

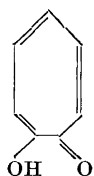
Studies in the Tropolone Series

I. Thujaplicins and Nootkatin

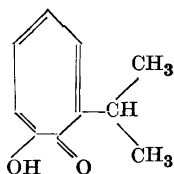
GUNHILD AULIN-ERDTMAN

*Cellulosaindustriens Centrallaboratorium and Organisk-Kemiska Institutionen,
Kungl. Tekniska Högskolan, Stockholm, Sweden*

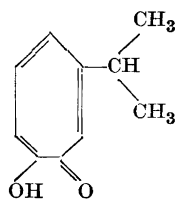
The cycloheptatrienolone (I), for which Dewar¹ proposed the name tropolone, was unknown until quite recently. However, two different syntheses of the substance have now been reported^{2,3} as well as some of its properties, *e. g.* ultra-violet absorption maxima.



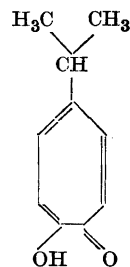
(I)



(II)

 α -

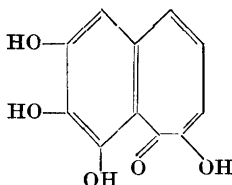
(III)

 β -

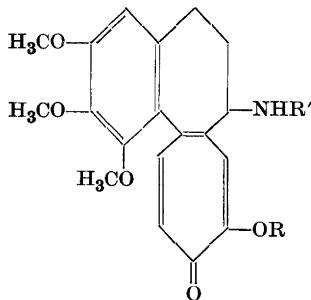
(IV)

 γ -thujaplicin

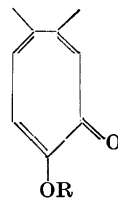
Tropolone forms part of the structure of several compounds of established constitution: the thujaplicins (II—IV)⁴⁻⁶, stipitatic and puberulic acid (*cf.* Part II), purpurogallin (V)⁷ and colchicine (VI, R = CH₃, R' = COCH₃)⁷⁻⁸, as well as derivatives and degradation products of these compounds, *e. g.* β -methyl-tropolone (III, —CH₃ instead of —CH(CH₃)₂)⁹. Recent members of the series which have been synthesised are 3,4-benz-tropolone¹⁰ and 4,5-benz-tropolone¹¹.



(V)

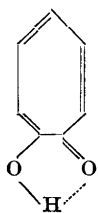


or

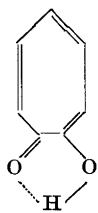


(VI)

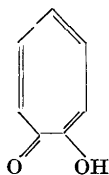
As Dewar pointed out¹, the ring system (I) represents a new type of "aromatic" structure of considerable theoretical interest. Its character was originally¹ explained by Dewar as depending upon resonance chelation (A). Later, however, he considered¹² that a hydrogen bridge is improbable in this case because it would mean a stretching of the O—H bond. Instead of the



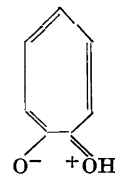
⇌



(A)



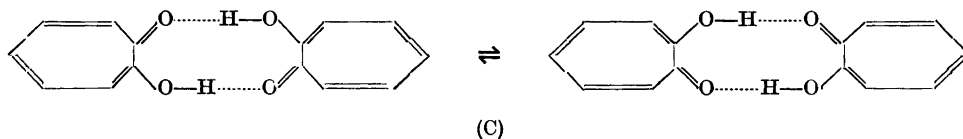
⇌



(B)

mesomerism (A) he therefore suggested a system of easily interconvertible tautomeric forms, each of which shows an ionic type of resonance (B). However, the latter explanation is also somewhat unsatisfactory, because the high water solubility of colchicine in contrast to for example colchicine (VI, R = H, R' = COCH₃) "is better explained if in it (colchicine) alone an ionic resonance (implying a semi-zwitterion structure) occurs"¹².

