[CONTRIBUTION FROM THE UNIVERSITY OF RHODE ISLAND]

The Racemization of Usnic Acid

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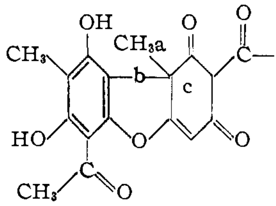
RECEIVED SEPTEMBER 24, 1954

The racemization of usnic acid (I) increased in rate with basicity of solvent for eight solvents examined. The proportionality of $\Delta S\ddagger$ to E_{act} suggested that a single mechanism prevailed in these eight cases.

Structure I has been proposed for the lichen acid usnic acid by Curd and Robertson.[1] Both they and Schöpf and Ross[2] discussed those reactions of usnic acid which could not, at the time, be reconciled easily with formula I.



I

The facile racemization[3] of the substance drew comment. Schöpf and Ross were inclined to focus attention on bond a (formula I) while Foster, Robertson and Healy[4] regarded bond c as a "center of weakness," but neither group made a concrete proposal. Homolysis of bond b was recently offered[5] as a possibility but this was objected to by Barton and Bruun[6] who mentioned that the reaction was "acid catalyzed."

The present work was undertaken in order to provide additional information regarding this racemization. The need for a detailed explanation of this reaction was recognized recently.[7]

Experimental

Materials.—Acetonitrile and methyl ethyl ketone were dried over anhydrous magnesium sulfate and distilled, liberal foreruns and residues being discarded. Chlorobenzene was dried over calcium chloride and similarly treated. Anisole was dried by distillation. Toluene was refluxed with, distilled from and stored over sodium metal. Decalin and bicyclohexyl, after being shaken with aqueous permanganate and with concentrated sulfuric acid repeatedly, were likewise purified. Dioxane was purified in the manner described by Fieser.[8]

Usnic acid was obtained by the countercurrent extraction of 7.5 kg. of lichens, previously ground in a meat chopper and dried in air, with acetone. The lichens, preponderantly of the Cladonia type, were gathered in the vicinity of Worden Pond, South Kingstown, R. I. The residue obtained by evaporation of the acetone was triturated alternately with petroleum ether and methanol in a manner recently described.[9] By calculations based on solids obtained from the first acetone recrystallization, the yield of usnic acid was found to be 1% of dextro and 0.2% of racemic acid. The major part of the dextro form was separated by systematic recrystallization from acetone. The acid used in this work, which exhibited the same ultraviolet absorption spectrum as that in previous work,[5] had a specific rotation of +493 ± 7°. Stark, Walter and Owens[9] reported 491–495° (2% in chloroform).

Manipulation will be described only for run 3, Table III In a 125-ml. Claisen flask there was placed 100 ml. of dioxane and 0.3843 g. (1.12 millimoles) of usnic acid. When a clear solution was obtained, there was added 4 ml. of methanolic sodium methoxide. This quantity contained, as was ascertained by titration with standardized hydrochloric acid, 1.04 millimoles of alkali. The solvent was then removed by distillation under reduced pressure (15–20 mm.) without application of heat. The glassy residue was dried under reduced pressure (0.3 mm.) over phosphorus pentoxide for 12 hours. The sample was then dissolved in anhydrous dioxane, the whole being made up to 100 ml. in a volumetric flask. The solution was placed in ampoules which were sealed after being cooled. These were placed in a constant temperature bath containing mineral oil and allowed to become thermally equilibrated (30 minutes was normally allowed for this purpose). The oscillation of bath temperature, as reported by thermometers graduated either in 0.1 or 0.2°, was in all cases less than 0.2° and was usually about 0.1°.

Polarimetry and Calculations.—The samples were removed from the ampoules and transferred to a polarimetry tube of 2 dcm. length. The polarimeter[10] was of the full circle type. For each α, 10 observations were taken and the average used. The standard deviation varied in best cases between 0.03 and 0.05° but sometimes reached 0.07°. In all cases in which there were employed bases stronger than dioxane, the solutions reddened as the racemization proceeded. In most cases, the standard deviation rose and occasionally reached 0.25°.

It was ascertained in separate experiments that the specific rotation of usnic acid in dioxane solutions was independent of concentration at levels employed in this work.

