[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 1022]

Phytofluene

BY L. ZECHMEISTER AND A. SANDOVAL

It was announced some time ago that a colorless polyene which possesses a characteristic spectrum and shows a strong fluorescence in ultraviolet light can be separated from some plant extracts by chromatography.[1] Subsequently, we found that this compound, termed "phytofluene," is unusually widespread in the vegetable kingdom where it has been observed in chlorophyll-free tissues which contain considerable amounts of carotenoid pigments.[2]

In the present paper we wish to describe the isolation of phytofluene from canned tomato paste and to give some chemical characterization of this compound. The experiments reported were made rather difficult by the oily nature of the phytofluene and its sensitivity to air and light in that state. Nevertheless, the extinction value in petroleum ether, $E^{1\%}_{1\,cm.}$ which in crude samples amounted only to 300–600, could be gradually increased to the value of about 1200. It then remained practically constant in the course of further operations.

The close relationship between phytofluene and the carotenoids is evident not only from their joint occurrence in numerous instances but, especially, from the isoprenic structure of phytofluene as shown by C-methyl estimations. Furthermore, molecular weight determinations yielded values between 500 and 520; the average, 505, is only 6% lower than the molecular weight of carotene, $C_{40}H_{56}$. It is, therefore, reasonable to assume that phytofluene contains a skeleton of forty carbon atoms.

In the great majority of our preparations the elementary analysis revealed the presence of 1 to 2% of oxygen as a result of rapid autoxidation. However, in two cases only 0 and 0.7% of oxygen were found. On the basis of all available data, the best empirical formula for phytofluene is $C_{40}H_{64}$ (± 2H). Of course, this symbol must be given with reservation.

We believe that the hydrocarbon phytofluene must be classed as the first naturally occurring representative of such C_{40}-polyenes, in which the degree of hydrogenation is higher than in common carotenoids. The catalytic reduction of phytofluene indicates the presence of seven double bonds. Considering the location of the maxima at 331, *348*, 367 mμ, probably only five of the phytofluene double bonds can be conjugated in an open chain. The wave length of the maximum extinction at 348 mμ in hexane (Fig. 1) is only slightly different from that of vitamin A_2 which, according to a recent study of Karrer and Bretscher,[3] shows in alcohol a flat maximum at 345 mμ. These authors assume for A_2 an entirely open structure containing one isolated and five conjugated double bonds. On the basis of the spectra the presence of a similar conjugated system could be postulated for the phytofluene molecule, in which, however, large sections are saturated, in contrast to vitamins A_1 and A_2.

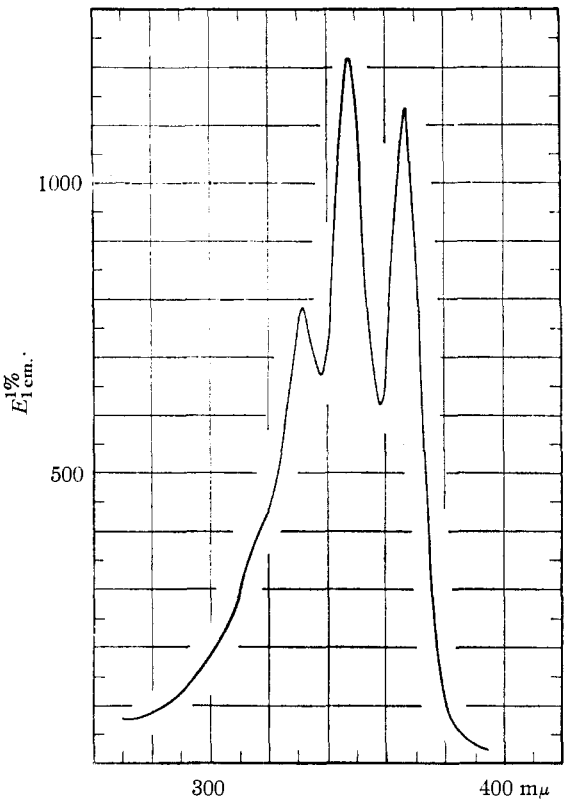

Fig. 1.—Extinction curve of phytofluene in hexane.