In an interesting study of the infra-red absorption properties of some tropolones Scott and Tarbell¹³ found a considerable displacement of the CO bond of these substances as compared with simple ketones. This displacement was explained as an effect of conjugation with the unsaturated ring rather than of chelation through a hydrogen bond. However, a decision between these alternatives could not be made.



A double molecule mesomerism (C), therefore, appeared to be worth consideration, even though the ring formed would be very wide. The molecular weight has not been determined — with one or very few exceptions — for any tropolone derivatives possessing the intact, “sterically unhindered” “ol-one” grouping. Abnormally high values were found by Zeisel and von Stockert¹⁴ in 1913 for trimethyl colchicic acid (VI, R = R' = H) in *acetic acid* solution (found 427—468, calc. 343). (The high molecular weights found by the same authors for colchicine and colchiceine were explained as depending upon associations involving the —NHC₂H₅ group.)

The molecular weight of β -thujaplicin has now been determined cryoscopically in benzene solutions of two different concentrations. In both cases, however, the values obtained coincide within a few per cent with the value calculated for the monomer (0.623 molal solution, depression 2.85°, mol. wt. 176; 0.155 molal solution, depression 0.72°, mol. wt. 173; calc. 164). It should be noted that, in the case of *e. g.* benzoic acid in benzene, these concentrations would have been high enough to cause nearly complete association as double molecules.

It is clear, therefore, that tropolone units do not associate in solution to any considerable extent. Some other explanation must be found for the high molecular weight reported for trimethyl colchicic acid in acetic acid solution.

As already mentioned, the question whether an intramolecular hydrogen bond occurs in the tropolone structure has not yet been definitely answered. Various properties of tropolones, *e. g.* the steam volatility of the thujaplicins⁶, point more or less strongly towards the existence of a hydrogen bridge. It is a well-known fact that hydrogen involved in chelate rings dissociates less easily than would be expected in the case of no hydrogen bonding. A good example is found in the pK value of 8.8 for 1-hydroxy-anthraquinone, and 5.7 for the 2-hydroxy compound in 96 per cent ethanol¹⁵.

With regard to this question it is of interest to note that the acidity of tropolone itself corresponds to pK 6.7² or 6.95³. A potentiometric titration curve for β -thujaplicin is shown in Fig. 1, giving the pK value of approximately 7.0. However, in the case of the tropolones it is difficult to find suitable model substances for a comparison of the acidity. The following may serve for this purpose:

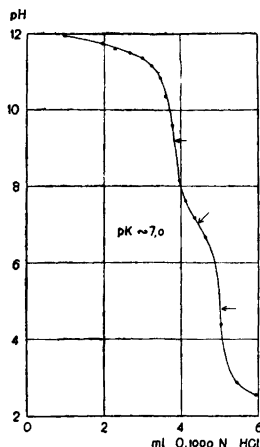


Fig. 1. Potentiometric titration of β -thujaplicin, dissolved in excess sodium hydroxide solution.

Substances with hydrogen bonds:	Salicylaldehyde ¹⁶	pK	8—9
	$\text{CH}_3\text{—C(OH) = CH—CO—CH}_3$ ¹⁷		8
Substances without hydrogen bonds:	Benzoic acid		5
	2,5-dihydroxy-benzoquinone ¹⁸		3 and 5
	(Phenol, catechol)		10)

It is seen by comparison that the tropolones — with pK around 7 — take an intermediate position between the two groups.

Besides the ultra-violet absorption maxima given for tropolone itself ^{2,3}, spectra in the ultra-violet have been reported for the thujaplicins by Erdtman and Gripenberg ⁴, for stipitatic and puberulic acid by Todd and co-workers (*cf.* Part II), and for purpurogallin and some of its derivatives by Haworth *et al.* ⁹, neutral solvents being used in all cases. The tropolone colchiceine (VI, R = H, R' = COCH₃) has been investigated both in neutral and alkaline solutions ¹⁹. The acidic — “semi-phenolic” — properties of the molecule give rise to a bathochromic shift of the absorption spectrum on proceeding from a neutral to an alkaline medium.