All constants which are slopes of lines, and all errors, were calculated by the method of least squares.[11]

Data collected during one thermal racemization are reported in detail in Table I; these are plotted in Fig. 1.

TABLE I

RACEMIZATION OF USNIC ACID IN METHYL ETHYL KETONE, 80.8°

t, hr.	α	ln α_0/α	10^2k, hr.$^{-1}$ [a]
0	4.04	0.000	
71	2.74	0.388	0.55
215	1.40	1.060	.49
412	0.50	2.090	.51
556	0.23	2.866	.52

[a] Constants, k, reported here and in Table II are first order constants, *i.e.*, have not been corrected for concentration of solvent. Values of activation constants in Table IV, however, include this correction.

Racemization of Usnic Acid by Ultraviolet Light.–Usnic acid (1.873 g.) was dissolved in anhydrous dioxane and the

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(1) F. H. Curd and A. Robertson, *J. Chem. Soc.*, 894 (1937).

(2) C. Schöpf and F. Ross, *Ann.*, **546**, 1 (1941).

(3) Inactive usnic acid is obtained when xylene solutions of active forms are refluxed briefly. The reaction has been assumed to be a racemization since O. Widman, *ibid.*, **310**, 230 (1899), produced a racemate having the same m.p. as the inactive acid by mixing *d*- and *l*-forms.

(4) R. T. Foster, A. Robertson and T. V. Healy, *J. Chem. Soc.*, 1595 (1939).

(5) S. MacKenzie, THIS JOURNAL, **74**, 4067 (1952).

(6) D. H. R. Barton and T. Bruun, *J. Chem. Soc.*, 603 (1953).

(7) F. M. Dean, P. Halewood, S. Mongkolsuk, A. Robertson and W. B. Whalley, *ibid.*, 1250 (1953). These authors resolved inactive usnic acid.

(8) L. F. Fieser, "Experiments in Organic Chemistry," 2nd. Ed., D. C. Heath and Co., New York, N. Y., 1941, p. 369.

(9) J. B. Stark, E. D. Walter and H. S. Owens, THIS JOURNAL, **72**, 1819 (1950).

(10) Kern Company, New York.

(11) W. J. Youden, "Statistical Methods for Chemists," John Wiley and Sons, Inc., New York, N. Y., 1951.

whole made up to 500 ml. The solution was placed in a round-bottomed quartz flask and was irradiated horizontally by a mercury vapor lamp,[12] 140 watts, at a distance of 1.5 inches. The temperature of the solution rose rapidly to 45° and did not exceed 47°. At the end of 89 hours, the usnic acid was 65% racemized.

Discussion

In solvents used in this work, the racemization of usnic acid proceeded in accordance with the law $v = k(\text{usnic acid})^n(\text{base})^m$. That $n = 1$ is shown by the constancy of k in three cases (Table II, runs 4, 5, 16, 17, 20, 22) in which the concentration of usnic acid was varied as strongly as possible consistent with solubility and a reasonable polarimetric error. That $m = 1$ is indicated by runs 5, 17 and 29 which reveal that in a mixture of dioxane and toluene, the rate is proportional to the first power of the dioxane concentration.

TABLE II

VELOCITY CONSTANTS FOR RACEMIZATION OF USNIC ACID

Run	t, °C.	Solvent	10^2 molarity, usnic acid	$10^2 k$, hr.$^{-1}$	10^2 error (stand. dev.)	α/α_0 final
1	59.3	Dioxane	1.43	0.0368	0.0009	0.48
2	77.6			0.366	.019	.49
3	96.5			3.36	.071	.10
4	116.3			26.2	.17	.16
5	115.0		4.84	24.0	Small	.14
6	80.8	Acetoni-	1.20	0.37	0.074	.21
7	94.0	trile		1.51	.048	.25
8	115.8			16.7	.73	.13
9	80.8	Methyl	1.40	0.521	.02	.057
10	94.0	ethyl		1.95	.18	.17
11	115.0	ketone	1.15	20.1	.70	.09
12	94.0	Anisole	1.31	0.374	.0068	.53
13	114.6			4.13	.00005	.38
14	139.9			57.0	.81	.18
15	94.0	Toluene	1.40	0.203	.0035	.37
16	114.8		0.39	2.55	.052	.55
17	115.0		1.25	2.62	.045	.27
18	140.0		1.40	35.4	1.28	.17
19	94.1	Chloro-	1.04	0.203	0.0057	.36
20	114.9	benzene		2.68	Small	.28
21	139.9			33.7	0.90	.18
22	115.0		3.16	2.55	.025	.28
23	94.1	Decalin	Small	0.131	.019	.53
24	115.0			1.89	.096	.26
25	139.8			30.0	1.35	.23
26	94.0	Bicyclo-	Small	0.0734	0.0051	.57
27	115.1	hexyl		2.09	0.12	.37
28	139.8			27.3	1.90	.27
29	115.0	Dioxane-toluene 50 mole %	1.15	13.17	0.74	.19

