is the case for these aqueous solutions of the sulphonilamides, the activity can be replaced by the mole fraction of the solute N. Equation ① then becomes

$$\text{②} \quad \left(\frac{\partial \log_e N}{\partial T} \right)_P = \frac{\bar{H} - H_o}{RT^2}$$

$\bar{H} - H_o$ is actually the differential heat of solution of the solute in the saturated solution under the given conditions, but for a dilute solution this is practically the same as the integral heat of solution:- ΔH.

Assuming a constant pressure equation ② reduces to

$$\text{③} \quad \frac{d(\log_e N)}{dT} = \frac{\Delta H}{RT^2}$$

which is the equation first deduced by Schroeder.[32] Thus it is possible to determine the heats of solution of the sulphonilamides from their solubilities at various temperatures by utilising the integral form of equation ③

Integrating between temperatures T_1 and T_2 and mole fraction solubilities N_1 and N_2, we obtain, on the assumption that ΔH remains constant over the temperature range,

④ $$\log_e \frac{N_1}{N_2} = \frac{\Delta H}{R}\left(\frac{1}{T_2} - \frac{1}{T_1}\right)$$

Integrating the Schroeder equation generally gives

⑤ $$\log_e N = -\frac{\Delta H}{RT} + \text{constant}$$

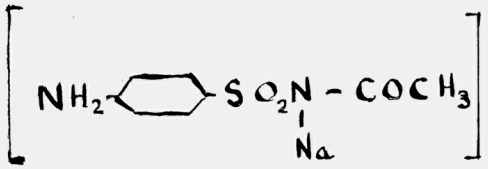
Thus, in order to calculate the heat of solubility from equations ④ or ⑤ mole fraction solubilities should strictly be used.

However, owing to the high molecular weights of the sulphonilamides compared to that of water even the saturated solutions of the sodium salts are dilute enough so that $\frac{N_1}{N_2} \simeq \frac{S_1}{S_2}$

where S is the solubility in grammes/ 100 mils water.

This can be illustrated for the case of the most

concentrated solution found, that of sulphacetamide sodium monohydrate.



$\cdot H_2O$ has a molecular weight of 254.2.

Its solubility is 100 G./ 100 mils (S_1) at 35° C.
and 150 G./ 100 mils (S_2) at 80° C.

at 35° C. $N_1 = \frac{100}{254\cdot2} \Big/ \frac{100}{254\cdot2} + \frac{18}{100}$

at 80° C. $N_2 = \frac{150}{254\cdot2} \Big/ \frac{150}{254\cdot2} + \frac{18}{100}$

$\therefore \frac{N_1}{N_2} = \cdot 689$ and $\frac{S_1}{S_2} = \cdot 667.$

The error is seen to be only 3%, which is within the experimental error.

Thus equation ③ can be written

⑥ $$\log_{10} S = -\frac{\Delta H}{2\cdot303\,R}\left(\frac{1}{T}\right) + \text{constant}$$

The plot of $\log_{10} S$ against $\frac{1}{T}$ should be a straight line, the slope of which is $\frac{-\Delta H}{2\cdot303\,R}$.

Graphs VII to XI show this plot for the compounds studied. In all cases reasonable straight lines were obtained, and ΔH was calculated from the slope.

For example:- for sulphathalidine, Graph VII, taking points A and B on line 2 the gradient

$$= \frac{-1.783 - (-1.284)}{.00300 - .00278}$$

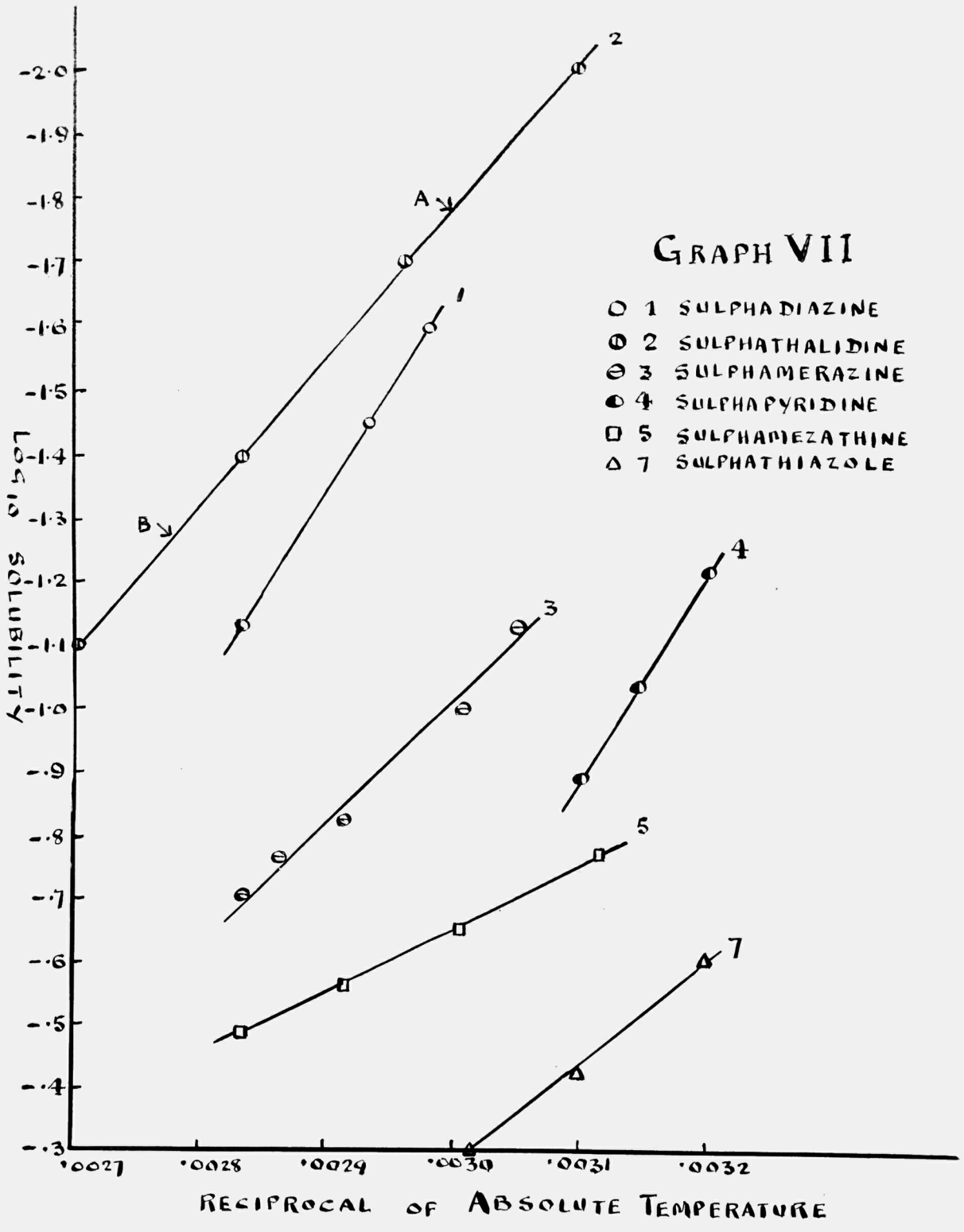
$$\therefore \frac{\Delta H}{2.303 \times 2} = -2268$$