If we consider a hypothetical conversion of vitamin A_2 into vitamin A_1-aldehyde (axerophthal),[4] the maxima would be shifted to shorter wave lengths by the cyclization but this would (in part) be compensated for by the appearance of a new, conjugated carbonyl group. Indeed, the main maxima of the aldehyde as given by Hawkins and Hunter[4] are located at 350, 368 mμ.

(1) L. Zechmeister and A. Polgár, *Science*, **100**, 317 (1944).

(2) L. Zechmeister and A. Sandoval, *Arch. Biochem.*, **8**, 425 (1945); Further data: 1 kg. of fresh persimmons (*Diospyros Kaki* L., Ebenaceae) contained 1 mg. of phytofluene; fruits of *Arbutus unedo* L. (Ericaceae): 0.8 mg. (unripe) and 1.5 mg. (ripe). A fluorescent oil in carrots was observed by H. H. Strain, *J. Biol. Chem.*, **127**, 191 (1939).

(3) P. Karrer and E. Bretscher, *Helv. Chim. Acta*, **26**, 1758 (1943).

(4) R. F. Hunter and E. G. E. Hawkins, *Nature*, **153**, 194 (1944); E. G. E. Hawkins and R. F. Hunter, *J. Chem. Soc.*, 411 (1944); *cf.* R. A. Morton and T. W. Goodwin, *Nature*, **153**, 69 (1944).

The phytofluene maxima lie also near those of the structurally unclarified iso-anhydro-vitamin A (330, 349, 370 mμ)[5] or those of anhydro-sub-vitamin A (332, 348, 367 mμ).[6] However, the anhydro-vitamin A spectrum is different (351, 371, 392 mμ).[7]

The extinction curve of phytofluene in benzene is shown in Fig. 2.

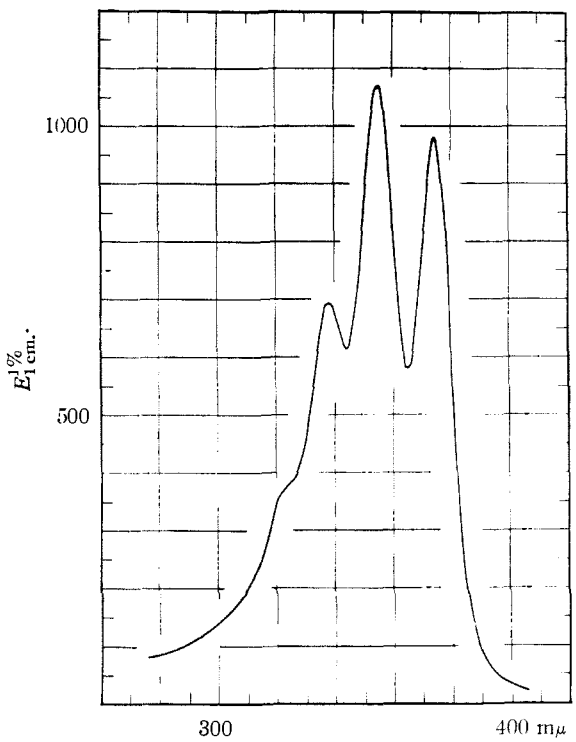

Fig. 2.—Extinction curve of phytofluene in benzene.

Evidently, phytofluene is related to the compounds mentioned but the position of its chromophore cannot be given with certainty. The oily character and, especially, the tendency toward autoxidation reminds us of the behavior of some artificial reduction products of carotenoids.[8]

Certainly, the conjugated system of phytofluene cannot extend into a β-ionone ring. While at first crude preparations seemed to possess some potency as a provitamin A, pure phytofluene is inactive in the rat, even in daily doses of 40 μg.

Surprising is the strong adsorption affinity of phytofluene, which is only slightly less than that of α-carotene. The position of the phytofluene on calcium hydroxide columns coincides with some members of the stereoisomeric α-carotene set which are adsorbed directly below their all-*trans* form.[9] Possibly, those very structural features which are responsible for the air- and photo-sensitivity of phytofluene may produce an "abnormally" high adsorbability.

