Summary

Since metagenin (Ia) and nogiragenin (IIa) have inherently 11α-hydroxyl group, both of them seemed to be the most convenient starting materials for the synthesis of cortical hormone intermediates. Several kinds of intermediates were prepared and during the course of the syntheses of them, an easy dehydration of the 11α-hydroxyl group was found.

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UDC 615.778.25-011 : 615.41-014 : 54-386

38. Keiji Ito and Keiji Sekiguchi: Studies on the Molecular Compounds of Organic Medicinals. II.*1 Application of the Solubility Product Principle and Consideration by the Phase Rule to the Solubility Phenomena of the Molecular Compound of Sulfanilamide and Sulfathiazole.*2

(*Faculty of Pharmaceutical Sciences, Hokkaido University**3)

Previously, the dissolution behavior of the molecular compound of sulfanilamide and sulfathiazole was investigated and it was observed that the compound dissociates to an appreciable extent into its components. Also, the stability constants were determined both at the stable and the metastable solubility equilibria. Validity of the assumption made for the determination was supported by the satisfactory agreement of the two constants.

In the present paper, solubility determination of the molecular compound is carried out in a series of aqueous solutions containing varying amounts of sulfanilamide in order to examine whether the solubility product principle can be applied to such a slightly soluble organic molecular compound. Based on this principle, a new method of calculating the value of the saturated concentration of the compound itself is proposed. Moreover, the influence of each one of the sulfonamides to the solubility of the other is investigated and the whole results are discussed by the phase rule.

Results and Discussion

Influence of Sulfanilamide on the Solubility of the Molecular Compound; Application of the Solubility Product Principle

So far as the solubility product principle is to hold in any saturated solution of the molecular compound, it can be shown that

$$L=[ST]_{sat}\cdot K'=[S][T] \qquad (1)$$

*1 Part I: This Bulletin, **13**, 405 (1965).

*2 This work was presented at the Hokkaido Branch Meeting of Pharmaceutical Society of Japan, Dec. 15, 1962.

*3 Kita-15-jo, Nishi-7-chome, Sapporo, Hokkaido, Japan (伊藤圭二, 関口慶二).

where L and K' are the solubility product and the equilibrium constant for dissociation; [S], [T] and $[ST]_{sat}$ are free sulfanilamide and sulfathiazole concentrations and the saturated concentration of the compound, respectively.

If the principle is applied to the incongruently saturated solution of the molecular compound in water, in which sulfathiazole must deposit as the second solid phase, [T] can be replaced by the solubility of sulfathiazole itself; hence the product is given by

$$L=[(\text{total concn. of sulfanilamide})-(\text{total concn. of sulfathiazole})+(\text{solubility of sulfathiazole})]\times(\text{solubility of sulfathiazole})$$

where all the values in brackets can be determined experimentally. Thus, L at 25° is computed at 8.654×10^{-6} from data in the preceding paper.

When the compound is congruently saturating in an aqueous sulfanilamide solution, equation (1) becomes

$$L=(a+x)\cdot x \qquad (2)$$

in which a is the concentration of sulfanilamide originally added; x is the concentration of each sulfonamide derived from the compound dissociated. Since L is known and a can be arbitrarily fixed, x will be calculated; so that the solubility of the compound in such a solution will be expressed by the sum of x and $[ST]_{sat}$.

In order to examine the limit of applicability of the principle, calculated solubilities of the molecular compound at 25° in a series of sulfanilamide solutions are given in Table I together with the total concentration of sulfathiazole determined experimentally. Also, in Fig. 1, observed concentrations of both total sulfonamides are plotted against the original concentrations of sulfanilamide and are compared with the theoretical ones.