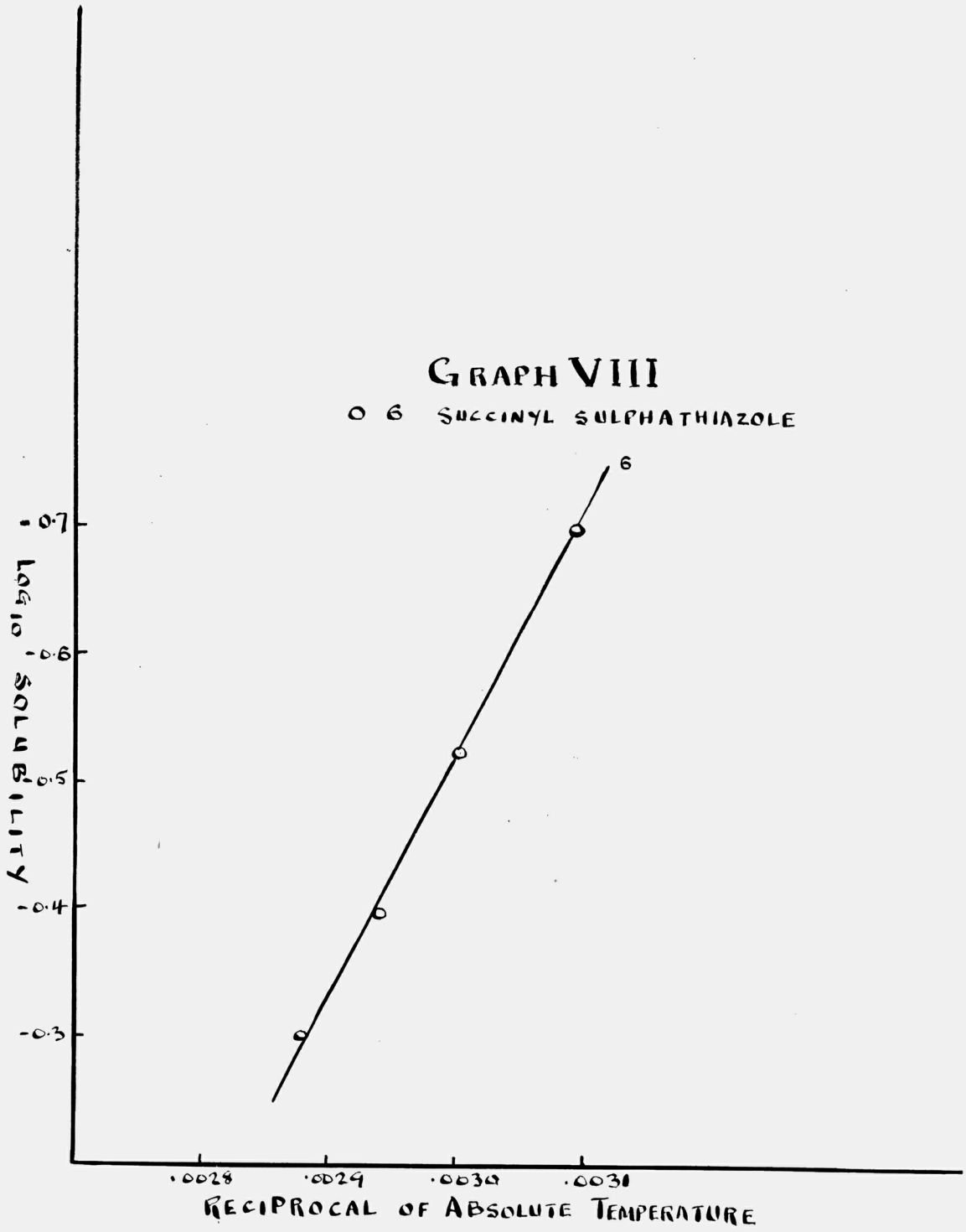
$$\Delta H = 10,400 \text{ cals.}$$

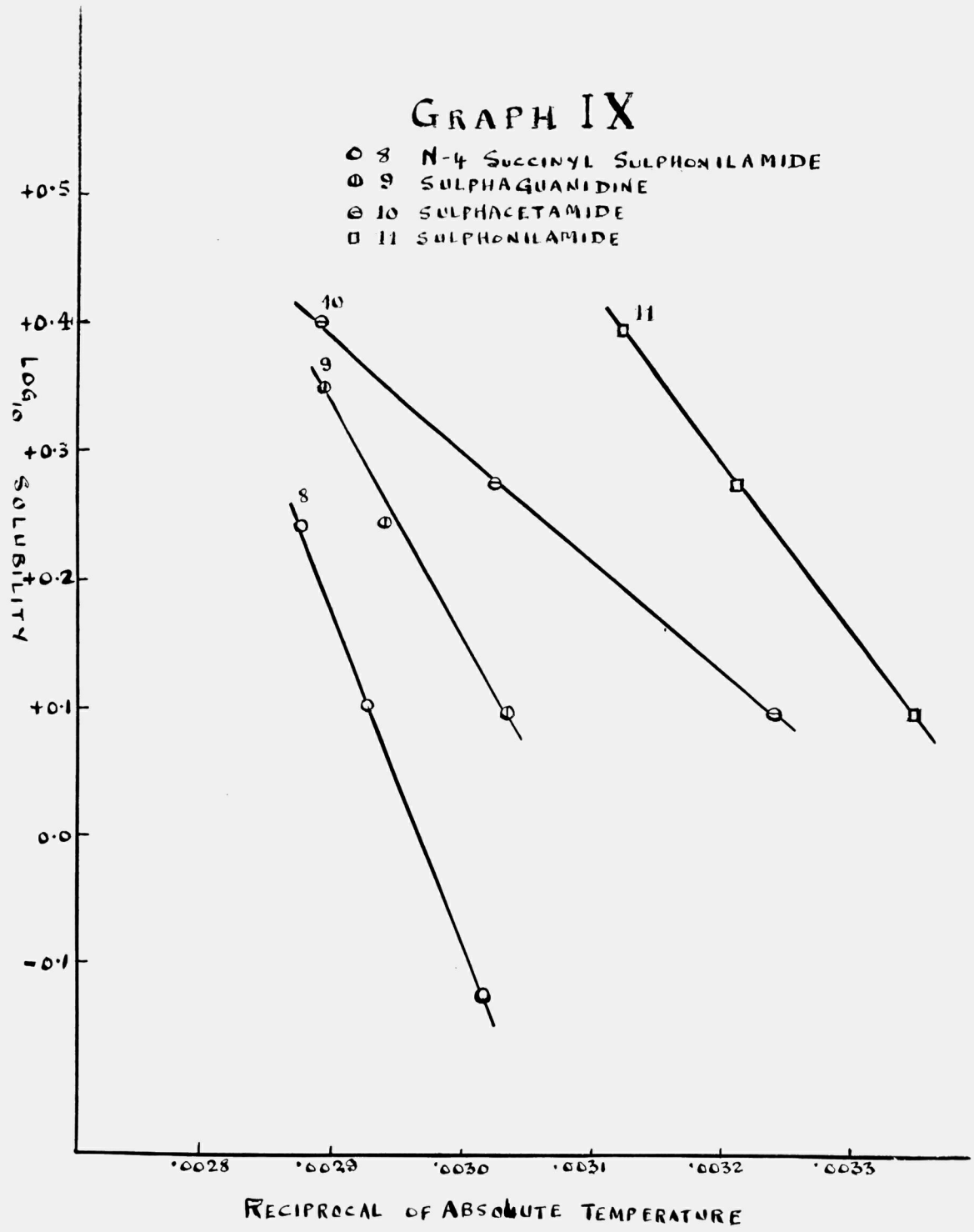
Equation (6) can be written as $\log_{10} S = a\left(\frac{1}{T}\right) + b$ (7) where a and b are constants for any compound. a and b can also be calculated from graphs VII to XI.

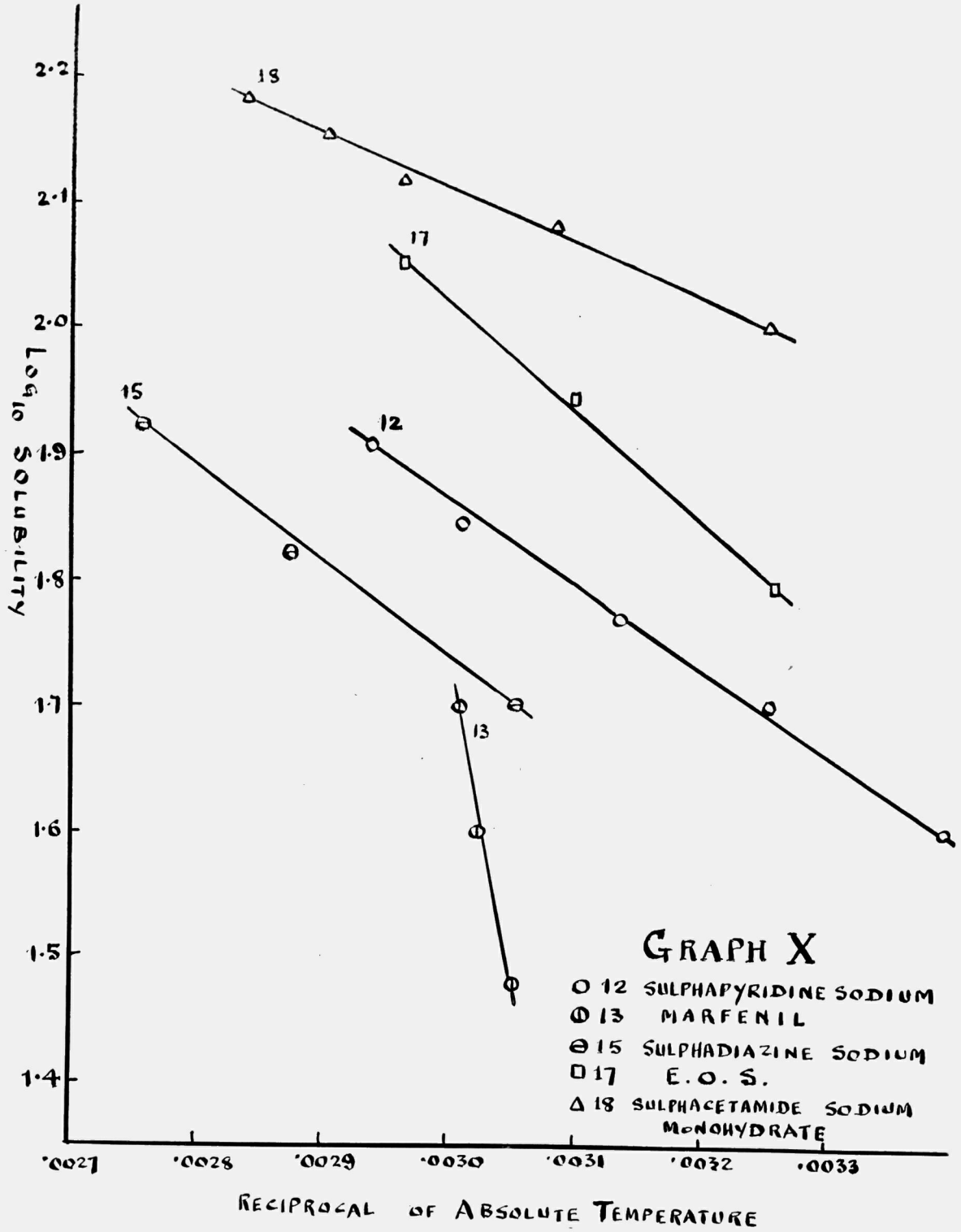
For example:- for sulphathalidine the gradient = a = - 2268 and for point A - 1.783 = .2268 (.0030) + b

$$b = 6.804 - 1.783 = 5.02.$$


GRAPH VII
1 SULPHADIAZINE
2 SULPHATHALIDINE
3 SULPHAMERAZINE
4 SULPHAPYRIDINE
5 SULPHAMEZATHINE
7 SULPHATHIAZOLE
Log 10 SOLUBILITY
-2·0
-1·9
-1·8
-1·7
-1·6
-1·5
-1·4
-1·3
-1·2
-1·1
-1·0
-·9
-·8
-·7
-·6
-·5
-·4
-·3
·0027
·0028
·0029
·0030
·0031
·0032
RECIPROCAL OF ABSOLUTE TEMPERATURE
A
B
1
2
3
4
5
7