The behavior of phytofluene in the Carr–Price test is remarkable. When this reaction was carried out in the presence of acetic anhydride, the following phenomena took place. First, a transient dark blue color appeared; at this stage the Zeiss grating spectroscope showed two bands which were located at 615 and 570 mμ (± 2 mμ). Then, within thirty seconds, the color of the solution changed to purple and a little later its shade resembled that of permanganate. Simultaneously, the 615 mμ band disappeared and about one-half of the 570 mμ band (facing the shorter wave lengths) cleared up.[9a] Gradually, the maximum of the single remaining band migrated to 585 mμ where it was observed for several minutes to weaken in intensity. Finally, the liquid turned brownish in color and no definite band could be seen in the spectrum.

As mentioned before, phytofluene[10] gives an azure blue coloration on acid earths, a test described for carotenoids and vitamin A by Emmerie and Engel.[11]

Phytofluene shows a marked tendency for *cis–trans* isomerization. Observations on some of its stereoisomers which can be demonstrated on a calcium hydroxide column in ultraviolet light, will be reported later.[12]

The formation of phytofluene in plants is evidently connected with the biosynthesis of the carotenoid pigments, and the simplest assumption would be that the colorless hydrocarbon constitutes an intermediate product. This would mean that a relatively short conjugated system is first formed which does not appear to be stabilized either by its own length or by some adjacent end groups. Such an assumption would agree with the well-known fact that during the ripening of tomatoes, red peppers, etc., oxygen is needed for the conclusion of the carotenoid synthesis.[13] On

(5) E. M. Shantz, J. D. Cawley and N. D. Embree, THIS JOURNAL, **65**, 901 (1943).

(6) N. D. Embree and E. M. Shantz, *ibid.*, **65**, 906 (1943).

(7) J. R. Edisbury, A. E. Gillam, I. M. Heilbron and R. A. Morton, *Biochem. J.*, **26**, 1164 (1932); P. Meunier, R. Dulou and A. Vinet, *Bull. soc. chim. biol.*, **25**, 371 (1943); E. G. E. Hawkins and R. F. Hunter, *Biochem. J.*, **38**, 34 (1944).

(8) *Cf., e. g.*, J. H. C. Smith, *J. Biol. Chem.*, **90**, 597 (1931); P. Karrer and R. Morf, *Helv. Chim. Acta*, **14**, 1033 (1931); R. Kuhn and H. Brockmann, *Z. physiol. Chem.*, **213**, 1 (1932).

(9) *Cf., e. g.*, L. Zechmeister and A. Polgár, THIS JOURNAL, **66**, 137 (1944).

(9a) This behavior is roughly the opposite of that shown by vitamin A epoxide (hepaxanthin) in the Carr–Price test. P. Karrer and E. Jucker, *Helv. Chim. Acta*, **28**, 717 (1945), first observed a band at 575 mμ which, however, faded out within a minute while a new band at 620 mμ appeared. The change was explained by the loss of the epoxide oxygen and the regeneration of the corresponding double bond.

(10) L. Zechmeister and A. Sandoval, *Science*, **101**, 585 (1945).

(11) A. Emmerie and C. Engel, *Rec. trav. chim.*, **58**, 283 (1939), wrote: "Carotenoids are adsorbed by Floridin XS earth with a greenish-blue color, vitamin A reacts with a dark blue color." This behavior was confirmed by G. G. Mayer and H. Sobotka, *J. Biol. Chem.*, **143**, 695 (1942); *cf. Science*, **102**, 158 (1945); a theoretical interpretation was given by P. Meunier, *Compt. rend. acad. franç.*, **215**, 470 (1942); *cf.* also H. B. Devlin and H. A. Mattill, *J. Biol. Chem.*, **146**, 123 (1942); A. Lowman, *Science*, **101**, 183 (1945); H. R. Kreider, *ibid.*, p. 377.

(12) For a survey of this field, *cf.* L. Zechmeister, *Chem. Rev.*, **34**, 267–344 (1944).

(13) A summary of early data can be found in L. Zechmeister, "Carotinoide," Julius Springer, Berlin, 1934, p. 24.

the other hand, it is not excluded that phytofluene and the polyene pigments have a common precursor; phytofluene could be formed by a hydrogenation process simultaneously with dehydrogenation which leads to the gradual development of an intense color in the tissue.