The main purpose of these ultra-violet absorption studies was to demonstrate structural similarities between the members of each group of substances. A discussion of the tropolone system itself from the point of view of U. V. spectrochemistry, however, is still missing although highly desirable on account of the general analogy between phenols and tropolones.

In the present paper spectra are given for the thujaplicins in *n*-heptane and alkaline water solutions. In a separate note a similar investigation of a new natural compound, nootkatin, is described.*

* *Cf.* second note on page 1035.

EXPERIMENTAL

The α -thujaplicin specimen * used was purified by distillation *in vacuo*, recrystallisation from *n*-heptane and redistillation, m. p. 33–33.5° (literature⁵ 34°). The β - and γ -thujaplicin samples were distilled *in vacuo* and recrystallised from *n*-heptane and light petroleum respectively. M. p. for the β -compound 51–51.5° (lit.⁶ 52–52.5°); for the γ -compound 79–79.5° (lit.⁴ 82°).

Solvents: *n*-heptane, purified for spectrophotometric purposes²⁰, and an aqueous phosphate buffer solution with pH 12.

The measurements were carried out with a Beckman Model DU spectrophotometer, using calibrated cells. The alkaline solutions of the thujaplicins are somewhat unstable, the absorption in the long wave portion of the spectra (round 400 $m\mu$ and above) tending to increase. In these cases, therefore, the absorption was determined soon after preparing the solutions (within an hour or less).

RESULTS AND DISCUSSION

The absorption spectra for the thujaplicins in heptane solution are shown in Fig. 2. Their mutual resemblance is great, except for slight differences in the ϵ -value for the symmetrical γ -compound, and the long wave part of the β -compound curve occurring at somewhat shorter wavelengths than the others. It could be expected that tropolone itself would show a spectrum similar to those of the thujaplicins. By analogy with the known difference between the absorption of benzene and its alkyl derivatives, however, the tropolone spectrum must be expected to occur at somewhat shorter wavelengths, the maxima being a little lower and more distinct than those of the thujaplicins. No spectrum of tropolone in a saturated hydrocarbon solvent has yet been published. von E. Doering and Knox² did not state which solvent they employed, and Cook and co-workers³ used ethanol. The data of the latter authors, however, fit in rather well with the values expected on the basis of the ethanol spectra of the thujaplicins⁴. **

* My thanks are due to Professor H. Erdtman and Dr. J. Gripenberg for providing samples of the thujaplicins.

** Note added in the proof (September 8th, 1950):

Thanks to the courtesy of Professor J. W. Cook, Glasgow, the author is able to include the absorption spectrum of tropolone in cyclohexane (Fig. 2) as determined in Glasgow by Mr. A. R. M. Gibb. The solvent used was "cyclohexane for spectroscopic purposes", supplied by British Drug Houses. Regions above 250 $m\mu$ were examined with the Hilger "Spekker" Quartz Spectrophotometer, slit width 0.03 m. m., match points being found with a microphotometer. For the region below 250 $m\mu$, the Unicam spectrometer was used.

The tropolone spectrum is in good agreement with the expected curve, keeping in mind the greater resolving power of the "Spekker" spectrophotometer as compared with the Beckman instrument.