The function of base cannot be to produce the ion of usnic acid for sodium usnate is not racemized[13] under conditions used in this work (Table III). Nor can this function be to assist the tautomerization II ($R = H$) to III since usnic acid diacetate II ($R = Ac$) is racemized in dioxane much more rapidly than is usnic acid.[14]

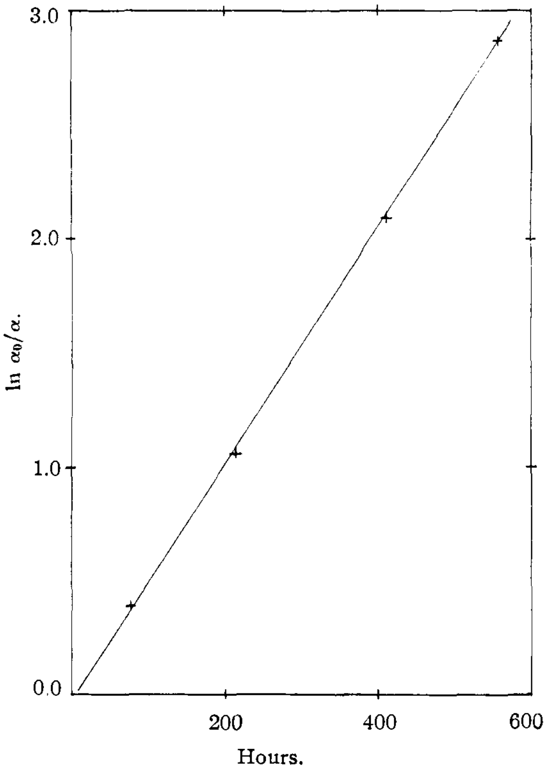
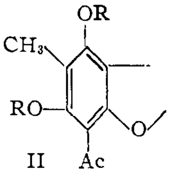


Fig. 1.—Racemization of usnic acid in methyl ethyl ketone, 80.8°.

TABLE III

RACEMIZATION OF USNIC ACID DERIVATIVES IN DIOXANE

Solute	t, °C.	Time, hr.	α/α_0 in %
Diacetate	98.9	1.5–2	0
Usnic acid	115.0	3	49
Sodium usnate	114.8	1.5	96 ± 5



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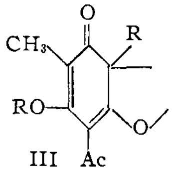

III

Accordingly, the base has another function, the details of which must await final proof of the structure of usnic acid. It should be pointed out, however, that the work reported herein can be reconciled with formula I in accordance with the mechanism which is perhaps implied in the work of Foster, Robertson and Healy.[4]

$$-\overset{|}{\underset{|}{C}}-\underset{\underset{O}{\|}}{C}- + B \longrightarrow -\overset{|}{\underset{|}{C}}-\overset{|}{\underset{\underset{O^-}{|}}{C}}-B \longrightarrow -\overset{|^-}{\underset{|}{C}}\cdots\underset{\underset{O}{\|}}{C}-B$$

bond c in I

Such a reverse aldol mechanism would account for an attack of a base upon free usnic acid and, since the formation of the salt of usnic acid involves the triketone group and hence deactivates the carbonyl group of bond C, for the failure of sodium usnate to racemize. Further, such a proposal is in harmony with other reactions of usnic acid in which the

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[12] Hanovia Chemical and Manufacturing Co., Newark, N. J.