Acknowledgment.—Our thanks are due to Professor Harry J. Deuel, Jr., of the University of Southern California who has tested phytofluene in rats; furthermore, to Professor A. J. Haagen-Smit as well as Dr. G. Oppenheimer and Mr. Swinehart for micro-estimations.

Experimental

Materials and Methods.—As adsorbents calcium hydroxide (Shell Brand lime chemical hydrate, 98% through 325 mesh) and alumina (Alorco, Grade F, −80 mesh or Grade A, 150–200 mesh) were used. "Petroleum ether" means Skellysolve B, b. p. 60–70°. Except for the preparation of crude extracts, most operations should be carried out in poor light or darkness. It is also advisable to cover at least nine-tenths of the surface of chromatographic tubes with black paper. Inspection with ultraviolet lamps should be reduced to a minimum, lest strongly adsorbed minor zones (without maxima above 300 mμ) be formed. All evaporations were carried out *in vacuo* in an all-glass apparatus while a slow stream of carbon dioxide was bubbled through (bath temperature 40°). Oily residues were dissolved in a few ml. of light petroleum ether (b. p. 28–38°) and transferred by means of a dropper into a 6-cm. long conic tube which was fitted with a standard joint and a glass stopper. Absorption spectra in petroleum ether or hexane solutions were measured with a Beckman photoelectric spectrophotometer.

Isolation of Phytofluene from Tomato Paste.—The extraction of the canned paste (Campania West Coast Packing Co., Long Beach, Calif.) and the first part of the following operations were carried out with 3-kg. portions. Each portion was mixed and covered with 4 liters of methanol, and was stored in a closed bottle with occasional shaking for at least four hours. The dehydrated residue was then separated by means of a basket centrifuge (diameter, 20 cm.). The methanol was usually free of phytofluene but sometimes contained small amounts of other fluorescing substances.

The fibrous material was mechanically shaken with 2 liters of methanol plus 2 liters of petroleum ether for ten minutes. After centrifuging, this extraction was repeated twice with 1 + 1.5 liters. If necessary a last treatment may be carried out with 0.5 + 2 l. of the solvents. To each extract which consisted of two phases, 6–7 liters of water was cautiously added in a 13-liter separatory funnel. The combined red upper layers (6–7 liters) were washed free of methanol, dried with sodium sulfate and evaporated to about 400 ml. This solution was treated with 1 vol. of 20% methanolic potassium hydroxide in a broad Erlenmeyer flask overnight at 20°, and then at 4° until six portions, corresponding to 18 kg. of tomato paste, were ready.

Water was added cautiously to the whole liquid and the layers were separated. An emulsion was extracted by a few gentle shakings with petroleum ether. The combined dark-red petroleum ether extracts were washed free of alkali, dried and concentrated to 150 ml. A thick gummy precipitate was removed by drawing the liquid through a 3-cm. layer of calcium hydroxide which was spread over a sintered glass Buchner funnel (diameter, 14 cm.) and by washing phytofluene and carotenoids into the filtrate with 1–2 liters of methanol. From the latter the main portion of the lycopene crystallized out spontaneously; it was filtered off and washed with methanol. The other polyenes were then transferred with water into 1 liter of petroleum ether which was washed, dried and concentrated to 100 ml.

About thirty to forty-five minutes were required to chromatograph this solution with petroleum ether on a 30 × 8 cm. column which was composed of calcium hydroxide plus alumina (Grade F, −80 mesh) 4:1. The figures on the left side which may vary considerably, denote the width of the zones, in mm.

25 Deep orange
5 Deep red
5 Orange
5 Deep red
} mixture of carotenoids
20 Yellow
75 Orange, β-carotene
8 Intensely yellow, neo-β-carotenes and α-carotene with some phytofluene
60 Almost colorless, strongly fluorescing in ultraviolet light, phytofluene

The phytofluene zone and the lower section of the 8-mm. zone were cut out together in ultraviolet light and were eluted with methanol on a large Buchner until the fluorescence of the flow had disappeared. To this filtrate (1.3 liters) 200 ml. of 20% methanolic potassium hydroxide was added. On the next day, 250 ml. of petroleum ether and excess water were added, the layers were separated and the emulsion (if any) was twice extracted with petroleum ether. The combined, only moderately colored petroleum ether solution, after it had been washed free of alkali and dried, was poured onto a 24 × 4.8 cm. column (alumina, Grade A, 150–200 mesh, with 10% Celite) and developed within one-half hour with 1–2 liters of petroleum ether containing 0.25% acetone.