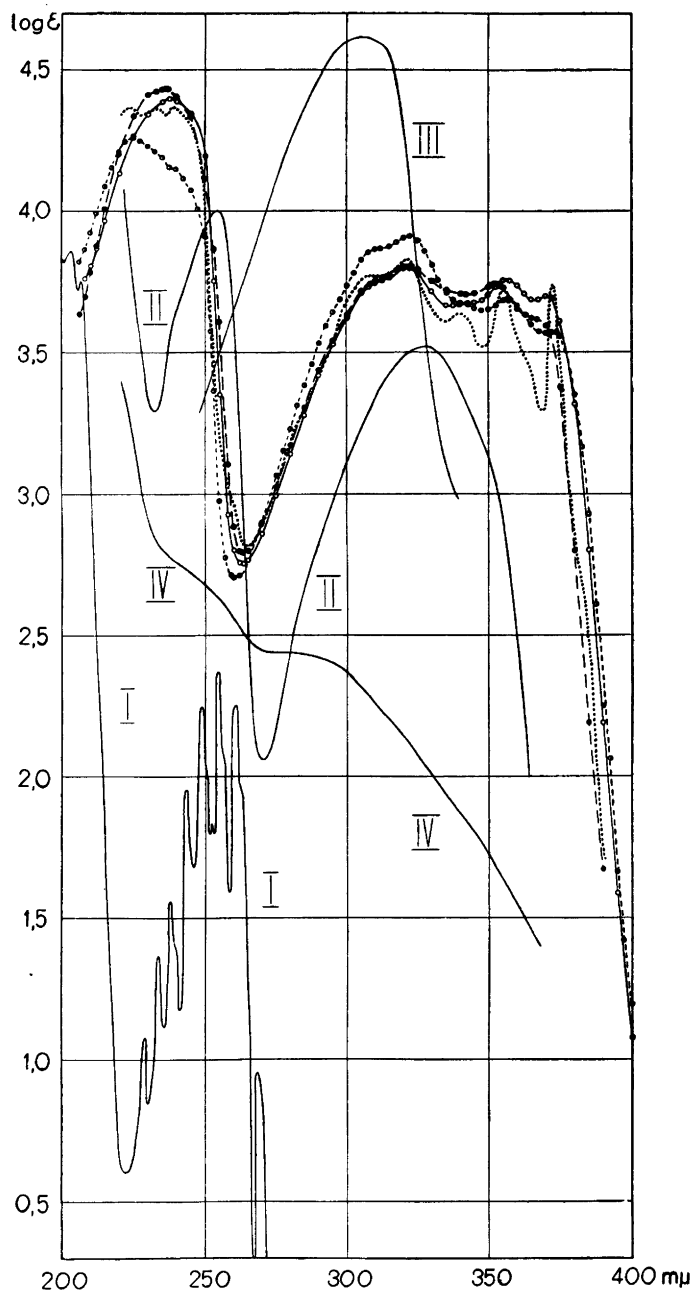


Fig. 2. Ultra-violet absorption spectra for α -thujaplicin (O—O—O), β -thujaplicin (●—●—●), and γ -thujaplicin (○—○—○), all in *n*-heptane, benzene in pentane²¹ (I), salicylaldehyde in hexane²² (II), octatrienal in hexane²³ (III), and cyclooctatetraene in cyclohexane²⁴ (IV). Dotted line: tropolone in cyclohexane (cf. note on page 1035).

The absorption of the thujaplicins in heptane differs only slightly from that in ethanol. Being a polar solvent, ethanol causes a smoothing of the curves and also a slight increase of the ϵ -values, trends that are characteristic for phenols and other polar solutes. In analogy with for example salicylaldehyde²² a small hypsochromic shift of the curves takes place on changing from the saturated hydrocarbon to ethanol. This may be taken as an indication of the existence of a hydrogen bond in the tropolone structure^{22*}. The shoulders around 400 $m\mu$ in the spectra of β - and γ -thujaplicin in ethanol⁴ are not found in heptane solution.

Two main absorption ranges are exhibited by the thujaplicins, one around 225—240 $m\mu$, the other at approximately 310—375 $m\mu$. The latter region is occupied by a most characteristic group of maxima of high and comparatively similar intensities. Both absorption ranges are remarkably wide. Moreover, in the long wave one the central part of the curve is somewhat depressed. Evidently, at least the long wave group of maxima is built up by two distinct sub-groups. This view is supported by the shape of the alkali curves (Fig. 3), which possess two separate long wave maxima. These curves also show an indication of a subdivision of the short wave band.