GRAPH VIII
O 6 SUCCINYL SULPHATHIAZOLE
6
-0·7
-0·6
-0·5
-0·4
-0·3
LOG 10 SOLUBILITY
·0028
·0029
·0030
·0031
RECIPROCAL OF ABSOLUTE TEMPERATURE


GRAPH IX
8 N-4 SUCCINYL SULPHONILAMIDE
9 SULPHAGUANIDINE
10 SULPHACETAMIDE
11 SULPHONILAMIDE
+0·5
+0·4
+0·3
+0·2
+0·1
0·0
-0·1
LOG SOLUBILITY
10
11
9
8
·0028
·0029
·0030
·0031
·0032
·0033
RECIPROCAL OF ABSOLUTE TEMPERATURE


2·2
2·1
2·0
1·9
1·8
1·7
1·6
1·5
1·4
Log10 Solubility
18
17
15
12
13
·0027
·0028
·0029
·0030
·0031
·0032
·0033
Reciprocal of Absolute Temperature
GRAPH X
O 12 SULPHAPYRIDINE SODIUM
Φ 13 MARFENIL
Θ 15 SULPHADIAZINE SODIUM
□ 17 E.O.S.
Δ 18 SULPHACETAMIDE SODIUM MONOHYDRATE

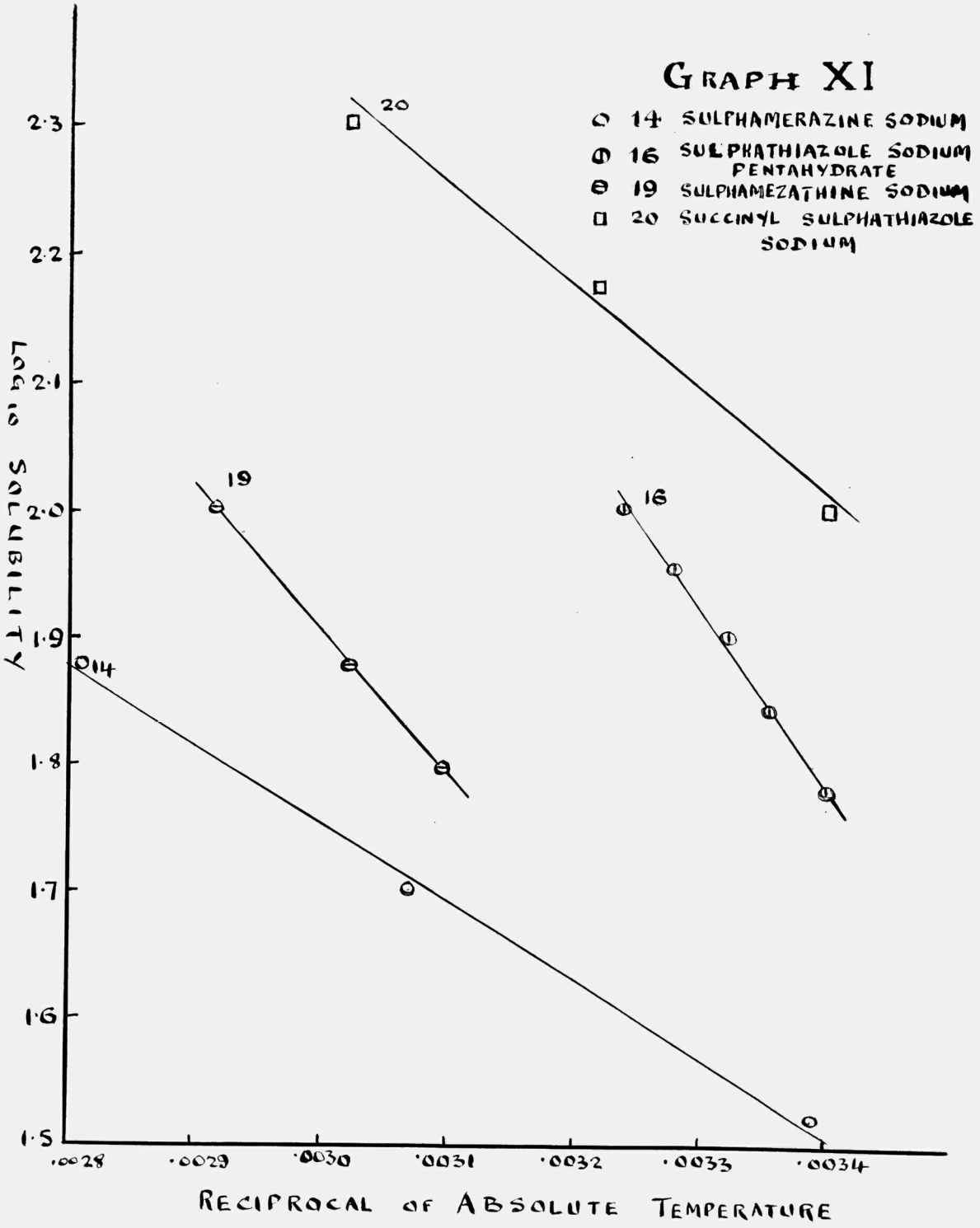

GRAPH XI
14 SULPHAMERAZINE SODIUM
16 SULPHATHIAZOLE SODIUM PENTAHYDRATE
19 SULPHAMEZATHINE SODIUM
20 SUCCINYL SULPHATHIAZOLE SODIUM
LOG 10 SOLUBILITY
2·3
2·2
2·1
2·0
1·9
1·8
1·7
1·6
1·5
·0028
·0029
·0030
·0031
·0032
·0033
·0034
RECIPROCAL OF ABSOLUTE TEMPERATURE

Table III gives the values of ΔH and a and b for the compounds.