When the original concentration of sulfanilamide is less than $2.874\times10^{-3}M$, so that x exceeds the solubility of sulfathiazole ($1.837\times10^{-3}M$), the total sulfathiazole in the fifth column of the table will become the metastable solubility of the molecular compound and the excess sulfathiazole will deposit soon or later to attain the stable equilibrium where both sulfonamide concentrations are completely fixed to the values obtained with the incongruently saturated solution of the compound in water. As is expected, experimental results in this range of concentrations differ much from the calculated ones. However, the product of both free sulfonamide concentrations, each of which is obtained as the difference between the observed total concentration and $[ST]_{sat}$ ($0.231\times10^{-3}M$) is found essentially identical with the L value above. The facts will indicate that the system is in the stable solubility equilibrium (No. 1) or still in a stage from the metastable to the stable solubility equilibrium, even by stirring for 12 hours. The actual difficulty to reach the final equilibrium will be attributed not only to the stability of the metastable state but to the fact that the increase in free sulfanilamide must be supplied by further dissolution of the molecular compound, and hence the deposition of sulfathiazole occurs still more slowly. In this connection, it is noticed that the closer is the original concentration of sulfanilamide to the limiting value of $2.874\times10^{-3}M$, the longer the metastable saturation persists. At the closest concentration adopted in the experiment (No. 4 in Table I), no change to the stable equilibrium was observed until after 9 hours. In a special case where $a=0$, the metastable solubility of the molecular compound at 25° is given by $[ST]_{sat}+\sqrt{L}$ and is computed at $0.231\times10^{-3}+\sqrt{8.654\times10^{-6}}=3.173\times10^{-3}M$. This theoretical value agrees well with the experimental results obtained previously at the congruent saturation of the compound in water.

TABLE I. Solubilities of the Molecular Compound in Aqueous Sulfanilamide Solutions at 25°: Calculated Values based on Solubility Product Principle and Experimental Results obtained after Stirring for 12 hours

No. of S soln. used	Molar concn. × 10^3					
	Original concn. of S: a	Calcd.			Exptly. obsd.	
		Dissocd. mol. compd.: x	Total S: $a+x+[ST]_{sat}$	Soly. of mol. compd: Total T: $x+[ST]_{sat}$	Total S	Total T
1	0	2.942	3.173	3.173	4.942	2.068
2	0.581	2.664	3.476	2.895	4.500	2.229
3	1.161	2.417	3.809	2.648	4.030	2.444
4	1.742	2.197	4.170	2.428	4.175[a]	2.432[a]
					4.233	2.381
5	2.903	1.828	4.962	2.059	4.964	2.037
6	4.065	1.544	5.840	1.775	5.830	1.766
7	5.807	1.230	7.268	1.461	7.230	1.472
8	11.614	0.702	12.547	0.934	12.653	1.003
9	17.421	0.483	18.135	0.714	17.525	0.650
10	23.228	0.367	23.826	0.598	22.751	0.646
11	29.034	0.295	29.560	0.526	28.285	0.554
12	34.841	0.246	35.318	0.477	34.632	0.501
13	>41.719[b]	0.206	42.156	0.437	41.345[c]	0.488[c]

S, T and ST represent sulfanilamide, sulfathiazole and the molecular compound, respectively, and $[ST]_{sat}$ is $0.231\times10^{-3}M$.

a) results obtained after stirring for 9 hrs.

b) The final soln. gives the one satd. with both sulfanilamide and the mol. compd.

c) The satd. soln. of sulfanilamide was used.

When the original sulfanilamide concentration is higher than $2.874\times10^{-3}M$; hence the solubility of sulfathiazole becomes greater than x, no solid sulfathiazole appears in the residue and accordingly, its total concentration in the solution will give the stable solubility of the molecular compound. Analogous to the common ion effect, the solubility of the compound decreases gradually with the increase of sulfanilamide concentration in the original solution until finally the solution is saturated with both the compound and sulfanilamide. At comparatively low concentration of the original sulfanilamide (No. 5~7), experimental results are in satisfactory agreement with the calculated ones. When the concentration is increased, much more sulfanilamide is involved in the solution as compared with sulfathiazole; hence, accurate determination of both components becomes more difficult. Also, the ignorance of the activity coefficients of freely dissolved sulfanilamide will exert some influence upon the results. By these reasons, differences between the experimental and the theoretical

