until they are thawed and removed. Where the banks consist of frozen sand and gravel or thawed material, they are also effectively eroded by wind-generated waves and river current.

Local residents reported erosion of a strip approximately 200′ wide along the north bank of the Yukon downstream from Beaver during a summer characterized by long periods of strong southwest winds. In June 1950, after breakup of the river ice, strong upriver winds produced waves which, together with the current, caved the frozen silt banks upstream from Beaver as much as 35′ in two days, whereas moving river ice had relatively little effect. In August 1949, a section of the bank was undercut by waves and current and slumped into the river. This block was circumscribed by a crack that extended 90′ back from the river.

Wind-generated waves erode lake margins in much the same way, although the added effects of current and rapid fluctuations in level are lacking. The shores of some of the larger lakes in the Yukon Flats are being eroded by waves. Elongation and orientation of lakes on the arctic coastal plain of Alaska (*6*) and enlargement of thaw lakes on Seward Peninsula (*7*) have been ascribed to this type of erosion.

From these observations it is concluded that waves generated in summer by strong upriver winds are an effective erosive agent on the north bank of the river and accelerate the northward migration of the Yukon River in the Yukon Flats.

References

1. RUSSELL, I. C. *Bull. Geol. Soc. Am.*, **1**, 112 (1890).
2. GOODRICH, H. B. *18th Annual Rept., U. S. Geol. Survey*, Pt. III, 279 (1898).
3. EAKIN, H. M. *J. Geol.*, **18**, 435 (1910).
4. GOODRICH, H. B. *Op. cit.*, 286.
5. *Ibid.*, 287.
6. BLACK, R. F., and BARKSDALE, W. L. *J. Geol.*, **57**, 113 (1949).
7. HOPKINS, D. M. *Ibid.*, 126.

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Crystalline Visnagan

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Khellin, a crystalline dimethoxymethylfurochromone obtained from the seeds (khella) of *Ammi visnaga* L. (bishop's-weed), has attracted attention because of its vasodilatory activity (*1*).

The "visnagan" fraction, which is obtained as a more ether-soluble by-product in the preparation of khellin, was described by Samaan (*2*) as a dark, oily liquid distilling at 160° at 20 mm, with decomposition. In a recent communication, Cavallito and Rockwell (*3*) reported the isolation of a glassy product from this fraction by fractional precipitation from ether with Skellysolve B (petroleum naphtha) followed by chromatography on silica. For this glassy product they reported the following analytical data: Probable formula: $C_{22}H_{26-28}O_7$; molecular weight: found 387, calcd 402–404; specific rotation, $[\alpha]_D + 30.5°$. Pharmacologically, this product was found to be about twice as active as khellin when tested on the isolated heart.

Although khellin is a useful and potent vasodilator, any product having greater potency with fewer side effects would be a valuable adjunct to the series of compounds used for the treatment of angina pectoris. A program designed to obtain pure principles from the amorphous fraction of extracts was therefore started in these laboratories.

In addition to the isolation of the above-described material, Cavallito and Rockwell described the separation of a product identified as a "crystalline impurity" possessing the following properties: mp, 133°–140°; empirical formula, $C_{15}H_{12}O_5$; molecular weight, 272.

Applying the general method of Cavallito and Rockwell, we chromatographed an extract of khella (RI-811) from which khellin and chellolglycoside had been removed and which was optically active ($[\alpha]_D + 5°$). Its vasodilatory effect was about two and one half times that of khellin (Table 1). Optical activity and ultraviolet absorption characteristics were employed as a guide in selecting eluted fractions. Optical activity was read on 0.5% solutions in 95% ethyl alcohol. We thus obtained an amorphous product possessing a specific rotation of $[\alpha]_D + 16°$ and additional fractions increasing in optical activity to $[\alpha]_D + 50°$. From this preliminary separation we subsequently obtained the two crystalline compounds described below.

TABLE 1

FLOW INCREASE ON ISOLATED RABBIT HEART IN COMPARISON WITH KHELLIN

Compound	Concentration	Flow		Flow increase (%)	Potency
		Control	Test		
Standard	1: 60,000	26.5	37	40	1
RI-811	1: 150,000	30.7	43	41	2.5
Standard	1: 30,000	28.5	42	48	1
RI-832	1: 240,000	25.9	40	55	8
Standard	1: 30,000	29.5	42.7	44.9	1
RI-832-3	1: 240,000	27.1	37.3	37.6	8
Standard	1: 30,000	32.4	46.3	42.9	1
RI-778-3	1: 30,000	29.9	41.5	38.9	1

The eluate ($[\alpha]_D + 16°$) possessed the absorption spectrum described by Cavallito and Rockwell for their amorphous visnagan and had a strong dilating action on the isolated rabbit heart. We rechromatographed this fraction, discarded the first eluate, and obtained a central fraction which, on trituration with methyl alcohol, crystallized after prolonged standing at 4° C. The crystalline visnagan (RI-832), after repeated recrystallization from methanol, had a melting point of 86°–88° and a specific rotation of $[\alpha]_D + 12.5°$. The ultraviolet absorption spectrum