TABLE III.

Compound	ΔH cals./mole (mean value over temperature range)	a	b
Sulphacetamide	3970	- 865	2.90
Sulphamezathine	4400	- 960	2.23
Sulphonilamide	5960	-1300	4.46
Sulphathiazole	7650	-1670	4.74
Sulphaguanidine	8570	-1870	5.75
Succinyl-sulphathiazole	8850	-1930	5.26
Sulphamerazine	9200	-2000	4.99
Sulphathalidine	10.400	-2268	5.02
N-4 Succinyl-sulphonilamide	11.460	-2500	7.43
Sulphapyridine	14.700	-3200	9.03
Sulphadiazine	15.260	-3330	8.31
Sulphacetamide-sodium	1940	-423	3.37
Sulphamerazine-sodium	2770	-605	3.57

TABLE III (continued)

Compound	ΔH cals./mole (mean value over temperature range)	a	b
Sulphapyridine-sodium	3000	- 655	3.82
Sulphadiazine-sodium	3415	- 745	3.97
Succinyl-sulphathiazole sodium	3740	- 815	4.78
E.O.S.	3970	- 865	4.615
Sulphamezathine-sodium	5180	-1130	5.29
Sulphathiazole-sidium	6190	-1350	6.38
Marfenil	21.500	-4700	15.82

By substituting the values of a and b in equation ⑦ the solubility of any sulphonilamide may readily calculated at any temperature.

Assuming equation ⑦ to be valid over the temperature range 20 - 100° C. in each case, values were calculated for the solubility of the compounds at 20° C., i.e. approximately room temperature, and at 35.5° C., i.e. normal body temperature. These values are obviously of interest pharmaceutically.

The solubilities are given in Table IV.

TABLE IV.

Derivative	Solubility at 20° C. in Grammes/100 mils.	Solubility at 35.5°C in Grammes/100 mils
Sulphadiazine	0.00087	0.0035(5)
Sulphathalidine	0.0019	0.0049
Sulphapyridine	0.013	0.049
Sulphamerazine	0.015	0.034
Succinyl-Sulphathiazole	0.047	0.10
N-4 Succinyl-Sulphonilamide	0.079	0.23
Sulphamezathine	0.091	0.135
Sulphathiazole	0.113	0.23
Sulphaguanidine	0.233	0.513
Sulphacetamide	0.89	1.27
Sulphonilamide	1.05	1.82
Marfenil	0.60	4.37
Sulphadiazine-sodium	26.7	36.5
Sulphamezathin-sodium	27.0	43.7
Sulphamerazine-sodium	32.0	41.3
Sulphapyridine-sodium	38.4	50.7

TABLE IV (continued)

Derivative	Solubility at 20° C. in Grammes/100 mils.	Solubility at 35.5°C. in Grammes/100 mils.
E. O. S.	45.9	66.2
Sulphathiazole-sodium	59.2	104.5
Sulphacetamide-sodium	84.3	101
Succinyl-sulphathiazole sodium	100	140

DISCUSSION.

Part I. Comparison of the results of different workers.

Other work on the solubilities of sulphonilamide derivatives in water is fragmentary. Solubilities given in the British Pharmacopoeia and the British Pharmaceutical Codex are often vague, e.g., the solubility of succinyl-sulphathiazole is said to be "very slight" in water, and sulphamezathine is said to be "sparingly soluble". Statements of approximate solubilities are intended to apply at ordinary room temperatures. The methods employed by commercial firms to determine the solubilities published in their pamphlets are not generally given. Probably a solution is evaporated to dryness and the residue weighed.

Clark, Strakosch and Levitan [5] found that sulphapyridine had a solubility of 0.0486 grammes per 100 mils at 36° C., and gave other solubilities by other workers as being in the range from 0.0495 to 0.0530. In a pamphlet published by a commercial firm, the solubility is given as 0.0520 grammes in 100 mils at 37° C. In the present investigation, a solubility of 0.0490 grammes in 100 mils at 35.5° C. resulted from several experiments, in good agreement with these previous values. Commercial sources gave the solubility of sulphamerazine and

sulphacetamide as 0.0318 and 0.110 grammes per 100 mils respectively at 37° C. ; in this investigation the solubilities were found to be 0.0340 and 0.127 grammes per 100 mils at 35.5° C. Kiele and Sayward [3] give the solubility of sulphonilamide as 1.37 grammes in 100 mils at 35.5° C., as compared with 1.82 grammes in 100 mils in the present work at the same temperature. At 50° C, however, there is good agreement; 2.68 as compared to 2.75 grammes per 100 mils.

These workers also found the heat of solubility of sulphonilamide to be 10,860 and 9,050 cals/mole above and below 37° C. respectively. The transition involves a monohydrate. Sapozhikova and Postovskii [4] found that the heats of solubility of sulphonilamide, sulphaguanidine, sulphapyridine and sulphathiazole lay between 9500 and 10,600 cals/ mole.

Any large differences between the solubilities or heats of solubility of any derivative as determined by independent workers is probably due to the different methods used, in which complication due to the possibility of hydrate formation is different. Some hydrates, e.g. of succinyl-sulphathiazole or sulphaguanidine, are the normal solid state of the substance. Many others are probably formed in solution and on crystallisation. In this investigation the same method has been used to

determine both the solubility and ΔH of each derivative, and the figures obtained may be legitimately compared.

Part II. Connections between the solubility of the compounds and pharmaceutical practice.

With the exception of N-4 succinyl-sulphonilamide, all the derivatives have been used in medicine. From the pharmaceutical viewpoint the necessity for a knowledge of the solubilities has been mentioned in the introduction, and the dosage is allied to their solubility and the danger of crystallisation in the body. For instance, sulphonilamide, with its relatively high solubility, is excreted rapidly. A high dose, 5 to 10 grammes per day for 2 to 3 days, has to be given, but there is not a serious danger of crystallisation in the urine. Sulphadiazine is excreted less rapidly than sulphathiazole, the solubility of the former being approximately one-sixty sixth of that of the latter at body temperature. In fact, sulphadiazine has such a low solubility that the urine must be kept alkaline and large quantities of liquid must be taken by the patient to prevent crystallisation. In the administration of sulphamerazine, with ten times the solubility of sulphadiazine at 35.5° C., the urine need not be alkaline.