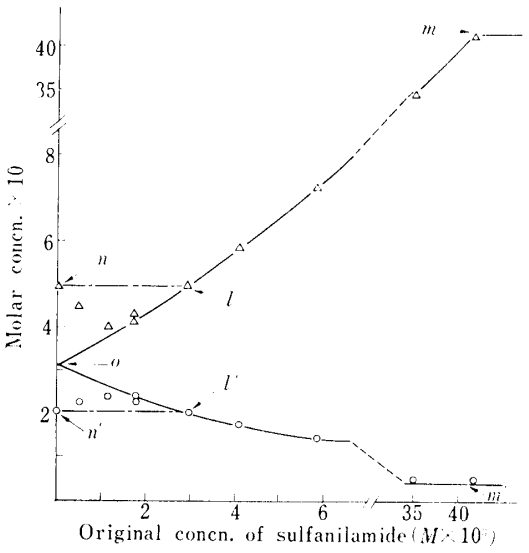

Fig. 1. Observed Total Concentrations of Sulfanilamide (triangles) and of Sulfathiazole (circles) plotted against the Original Concentration of Sulfanilamide

curves *o-m'* and *o-m*: theoretical curves for total sulfathiazole (soly. change of the mol. compd.) and sulfanilamide, respectively; *o-l'*: metastable soly. change

horizons *m'-* and *m-*: total sulfathiazole and sulfanilamide in the satd. soln. of both sulfanilamide and the mol. compd., respectively; *n'-l'* and *n-l*: the ones in the incongruently satd. soln. of the mol. compd.

data become more evident and amount up to even 10%. Although the discrepancies can not completely be neglected, if these sources of error are taken into consideration, it will certainly be admitted that the applicability of the solubility product principle is proved.

Application of a New Method for Evaluating the Saturated Concentration of the Molecular Compound

Although in the studies of complex formation in solution, the solubility increase of a slightly soluble compound due to addition of a solubilizer has been regarded as the concentration of the "complex" or the molecular compound formed,[1] the treatment is not suitable for the system under investigation, because the solubility equilibrium between the two components is practically difficult to attain. As is seen in the previous paper, the experimental difficulty will be largely eliminated by using the isolated molecular compound; however, unless it is incongruently saturated, its concentration can never be evaluated by solubility measurement alone. For these reasons, an alternative method which is based on the solubility product principle is proposed, and its applicability to the present system is examined.

When the molecular compound is either congruently or incongruently saturating in an aqueous sulfanilamide solution, concentrations of both free sulfonamides are given by

$$\left.\begin{aligned}[S]&=\text{total sulfanilamide}-[ST]_{sat}\\ [T]&=\text{total sulfathiazole}-[ST]_{sat}\end{aligned}\right\} \qquad (3)$$

Combination of equations (1) and (3) leads to

$$Y=X\cdot[ST]_{sat}+(L-[ST]_{sat}^{2}) \qquad (4)$$

where Y and X are the product and the sum of both total sulfonamide concentrations. If $[ST]_{sat}$ can be assumed to be constant at a certain temperature, the value of L will also become constant; therefore, it follows from equation (4) that there is a linear relationship between Y and X. The slope of the line gives the value of $[ST]_{sat}$ and the solubility product can be computed from Y-intercept.

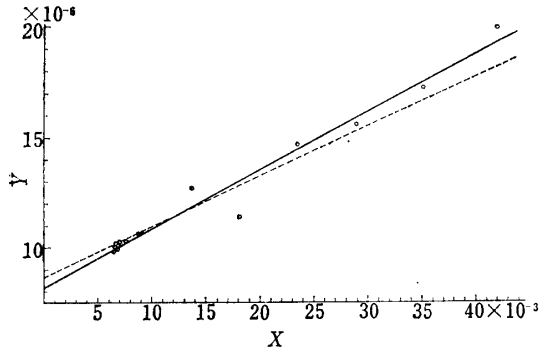

Fig. 2. (Total Sulfanilamide × Total Sulfathiazole) plotted against (Total Sulfanilamide + Total Sulfathiazole)