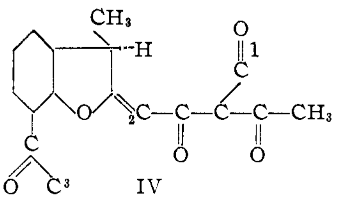
[13] C. Schöpf and K. Heuck, *Ann.*, **459**, 233 (1927), noted that *d*-usnic acid was stable when refluxed with an excess of sodium methoxide in absolute ethanol for 45 minutes.

[14] Y. Asahina and M. Yanagita, *Ber.*, **72**, 1140 (1939), noted that treatment of usnic acid with acetic anhydride in the presence of a "few drops" of sulfuric acid for 30 minutes at 90° produced the racemic diacetate.

base B is such as to permit hydrogen transfer and formation of a stable product.[15]

In order to ascertain whether or not an addition product might also be formed from usnic acid and an aromatic hydrocarbon, a sample of the acid was refluxed with *m*-xylene for 45 hours. Only racemic usnic acid was formed. However, this fact is not necessarily an argument against the reverse aldol proposal since aromatic hydrocarbons can serve as bases by participation in so-called "π-complexes."[16]

It is also important to point out that usnic acid may have other formulas permitting ready explanation of observations in this work. While the skeleton IV appears well settled, there has been recorded, as yet, no forcing demonstration of the manner of joining carbon 1 (formula IV). Thus, lately, Barton and Bruun[6] wrote, and criticized, a formula involving union of carbons 1 and 2. Union of carbons 1 and 3 appears to be, from models, sterically possible also. In either event, loosening of hydrogen at the asymmetric carbon atom could account for the observed base catalysis. Indeed, since the constants of Table IV arrange themselves so well in accordance with the basicity of the solvents *to the proton*,[17] this latter interpretation of the racemization process appears at least equally likely.



IV

No evidence supporting a mechanism for the racemization involving homolytic fission of bond b has been found.[18] The constants reported in Table IV suggest additionally that there is no reason to believe that a second manner of racemization prevails in the less basic solvents. Over the wide range, $\Delta S^{\ddagger}$ is proportional to E_{act} (the slope is 2.2 ± 0.1 e. u. per kcal.). This proportionality of constants has been noted previously and has been interpreted[19] as implying constancy of mechanism.

TABLE IV

RACEMIZATION OF USNIC ACID IN VARIOUS SOLVENTS

Solvent	E_{act}, kcal.	$\Delta S^{\ddagger}$, cal./mole-deg.
Dioxane	29.0 ± 0.04	−10.5
Acetonitrile	29.1 ± 0.52	−12.1
Methyl ethyl ketone	28.6 ± 0.82	−11.4
Anisole	32.5	− 4.2
Toluene	33.3 e<0.1	− 3.1
Chlorobenzene	33.2	− 2.4
Decalin	34.3 ± 0.33	− 0.6
Bicyclohexyl	38.8 ± 1.5	+11.1

Acknowledgment.—We wish to thank Professor E. A. Palmatier, Dept. of Botany, for advice concerning identification and location of lichens used in this work. We are indebted also to B. D. Wilks, G. H. Wilks and L. MacKenzie who assisted with preparation of lichens for extraction.

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[15] Y. Asahina and M. Yanagita, *Ber.*, **71B**, 2260 (1938), reported the reaction of monoacetylusnic acid with absolute ethanol. An ethyl ester was formed by addition.

[16] H. C. Brown and J. D. Brady, THIS JOURNAL, **74**, 3570 (1952).

[17] H. Lemaire and H. J. Lucas, *ibid.*, **73**, 5198 (1951), showed that dioxane was slightly more basic than acetonitrile while acetone was much weaker. H. C. Brown and J. D. Brady, ref. 16, demonstrated that chlorobenzene was less basic than toluene.

[18] For such a reaction, the effect of solvent might well be quite different. T. L. Chu and T. J. Weismann, *ibid.*, **76**, 3787 (1954), showed that the dissociation of tetrafluorenylhydrazine decreased for the sequence pyridine, toluene, benzene and dioxane.

[19] M. D. Cohen, J. E. Leffler and L. M. Barbato, *ibid.*, **76**, 4169 (1954).