TABLE V.

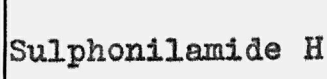
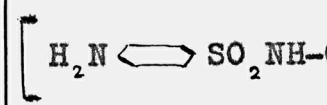
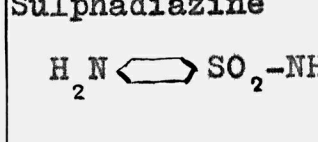
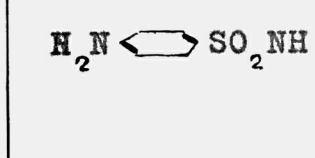
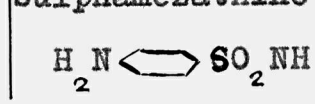
Substance and formula	Molecular Weight	ΔH cals/mole	Solubility at 20° C. G/100 mils.
Sulphonilamide 	172.2	5960	1.05
Sulphacetamide 	214.2	3970	0.89
Sulphaguanidine (as monohydrate) 	214.3	8570	0.233
Sulphapyridine 	249.2	14700	0.013
Sulphadiazine 	250.2	15260	0.00087
Sulphathiazole 	255.3	7650	0.113
Sulphamerazine 	264.3	9220	0.015
Sulphamezathine 	278.3	4400	0.091

TABLE V. (continued)

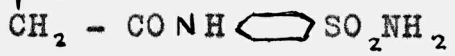
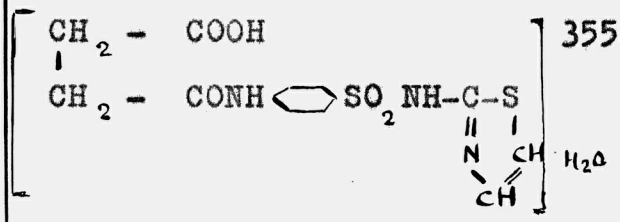
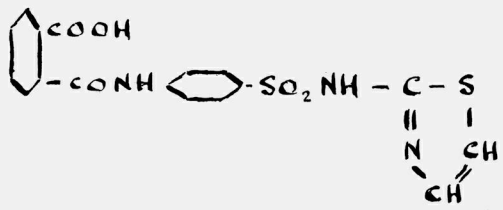
Substance and formula	Molecular Weight	Δ H cals/mole	Solubility at 20° C. G/100 mils.
N-4 Succinyl-sulphonilamide 	272	11460	0.079
Succinyl-sulphathiazole 	355.4	8850	0.047
Sulphathalidine 	403.3	10400	0.0019

TABLE VI.

Substance	Melting Point °C.	△ H cals/mole	Solubility at 20° C. G/100 mils.
Sulphonilamide	164.5 - 166.5	5960	1.05
Sulphacetamide	181 - 184	3970	0.89
Succinyl-sulphathiazole	188-195 (decomposes)	8850	0.047
Sulphaguanidine	190-192.5 (after drying at 110° C.)	8570	0.233
Sulphapyridine	191 - 193	14700	0.013
Sulphamezathine	196 - 199	4400	0.091
Sulphathiazole	200 - 203	7650	0.113
N-4 Succinyl-sulphonilamide	209 - 211	11460	1.079
Sulphamerazine	235-239 (decomposes)	9200	0.015
Sulphadiazine	252-256	15260	0.00087
Sulphathalidine	272-273	10400	0.0019

Part III. The influence of structure on solubility.

(a) Sulphonilamide and its ten derivatives (not sodium salts and Marfenil).

In a series of related compounds it is generally true to say that the larger the molecule the smaller the solubility. Theoretical calculations [33] and experimental measurements on the system benzene-diphenyl [34] and on a number of hydrocarbon mixtures [35-36] emphasise the extent to which the heat and entropy of solution depend on the difference in size of the molecules of the solute and solvent. Therefore, in Table V, for comparison purposes, the sulphonilamide derivatives are listed with their structures, molecular weights, heats of solution and solubilities at 20° C.

Also, the theory of ideal solubility leads to the expression

$$\log_{10} N = \frac{\Delta H_f}{2.303\ R}\left(\frac{1}{T_m} - \frac{1}{T}\right) \qquad (8)$$

where T_m and ΔH_f are the melting point and heat of fusion of the solute, T the temperature of the solution and N the mole fraction solubility. Table VI lists the melting points and solubilities of the derivatives. Of course, the relative solubilities of the different compounds

depends on the temperature chosen, in this case 20° C., owing to the different heats of solubility. However, graphs I to VI show that the order of increasing solubility is little changed over the temperature range within which aqueous solutions are possible.

There are 3 types of hydrogen atom in sulphonilamide, made up of 4 nuclear hydrogen atoms, 2 amino hydrogen atoms and 2 sulphamido hydrogen atoms. It has been found that replacement of the nuclear hydrogen atoms has no effect on the activity of the compound.

Table V shows that substitution in either the $-NH_2$ or $-SO_2NH_2$ groups results in a diminution in solubility which may be as much as over a thousandfold, and the compounds with the smallest substituents, e.g. sulphacetamide and sulphaguanidine have higher solubilities than those containing heterocyclic rings. A second substituted grouping, e.g. in sulphathalidine as compared with sulphathiazole, further lowers the solubility.

Equation ⑧ suggests that, in a series of compounds, if the heats of fusion are not too different, a solid with a higher melting point should be less soluble than one with a lower melting point.[19] Unfortunately there appears to be no data in the literature on the heats of fusion of the sulphonilamides. It can be seen from Table VI that, although the two compounds with the lowest melting points

(sulphonilamide and sulphacetamide) have the highest solubility and sulphadiazine and sulphathalidine, with the lowest solubilities have the highest melting points, there is little correlation in between. In fact, succinyl sulphathiazole and sulphaguanidine, with approximately the same melting point and even heats of solution, have very different solubilities. If equation ⑧ did apply, then the heat of solution should actually equal the heat of fusion and at the melting point of the substance, log N should equal zero. This condition is not fulfilled. Assuming ΔH is equal to ΔHf, at 165.5°C. for sulphonilamide using equation ④, $\log_{10} N = -1.484$ and for the other substances the value is even less at their melting points. In any case it seems very unlikely that ideal conditions are present owing to the highly polar nature of the solvent water.