The slope of this line gives $[ST]_{sat}$, and the L-value is computed from Y-intercept.
circles and full line: obtained from exptl. data in Table I;
$Y=(0.2693\times10^{-3})\cdot X+8.1940\times10^{-6}$
dotted line: introduced by $[ST]_{sat}$ and L at incongruent satn. of the mol. compd.;
$Y=(0.231\times10^{-3})\cdot X+8.601\times10^{-6}$

Using the experimental data in Table I, the two variables are computed and the results are plotted in Fig. 2. By the method of least squares, an equation expressed by

$$Y=(0.2693\times10^{-3})\cdot X+8.1940\times10^{-6}$$

is obtained and is shown by the full line. Thus, the saturated concentration of the molecular compound itself and the solubility product at 25° are given by

$$[ST]_{sat}=0.2693\times10^{-3}M, \qquad L=8.2665\times10^{-6}.$$

These values agree fairly well with the

1) R. Labe, H. Rutenbeck: Arch. exptl. Pathol. Pharmakol., **169**, 557 (1933); T. Higuchi, D. A. Zuck: J. Am. Pharm. Assoc., **42**, 138 (1953).

corresponding ones obtained at incongruent saturation of the molecular compound ($0.231\times10^{-3}M$, 8.654×10^{-6}). The fact will suggest that the method can in general be adopted for the evaluation of the saturated concentration of a slightly soluble molecular compound formed between two organic compounds.

Influence of One Sulfonamide to the Solubility of the Other

Concentrations of sulfathiazole in various sulfanilamide solutions were measured after stirring for 12 hours at 25°. As shown in Fig. 3, all of them lie below the theoretical curve consisting of an ascending line between the solubility of sulfathiazole and the point of incongruent saturation of the molecular compound and a horizon. It was also observed that when the original concentration of sulfanilamide is more than that at the incongruent saturation, no solid molecular compound appears in the residue. Since in this case, the coating effect by the compound does not occur, these facts will indicate that the solubility equilibrium becomes difficult to attain by slow dissolution of sulfathiazole in the presence of sulfanilamide. For this reason, if Higuchi's approach to evaluate the concentration of the "complex" is applied to such a system, erroneous results will be obtained.

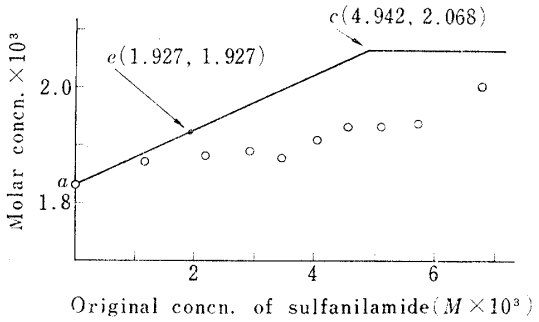

Fig. 3. Influence of Sulfanilamide on the Solubility of Sulfathiazole at 25°

circles: results obtained after stirring for 12 hrs.
full line: obtained theoretically
points *a*, *c* and *e*: corresponds to those in Fig. 4

The curve *b*-*d* in Fig. 4 shows the solubility change of sulfanilamide in sulfathiazole solutions. Since the solubility increases only slightly as compared with that of sulfanilamide itself, precise determinations of both components will become all the more difficult. Therefore, the results obtained in such experimental conditions as above can not be used for the quantitative investigation of "complex" formation.