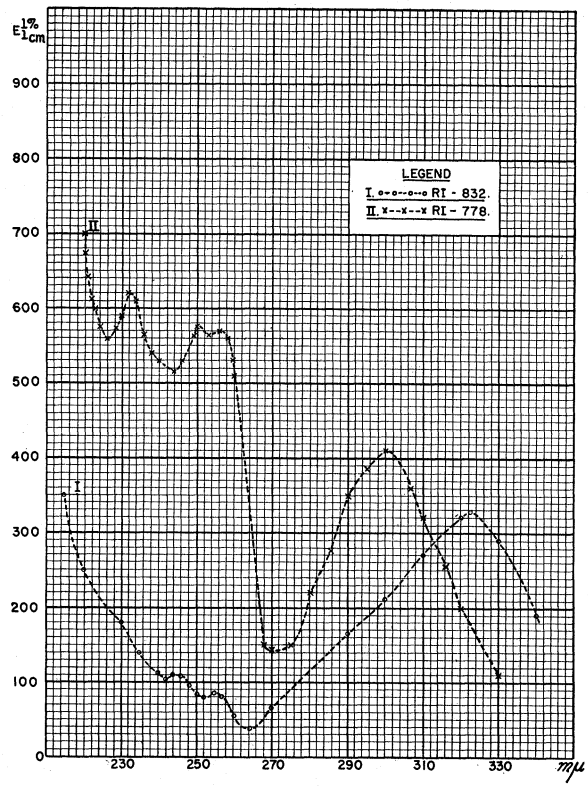

FIG. 1.

given in Fig. 1 is similar to the curve obtained by Cavallito and Rockwell. Anal:[1] C, 66.84%; H, 7.28% (calcd for $C_{21}H_{28}O_6$: C, 66.98%; H, 7.50%). Its molecular weight, determined cryoscopically, is 373 (calcd, 376.45).

Insofar as we are aware, this is the first description of the isolation of a crystalline compound from the amorphous visnagan fraction of khella extracts that has the ultraviolet absorption properties of the main amorphous product. Three preparations of the compound (RI-832) have been made, two of which have been tested by the Hazleton Laboratories, of Falls Church, Va., in isolated rabbit hearts and found to possess a vasodilating effect approximately eight times that of khellin (Table 1, RI-832 and RI-832-3).

The eluate having the specific rotation $[\alpha]_D + 50°$ also yielded a crystalline compound (RI-778), melting point, 157°–159°, and $[\alpha]_D + 96°$ after repeated recrystallization from ethyl acetate. Anal: C, 65.15%; H, 5.80% (calcd for $C_{15}H_{16}O_5$: C, 65.20%; H, 5.84%). The molecular weight by cryoscopic method was found to be 276 (calcd, 276.28). The ultraviolet absorption spectrum of this substance is given in Fig. 1.

This compound may correspond to the "crystalline impurity" of Cavallito and Rockwell, since it also yields a hydrochloride with ethereal hydrochloric acid. The hydrochloride is markedly different from the oxonium salt of khellin or visnagin in being readily soluble in excess ether. The ultraviolet absorption closely resembles the absorption spectrum reported by Davies and Norris (*4*) for dihydrokhellin. The basic structure of the compound seems, therefore, to be a dihydrofuranochromone. Its vasodilatory activity is given in Table 1.

[1] Microanalyses by Schwarzkopf Microanalytical Laboratory, Middle Village, L. I., N. Y.

References

1. HUTTRER, C. P., and DALE, E. *Chem. Revs.*, **48**, 543 (1951).
2. SAMAAN, K. *Quart. J. Pharm. Pharmacol.*, **4**, 14 (1931).
3. CAVALLITO, C. J., and ROCKWELL, H. E. *J. Org. Chem.*, **15**, 820 (1950).
4. DAVIES, J. S. H., and NORRIS, W. L. *J. Chem. Soc.*, 3195 (1950).

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Association of Enzymatic Activity with Submicroscopic Particles

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Considerable study of the mitochondrial fraction of tissues has shown that these particulates possess the major portion of the activity of a number of tissue enzyme systems (*1*). Although preparations of submicroscopic particles (microsomes) have been found to possess a few enzyme activities in relatively high concentration, previous studies (*1*) have not indicated exclusive localization of an enzymatic activity in these particles. In the course of investigations on the hydrolysis of triacetic acid lactone by rat kidney homogenates, it was noted that almost all the lactonase activity could be sedimented at $18{,}000 \times g$ (*2*). Fractionation according to the methods of Schneider (*3*) and Schneider and Hogeboom (*4*) indicated that about 70% of this activity was associated with the submicroscopic particles, whereas the mitochondrial frac-

TABLE 1

INTRACELLULAR DISTRIBUTION OF TRIACETIC ACID LACTONASE IN RAT KIDNEY

Fraction	Expt. 1*		Expt. 2†		
	Activity‡	Percentage	Activity‡	Percentage	Activity: Nitrogen‖
Whole homogenate	8.95	(100)	7.94	(100)	0.164
Nuclei + whole cells	1.66	18.5	1.55	19.5	.139
Mitochondria	.667	7.5	.474	6.0	.054
Submicroscopic particles	6.34	70.9	5.55	70.0	.607
Supernatant	1.00	11.2	.700	8.8	0.040
Sum of fractions	9.67	108	8.27	104	—

* Fractionated by the procedure of Schneider (*3*).
† Fractionated by the procedure of Schneider and Hogeboom (*4*) using 0.25 *M* sucrose.
‡ Activity expressed in terms of the rate constant, $k \times 10^3$ (*5*).
‖ $k \times 10^3$/mg nitrogen.