Before looking more closely into the variation of solubility with the structure of the derivatives, it is necessary to consider the process of solution of the solid. Following Calvat and Sebille[37] two stages may be distinguished with water as a solvent. Firstly, absorption of some solvent into the lattice structure, an exothermic process, and secondly, the rapid destruction of this structure, giving the solution. This final process will, of course, be endothermic, and the total heat change

will be equal to the heat of solution ΔH. Since ΔH is positive, heat is absorbed during solution of any derivative investigated, as expected. In other words any heat liberated (ΔH_a) in the first process of solution is more than compensated for by a larger amount of heat absorbed (ΔH_d) in the second. The value of ΔH_a and ΔH_d will depend on the crystal structure of the substance, whether open enough for water molecules to penetrate inside easily; and the intermolecular forces between molecules in the crystal and molecules of the sulphonilamide and water. All these factors will be influenced by the molecular structure of the derivative.

Thus it is possible to discuss the connection between both the heat of solution and the solubility of the series of drugs and their formulae. However, ΔH and S are to a certain extent interconnected. For instance, from Tables V or VI, it appears that to some extent derivatives with high solubility have low ΔH_s and vice versa. So variations in both will be considered together.

All derivatives are weak acids except sulphaguanidine, which is basic only. However, sulphonilamide, sulphacetamide, sulphapyridine, sulphadiazine, sulphathiazole sulphamerazine and sulphamezathine contain both acidic and basic groups. No one appears to have measured the dissociation constants of these acids, and so it would be

unprofitable to attempt to find any connection between acidity or basicity and solubility. Sulphaguanidine has a higher solubility than the acid derivatives generally, but less than sulphacetamide of the same molecular weight. One point may be noted, however: N-4 succinyl- sulphonilamide and succinyl sulphathiazole, which can be considered as derivatives of succinic acid have comparable solubilities, while sulphathalidine, a derivative of phthalic acid is twenty to forty times less soluble.

The simplest molecules, sulphonilamide and sulphacetamide, have the two lowest heats of solubility. This might imply that less energy is required to break up the crystal lattice in these cases, than with the larger molecules, which might be partly coiled round each other in the solid state. Sulphathiazole, succinyl sulphathiazole and sulphathalidine show a progressive increase of ΔH, with increase in size of the side group attached in the para position to the $-SO_2NH-Th$ group. However, sulphaguanidine and succinyl sulphathiazole, though greatly different in size, have very much the same heats of solubility, 8570 as compared with 8850 cals.

Sulphadiazine is formed from sulphapyridine by the replacement of a -CH group by a nitrogen atom in the pyridine ring. This has little effect on the heat of solubility, which is relatively very high. Evidently the

crystal forces are strong; and probably the molecules are close-packed, owing to the symmetry of the two six-membered rings, and water molecules cannot penetrate the lattice easily. The substitution of a diazine for a pyridine ring, apparently does not affect this, but it does affect their solubilities. The solubilities of both are relatively low, but sulphadiazine is surprisingly about fifteen times less soluble than sulphapyridine.

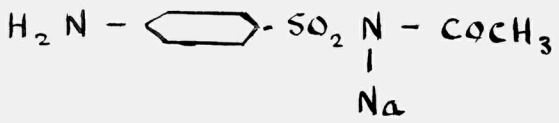
However, the change to a five-membered heterocyclic ring in sulphathiazole, as well as the substitution of a sulphur for a nitrogen atom, approximately halves the heat of solubility, while increasing the value of the solubility considerably. It is impossible to say whether one or both of the structural changes is the cause of the change in ΔH and S.

The most startling result, perhaps, is the large change in solubility and heat of solution by the introduction of one, and then two, methyl groups into the heterocyclic ring of sulphadiazine. ΔH drops from 15,260 to 4,400 cals/mole, while the solubility increases one hundred fold. The replacement of a hydrogen atom in a -CH group in a heterocyclic ring by $-CH_3$ does not generally change the physical or even the chemical properties of the compound to any great extent. It seems unlikely that the intermolecular forces in sulphadiazine,

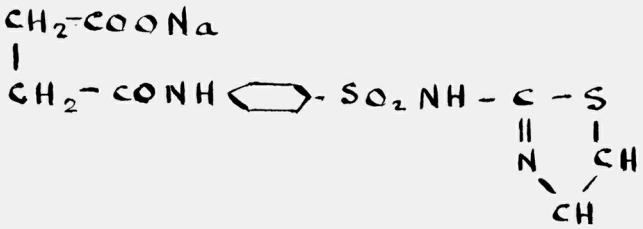
sulphamerazine and sulphamezathine are greatly different. Thus the effect on the heat of solution is probably due to steric hindrance. The introduction of one, and then two $-CH_3$ groups progressively disorders the close-packed structure. Water molecules can penetrate more readily as a preliminary to the easier breakdown and dissolution of the crystals.

(b) The Sodium salts, E.O.S. and Marfenil.

The sodium salts are formed by the replacement of the amido hydrogen atom by sodium, e.g. sulphacetamide sodium has the formula



except succinyl sulphathiazole sodium: formula



E.O.S. has the formula $NaSO_3 \cdot CH_2HN \langle\bigcirc\rangle SO_2NH_2$ while Marfenil is the hydrochloride $NH_2 \cdot CH_2 \langle\bigcirc\rangle SO_2NH_2 \cdot HCl$ The latter is in a class by itself. Owing to its being a strongly electrovalent compound (the formula should be written $NH_2 \cdot CH_2 \langle\bigcirc\rangle SO_2NH_3^+ Cl^-$), the crystal will

be ionic and the lattice energy very high. This accounts for the abnormally high heat of solution.

Tables III and IV show that the solubilities of the sodium salts are very much greater than the corresponding weak acids, but the variation in solubility is much less (only about four fold). This is not unexpected as substitution is in the basic structure of the acid radical. The heats of solubility are all less than those of the acids except in the case of sulphamezathine, and are also relatively low.

The sodium salts are to some extent ionic compounds and thus it would seem likely that the lattice forces in the solid would be stronger than in the corresponding parent compounds. The reduced heats of solution are, therefore, probably due to easy absorption of water molecules in the first stage of dissolution.

From the survey of structure in relation to solubility it is obvious that there can be no general correlation between any one property and ΔH or S. Many considerations must be taken into account in each case.