Change of Solid Phases in the System of the Molecular Compound and Water

When the molecular compound is dissolved into water, appearance or disappearance of solid phases and the kinds of them at the stable equilibrium depend on the relative amount of the compound. Up to a certain limit where free sulfathiazole concentration is equal to the solubility of sulfathiazole, the compound dissolves completely and a clear solution is obtained. Once the added amount increases over the limit, excess of sulfathiazole caused by dissolution and successive dissociation of the molecular compound must deposit. The total concentration of either sulfonamide at which solid sulfathiazole begins to appear is given by

$$\begin{aligned}&\text{total concentration of sulfanilamide or sulfathiazole}\\&=\text{solubility of sulfathiazole}+[\mathrm{ST}]\\&=\text{solubility of sulfathiazole}+K\times(\text{solubility of sulfathiazole})^2\end{aligned}$$

where [ST] and K are the concentration of the molecular compound and the stability constant, respectively. Since the solubility of sulfathiazole at 25° expressed by molarity is $1.837\times10^{-3}M$ and $K=26.7$, [ST] is calculated at $1.927\times10^{-3}M$. The amount of the compound necessary to cause deposition of sulfathiazole is therefore more than 0.0824 g. per 100 ml.

By further addition of the molecular compound, excess of it remains undissolved and the solution becomes saturated with both sulfathiazole and the compound. As the

total concentration of sulfanilamide at the incongruent saturation was measured previously as $4.942\times10^{-3}M$(also that of sulfathiazole was $2.068\times10^{-3}M$), the amount of the molecular compound required to separate the two solid phases is 0.2113 g. per 100 ml. Thus, the composition of the solution at equilibrium should be fixed beyond this amount.

Experimental results obtained when various amounts of the molecular compound were added into 100 ml. of water are shown in Table II. Similarly as the above theoretical considerations, no solid sulfathiazole was detected until the amount of the compound exceeds the first limit. In the range from this amount to that at the incongruent saturation, only one solid phase of sulfathiazole was observed; however, its concentrations are a little more than the theoretical values given by the line *e-c* in Fig. 3. These discrepancies will be attributed to the incomplete deposition of sulfathiazole, since it is formed by decomposition of the compound once passed into solution.

When the more molecular compound was added, it appeared in the solid residue along with sulfathiazole. In this case, the observed concentrations of both total sulfonamides were found somewhat less than those at the stable equilibrium except when the amount of the compound exceeds about twice that required for incongruent saturation. This will presumably be ascribed to the fact that with a small excess of the compound, the surface available for dissolution becomes much restricted by the coating effect of sulfathiazole deposited onto the compound and as the result, the attainment of the final equilibrium becomes more time-consuming.

Table II. Change of Solid Phases in the Molecular Compound and Water System

Sample No.	Used amount of ST, g. per 100 ml. of water	Total S, $M\times10^3$	Total T, $M\times10^3$	Solid phase[a)]
1	0.0186	0.423	0.423	absent
2	0.0506	1.167	1.171	〃
3	0.0801	1.899	1.853	〃
4	0.0902	2.090	2.037	T
5	0.1276	3.002	2.076	〃
6	0.1538	3.531	2.088	〃
7	0.1993	4.181	2.115	〃
8	0.25	4.715	1.986	T and ST
9	0.3	4.884	2.009	〃
10	0.4	4.947	2.060	〃
11	0.5	4.930	2.068	〃
12	0.7	4.942	2.068	〃

S, T and ST represent sulfanilamide, sulfathiazole and the molecular compound, respectively.
a) identified by IR spectra

Consideration of the Ternary System of Sulfanilamide, Sulfathiazole and Water by the Phase Rule

In Fig. 4, the phase diagram of the system was constructed in which the composition of each component was expressed by per cent weight by weight. In the case of the system composed of the molecular compound and water, the composition of the solution and the kinds of solid phases are given by triangles. As discussed above, those between the point *e* and *c* represent slighthly supersaturated solutions obtained when the amounts of the compound are large enough to separate sulfathiazole only. The theoretical composition where a trace of sulfathiazole begins to deposit is shown by the point *e*. The triangle *c* represents an invariant point where the solution is stably saturated with both sulfathiazole and the molecular compound, while the one

at c' gives the metastable solubility of the compound itself which appears in the initial period of dissolution.*[1]

The crosses in the figure are the concentrations of both sulfonamides observed by dissolving excess sulfathiazole into solutions containing varying amounts of sulfanilamide. Because sulfathiazole is not saturated in the resultant solutions under the experimental conditions, the theoretical saturation curve of the sulfonamide a-c is expected to lie between the arrays of crosses and the triangles in the range from e to c.