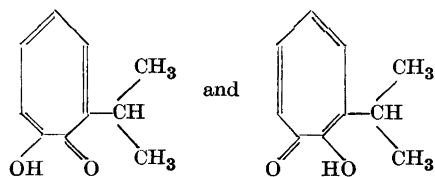
The strong absorption of the thujaplicins in the near ultra-violet ($\log \epsilon = 3.7$ — 3.9) shows beyond doubt that the double bonds are conjugated, in other words, that the molecules are planar. Cycloöctatetraene, on the contrary, exhibits a low and sloping absorption curve in this region (Fig. 2) due to the predominating non-planar structure of the molecule.

A definite interpretation of the absorption curve of tropolone will require a quantum mechanical treatment. However, a few more conclusions can be drawn empirically.

In benzene, the long wave maxima are the result of "forbidden transitions". A characteristic property of benzeneoid compounds, therefore, is a depressed absorption in the long wave region as compared with non-cyclic substances containing the same number of conjugated double bonds. The absorption intensity of the thujaplicins in this region is intermediate between that of octatrienal and salicylaldehyde although closer to the latter (Fig. 2). This conforms with the aromatic character of the tropolone derivatives.

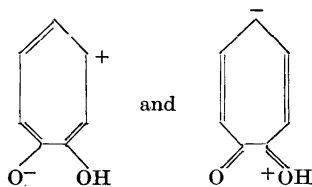
* Morton and Stubbs²² found a difference of nearly 20 $m\mu$ between the long wave λ_{\max} for salicylaldehyde and its methyl ether in hexane solution. The higher value of λ_{\max} for the former substance was ascribed to the hydrogen bond. An analogous comparison of a simple tropolone and its methyl ether might throw some light upon the question of the existence of a hydrogen bond in tropolone.

Assuming no hydrogen bridge in the tropolone molecule, two different structures are possible for the unsymmetrical tropolone derivatives, *e. g.* for α -thujaplicin:



There is no reason why, in solution, either form should be greatly predominant. In tropolone and γ -thujaplicin the two forms are identical. The close spectral resemblance between γ -thujaplicin and the α - and β -compound shows that the above tautomerides, if existing side by side, must possess very similar absorption properties. Otherwise, the α - and β -curves would be levelled as compared with the γ -curve.

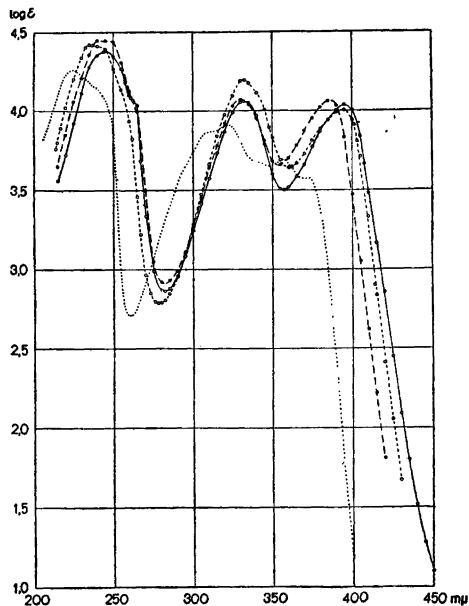
At present it is difficult to understand why the thujaplicins exhibit two groups of long wave maxima. Due to the complexity of the bands it is impossible to determine precisely the frequency corresponding to each electronic transition, but the ratio of them is approximately 1.1—1.2. Assuming the same ground state in each case, this implies that the difference in energy between the excited states is remarkably small. Several types of zwitterion structures can be constructed which may contribute to the excited states, *e. g.*:



Apart from the characteristics already discussed, the vibrational fine structure is the most prominent feature of the thujaplicin spectra. Although not very marked, it is clear enough to indicate a rigid ring structure. Among benzene derivatives, phenol exhibits a similar degree of subdivision of electronic bands. With salicylaldehyde, on the other hand, the long wave maximum is completely smoothed (Fig. 2), which can be explained as a "loose bolt" effect²⁵ of the aldehyde group.