SUMMARY.

The solubilities in water of Phthalyl-sulphathiazole (sulphathalidine), 2(p-aminobenzene-sulphamide) pyrimidine (sulphadiazine), 2(p-aminobenzene-sulphamido)-4 methyl pyrimidine (sulphamerazine), 2(p-aminobenzene-sulphonilamido) pyridine (sulphapyridine), 2(p-aminobenzene sulphonamido) 4:6 dimethyl pyrimidine (sulphamezathine), 2(p-aminobenzene-sulphonamido) thiazole (sulphathiazole), 2(p-succinyl-aminobenzene-sulphonamide) thiazole (succinyl-sulphathiazole monohydrate), N-4 succinyl sulphonilamide, p-aminobenzene-sulphonyl-guanidine (sulphaguanidine monohydrate), p-aminobenzene- sulphonacetamide (sulphacetamide), p-aminobenzene-sulphonamide (sulphonilamide), seven sodium salts, and 4-amino-methyl-benzene-sulphonamide hydrochlorude (Marfenil) and p-ethyl, a-sodium sulphonate-aminobenzene sulphonamide (E.O.S.) have been determined by measuring the temperature of initial crystallisation for solutions of different concentrations.

It is found that the plots of $\log_{10}$ against $\frac{1}{T}$ where S is the solubility in grammes per 100 mils and T the absolute temperature are straight lines and heats of solubility of the compounds have been calculated. The constants a and b in the equation $\log_{10} S = a\left(\frac{1}{T}\right) + b$, and thus the solubilities at 20° C. and 35.5° C. have also been calculated.

The connection between the pharmaceutical action of the drugs and their solubility is discussed.

There is little correlation between the melting points of the derivatives and their solubilities.

Substitution in either the - NH_2 or $-SO_2NH_2$ groups results in a diminution in solubility which may be as much as a thousandfold, and generally the larger the molecule the smaller the solubility. To some extent derivatives with a high solubility have a low heat of solution and vice versa.

The variation in the heat of solubility is discussed from the point of view of the packing of the molecules in the crystal.

The sodium salts have a higher solubility and a lower heat of solubility than the parent compounds, though the variation in solubility is less (about fourfold).

There appears to be no general correlation between any one property and the heat of solution or solubility, but a number of factors must be taken into account.

REFERENCES.

1. P. Gelmo, J. Prakt. Chem., 77, 369 (1908)
2. G. Domagk, Klin. Wschr., 16, 1412 (1937) and Klin. Wschr., 21, 448 (1942).
3. R. H. Kiele and J. M. Sayward, J.A.C.S., 64, 2464 (1942).
4. N. V. Sapozhikova and I. V. Postovskii, J. Appl. Chem. U.S.S.R., 437 (1944).
5. W. G. Clark, E. A. Strakosch and N. I. Levitan, J. Lab. Clin. Med., 28, 188, 189 (1942).
6. E. Hug, Rev. Soc. Argentina Biol., 16, 662 (1940).
7. F. L. Rose, A. R. Martin and H. G. L. Bevan, J. Pharmacol., 77, 127 (1943).
8. D. R. Gilligan and N. Plummer, Proc. Soc. Expth. Biol. Med., 53, 142 (1943).
9. A. R. Frisk, G. Hagerman, S. Helander and B. Sjorgen, Gac. Med. Uraguay, 8, No. 80, 6, 17, 19 and No. 81, 9, 15, 23 (1947).
10. J. Druey and R. Meier Schweiz, Med. Wschr., 72, 316 (1942)
11. R. W. Barnes and G. K. Kawaichi, J. Orol., 49, 324-30 (1943)
12. H. A. Krebs and J. C. Speakman, B.M.J., I, 47 (1946).
13. E. Kruger-Thiemer, Arch. Dermatol. Syphilis, 183, 90 (1942).
14. H. Langecker, Arch. Expth Path. Pharmakol, 205, 291 (1948).
15. R. Becher and S. Leya, Experientia, 2, 459 (1946).
16. Meyer., Pharm. Weekblad, 76, 977 (1939).
17. F. H. Gutiemer, Anales fis y quin. (Madrid), 41, 537 (1945).
18. H. M. Burlage, J. Am. Pharm. Assoc. Sci. Ed., 37, 345 (1948).
19. J. H. Hildebrand and R. L. Scott, The Solubility of Non-electrolytes (3rd Ed.), Reinhold Publishing Co.

20. H. J. Prins, Rec. Trav. Chem., 42, 25 (1923).

21. J. Pastak, J. Chim. Phys., 26, 65 (1929).

22. C. N. Ruber and N. A. Spenser, Kgl. Norske Videnslab Selskabs Skifter, No. I, 38 pp. (1938).

23. A. Nossini, Boll. Chim. Farm., 77, 251 (1938).

24. G. L. Dorough, H. B. Glass, T. L. Graham, G. B. Malone and E. E. Reid, J.A.C.S., 63, 3100 (1941).

25. A. W. Ralston, C. W. Hoerr and L. T. Crews, J. Org. Chem., 9, 319 (1944).

26. C. W. Hoerr, H. J. Harwood and A. W. Ralston, J. Org. Chem., 9, 267 (1944).

27. F. M. Garland, C. W. Hoerr, W. O. Pool and A. W. Ralston J. Org. Chem., 8, 344, (1943).

28. A. W. Ralston and C. W. Hoerr, J. Org. Chem., 7, 546 (1942), II, 603 (1946).

29. A. W. Ralston, C. W. Hoerr and W. O. Pool, J. Org. Chem., 8, 473 (1943).

30. C. W. Hoerr, H. J. Harwood and A. W. Ralston, J. Org. Chem, 9, 102, 201 (1944).

31. E. Miller, H. J. Rock and H. L. Moore, J. Amer. Chem. Soc., 61, 1198 (1939).

32. I. Schroder, Z. Phys. Chem. II, 449 (1893).

33. See Reference 19, Chap. VII.

34. H. Tompa, J. Chem. Phys, 16, 292 (1948).

35. I. Prigogine & V. Mathot, J. Chem. Phys., 18, 765 (1950)

36. J. H. Van der Vaals and J. J. Hermans, Rec. Trav. Chim. 69, 949, 971 (1950).

37. E. Calvat and G. Sebille, Bull. Soc. Chim. de France, (5), 14, 286 (1947).

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