The curve b-d drawn through the solid circles which are the results when excess amounts of sulfanilamide are added into sulfathiazole solutions can be regarded as the approximate solubility curve for sulfanilamide. In this connection, the solid phase in contact with the solutions is not sulfanilamide itself but is identified to be its hydrate containing one mole of water. The point d is also invariant since the solution co-exists with the hydrate and the molecular compound.

When the solutions are in equilibrium with the molecular compound, compositions of them are represented by open circles. By joining these circles, the saturation curve of the compound is obtained. As mentioned previously, the curve is composed of two parts; the one between the two invariant points c, d gives the stable saturation curve, while that extended from c to c' shows the metastable one. Thus, the system belongs to the type in which a one-to-one molecular compound of the two components is formed but is decomposed by water.

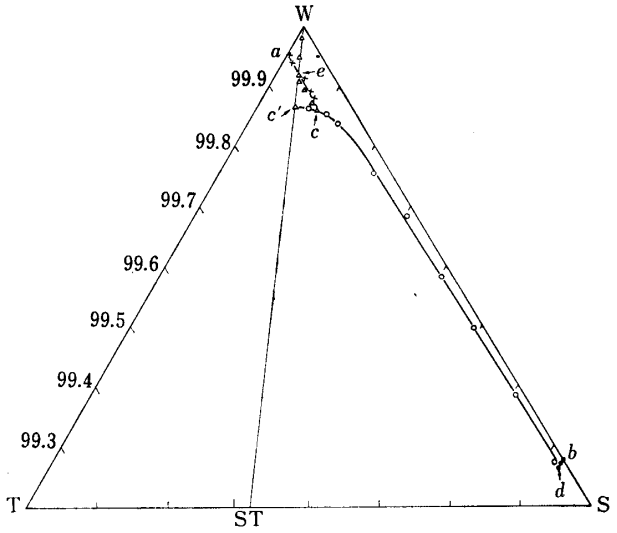

Fig. 4. Phase Diagram for Sulfanilamide, Sulfathiazole and Water System

points a and b: solubilities of sulfathiazole and sulfanilamide, respectively; c: composition of the soln. in which the mol. compd. is incongruently saturating; c': composition of the metastably satd. soln. of the mol. compd. in pure water; e: composition of the mixture of the mol. compd. and water where the solid sulfathiazole begins to deposit; d: composition of the soln. in which the soln. co-exists with both solids of the mol. compd. and sulfanilamide hydrate.

Experimental

Materials——Sulfanilamide, sulfathiazole and the molecular compound were the same as those in the preceding paper. Particles of them were arranged between 100 and 200 mesh by sieving.

Determination of Sulfanilamide and Sulfathiazole——The method is the same as described in Part I.

Procedure for Solubility Studies——The experiments concerning the influence of sulfanilamide on the solubility of the molecular compound or sulfathiazole were carried out by adding 0.7 g. of the compound or 0.4 g. of sulfathiazole into 100 ml. of sulfanilamide solution of which concentration was varied systematically. Also, the influence of sulfathiazole on the solubility of sulfanilamide was investigated by adding 1.5 g. of sulfanilamide to 100 ml. of sulfathiazole solution. Agitation by an electric stirrer was applied to the mixture for 12 hrs., and the temperature was always maintained at $25 \pm 0.05°$. The other procedure was similar as that in Part I.

The authors express their hearty gratitude to Prof. Dr. H. Nogami of the University of Tokyo for the great encouragement throughout this work.

Summary

Solubilities of the molecular compound of sulfanilamide and sulfathiazole in aqueous solutions containing varying amounts of sulfanilamide were determined. It was found from the results that the solubility product principle can be applied to such mixtures. Based on the principle, a method for calculating the value of the saturated concentration of the compound was proposed.