The spectra of the anions of the thujaplicins were determined in aqueous buffer solutions of pH 12. It is true that strong steric hindrance exhibited by

Fig. 3. Ultra-violet absorption spectra for α -thujaplicin (○—○—○), β -thujaplicin (●—●—●), and γ -thujaplicin (○—○—○), all at pH 12. Dotted line: γ -thujaplicin in *n*-heptane.



ortho-substituents can prevent dissociation of phenols to such an extent that ionisation is not nearly complete at pH 12 or even higher²⁶. Therefore, α -thujaplicin, being the only one that might show this effect, was submitted to a control investigation at pH 14. No spectral difference was found, however, between pH 12 and 14.

The alkaline solutions of the thujaplicins are all yellow. Their absorption spectra are shown in Fig. 3. As compared with the spectra in heptane the entire curves are shifted bathochromically to an extent which would be about normal for a phenol. Moreover, the fine structure disappears due to electrostatic interaction between solvent and solute, so that two distinct maxima — at 330—332 $m\mu$ and 385—396 $m\mu$ respectively — remain instead of the groups of long wave maxima of the non-ionised molecules. A marked increase of the absorption coefficients in this range is also brought about by alkalisation, a clear analogy with the normal phenol-phenolate ion shift. Tropolone itself will no doubt show an alkali spectrum very similar to those of the thujaplicins.

NOTE ON A NEW NATURAL PRODUCT, NOOTKATIN, ISOLATED FROM CHAMAECYPARIS NOOTKATENSIS

According to a private communication from Professor H. Erdtman, a new compound with m. p. 91.5—92° and corresponding to the formula $C_{15}H_{20}O_2$ has been isolated from the heart wood of *Chamaecyparis nootkatensis*. As the

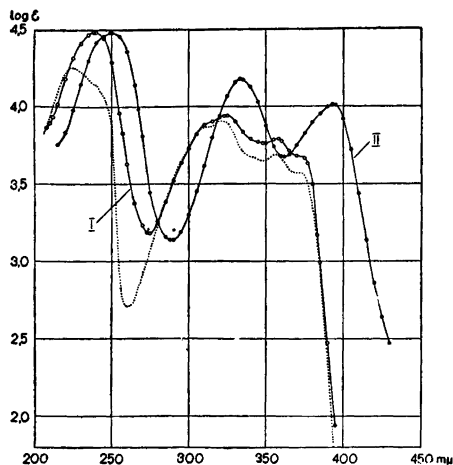


Fig. 4. Ultra-violet absorption spectra for nootkatin in *n*-heptane (I) and at pH 12 (II). Dotted line: γ -thujaplicin in *n*-heptane.

substance, which has been named nootkatin, bears a close chemical resemblance to the thujaplicins, it has been subjected to a physico-chemical investigation in connection with the thujaplicin work just reported*.

The molecular weight was determined cryoscopically in a benzene solution (0.907 g nootkatin, 12.68 g benzene, depression 1.41°). Found: mol. wt. 249, calculated for $C_{15}H_{20}O_2$: 232.

Using a Beckman Model DU spectrophotometer, the ultra-violet absorption curves of nootkatin were determined in *n*-heptane and in a phosphate buffer solution of pH 12 (Fig. 4). The spectra resemble those of all three thujaplicins, the curves of the γ -compound being slightly more similar than the others. Thus, nootkatin is evidently a tropolone derivative. If an extra double bond exists in the molecule it will not be conjugated with the ring chromophore. Assuming a single alkyl substituent in the ring, the γ -position is to be slightly preferred to the others.