Besides, the influence of each one of the sulfonamides to the solubility of the other was investigated. Using all these data, the phase diagram of the system of sulfanilamide, sulfathiazole and water was constructed which indicates that the system belongs to the type where a one-to-one molecular compound is formed but is decomposed by water. It was also confirmed that the metastable solubilities of the compound observed in water and in the sulfanilamide solution can be represented by the points on the extention of the saturation curve of the molecular compound in the diagram.

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UDC 547.314.04 : 547.92.07 : 615.76

39. Tetsuo Hiraoka and Issei Iwai : Studies on Acetylenic Compounds. XLII.*1 Total Synthesis of Estrone by the Double Cyclization of Acetylenic Compounds.*2

(*Central Research Laboratories, Sankyo Co., Ltd.**3)

Recently much attention has been focused on the total synthesis of 19-nor-steroids from an industrial standpoint since useful pharmacological activities of 19-nor-steroids have been found. Hughes and Smith[1] succeeded in the synthesis of estrone by a very short route which greatly contributed to its industrialization.[2] These kinds of approaches was followed by Torgov, *et al.* who skillfully synthesized estrone starting from methoxy-tetralone.[3] The successive notable total synthesis on the industrial scale was developed by Velluz, *et al.* who resolved a racemic intermediate in an earlier stage.[4] Even in 1964 the total syntheses of steroidal skeletons were a target for

*1 Part XLI : I. Iwai, J. Ide : This Bulletin, **13**, 663 (1965).

*2 Presented at the 8th annual simposium of the Chemistry of the Natural Products (Nagoya, Japan) (1964).

*3 Hiromachi, Shinagawa-ku, Tokyo (平岡哲夫, 岩井一成).

1) G. A. Hughes, H. Smith : Proc. Chem. Soc., **1960**, 74; *Idem* : Chem. & Ind., **1960**, 1022; H. Smith, G. A. Hughes, *et al.* : J. Chem. Soc., **1963**, 5072; H. Smith, G. A. Hughes, *et al.* : *Ibid.*, **1964**, 4472, 4492.

2) Chem. Eng. News, Aug. 26, 1963, Page 32; *Ibid.*, March 2, 1964, Page 42.

3) S. N. Ananchenko, I. V. Torgov : Dokl. Akad. Nauk. S. S. S. R., **127**, 553 (1959); *Ibid.*, **135**, 73 (1960); Tetrahedron Letters, **1963**, 1553; *Ibid.*, **1964**, 171; V. E. Limanov, S. N. Ananchenko, I. V. Torgow: Izvest. Akad. Nauk. S. S. S. R., Ser. Khim, **1964**, 1814; K. K. Koskoev, S. N. Ananchenko, A. V: Platonov, I. V. Torgov : Izvest. Akad. Nauk. S. S. S. R., Otdel. Khim. Nauk., **1963**, 2058; I. V. Torgov, T. I. Sorkina, I. I. Zaretskaya : Angew. Chem., **76**, 794 (1964); A. V. Zakharychev, S. N. Ananchenko, I. V. Torgov : Steroids, **4**, 31 (1964).

4) L. Velluz, G. Nominé, J. Mathieu : Angew. Chem., **72**. 725 (1960); L. Velluz, G. Nominé, J. Mathieu, E. Toromanoff, D. Bertin, J. Tessier, A. Pierdet : C. R. Hebd. Seances Acad. Sci., **250**, 1084 (1960); L. Velluz, G. Nominé, E. Toromanoff, D. Bertin, R. Bucourt, J. Tessier : *Ibid.*, **250**, 1293 (1960); L. Velluz, G. Nominé, J. Mathieu, E. Toromanoff, D. Bertin, M. Vignau, J. Tessier : *Ibid.*, **250**, 1510 (1960); L. Velluz, G. Nominé, G. Amiard, V. Torelli, J. Cérede : Compt. rend., **257**, 3086 (1963).