SUMMARY

Ultra-violet absorption spectra are given for the thujaplicins and a new natural compound, nootkatin, in heptane and alkaline water solutions as well as for tropolone in cyclohexane solution (added in the proofs). A potentiometric titration curve for β -thujaplicin and molecular weight determinations for the latter substance and nootkatin are presented.

* The providing of a specimen by Professor Erdtman is gratefully acknowledged.

These data are discussed in connection with known properties of the tropolones. It is shown that the molecule is planar and does not associate with other tropolone molecules in solution. The problem of an intramolecular hydrogen bond is discussed on the basis of acidity and spectro-chemical evidence. The "aromatic" nature of the tropolone ring system is confirmed and some analogies with phenols are pointed out.

REFERENCES

1. Dewar, M. J. S. *Nature* **155** (1945) 50.
2. von E. Doering, W., and Knox, L. H. *J. Am. Chem. Soc.* **72** (1950) 2305.
3. Cook, J. W., Gibb, A. R., Raphael, R. A., and Somerville, A. R. *Chem. and Ind.* (1950) 427.
4. Erdtman, H., and Gripenberg, J. *Acta Chem. Scand.* **2** (1948) 625.
5. Gripenberg, J. *Acta Chem. Scand.* **2** (1948) 639.
6. Anderson, A. B., and Gripenberg, J. *Acta Chem. Scand.* **2** (1948) 644.
7. For references, see: Loudon, J. D. *Ann. Rep. Progr. Chem.* **XLV** (1948) 187.
8. Dewar, M. J. S. *Nature* **155** (1945) 141.
9. Haworth, R. D., Moore, B. P., and Pauson, P. L. *J. Chem. Soc.* (1948) 1045.
10. Cook, J. W., and Somerville, A. R. *Nature* **163** (1949) 410.
11. Tarbell, D. S., Scott, G. P., and Kemp, A. D. *J. Am. Chem. Soc.* **72** (1950) 379.
12. Dewar, M. J. S. *Nature* **155** (1945) 479.
13. Scott, G. P., and Tarbell, D. S. *J. Am. Chem. Soc.* **72** (1950) 240.
14. Zeisel, S., and von Stockert, K. *Monatsh.* **34** (1913) 1327.
15. Treadwell, W. D., and Schwarzenbach, G. *Helv. Chim. Acta* **11** (1928) 386.
16. Arnold, R. T., and Sprung, J. *J. Am. Chem. Soc.* **61** (1939) 2475.
17. Schwarzenbach, G., and Lutz, K. *Helv. Chim. Acta* **23** (1940) 1147, together with Schwarzenbach, G., and Felder, E. *Helv. Chim. Acta* **27** (1944) 1044.
18. Schwarzenbach, G., and Suter, H. *Helv. Chim. Acta* **24** (1941) 617.
19. Šantavý, F. *Czechoslovak Chem. Communications*, Coll. XIV, no. 3 (1949) 145.
20. Weigert, F. *Optische Methoden der Chemie*, Leipzig (1927) p. 212.
21. Henri, V. *J. d. Phys. et le Radium* [6] **3** (1922) 181.
22. Morton, R. A., and Stubbs, A. L. *J. Chem. Soc.* (1940) 1347.
23. Hausser, K. W., Kuhn, R., Smakula, A., and Hoffer, M. *Z. phys. Chem.* **B 29** (1935) 371; cf. Blout, E. R., and Fields, M. *J. Am. Chem. Soc.* **70** (1948) 189.
24. Cope, A. C., and Overberger, C. G. *J. Am. Chem. Soc.* **70** (1948) 1433.
25. Lewis, G. N., and Calvin, M. *Chem. Rev.* **25** (1939) 273.
26. Coggeshall, N. D., and Glessner, A. S., Jr. *J. Am. Chem. Soc.* **71** (1949) 3150.

Received July 15, 1950.