1 Deep red
20 Orange
} mixture of carotenoids
20 Almost colorless
45 β-Carotene, in its lower section, phytofluene
15 α-Carotene, neocarotenes, phytofluene

The phytofluene and the carotene zones partially overlapped to an extent which was shown by a green fluorescence of a part of the carotene sections. (The overlapping will be greater if a stronger adsorbing alumina is employed and a section of the colored layers may then show a distinctly yellowish fluorescence.) The column was cut at the upper border line of the fluorescing section, regardless of the presence of pigment, *i. e.*, about 35 to 40 mm. above the base of the 15-mm. zone. After elution, the polyenes were transferred into 15–20 ml. of petroleum ether and developed with the same solvent on a 27 × 5.8 cm. calcium hydroxide plus alumina column until the pigment was considerably spread out.

150 Pale orange
5 Deep orange
} carotenes
50 Colorless, strongly fluorescing, phytofluene

(In another experiment good separation was achieved by using calcium hydroxide alone.)

Since no empty interspace appeared between the two bottom zones, the main portion of the phytofluene zone (without pigments) was cut out separately from its uppermost part which because of the irregular border line contained some carotenes. This latter fraction was rechromatographed on calcium hydroxide plus alumina (18 × 2.4 cm.) and the eluate of its phytofluene section was added to the main eluate. Finally, an adsorption was carried out on alumina (Grade A, 150–200 mesh and Celite 9:1; column, 20 × 3.8 cm.) by developing with 0.4 liter of petroleum ether plus 0.25% acetone. Essentially only one, very strongly fluorescing, nearly colorless 40-mm. zone appeared from which the phytofluene was transferred into light petroleum ether (b. p. 28–38°). This solution was evaporated in a small weighed conical tube with a ground glass stopper. The thick oily residue was dried in an Abderhalden apparatus at room temperature, over phosphorus pentoxide and paraffin at 0.1 mm. pressure for sixty to ninety minutes.

At different stages of the described operations, aliquot samples were taken, in order to estimate extinctions and

yields. For example, 18 kg. of tomato paste contained roughly 400 mg. of phytofluene. In the saponified crude extract 364 mg. was present, and this amount decreased upon the filtration through calcium hydroxide and three successive chromatograms to 300, 272, 201 and 171 mg. After the second saponification the amount was 163 mg. and, after the last adsorption, 117 mg. or about 30% of the initial content.

The best phytofluene samples as obtained in four independent isolations showed the following values for $E^{1\%}_{1\,cm.}$: 1160, 1230, 1164 and 1080. One 100 mg. sample ($E^{1\%}_{1\,cm.}$ 1080) was distilled at a pressure of about 10^{-4} mm. of mercury; the temperature of the bath was slowly increased from 140 to 185° in the course of two hours. On the inner tube, the bottom of which was located 3–4 mm. above the level of the starting material and was cooled with Dry Ice–acetone, 79 mg. of phytofluene condensed ($E^{1\%}_{1\,cm.}$ 1047); the residue (18 mg.) showed an extinction value of 359.

Isolation of a Crude Phytofluene Sample from *Pyracantha Angustifolia*.—Eight kg. of ground ripe berries was extracted in the manner as described above, and the solution was concentrated to 120 ml. Upon cooling with Dry Ice–acetone, colorless crystals filled the liquid and were centrifuged off. After saponification and repeated chromatographic resolutions on calcium hydroxide (finally on alumina) about 25% of the original phytofluene content was obtained in form of a strongly fluorescing oil, showing the characteristic phytofluene spectrum and $E^{1\%}_{1\,cm.}$ 700.

Analytical Data

The phytofluene samples were kept in darkness and vacuum until the start of the estimations. All substances were free of ash. Most parallel determinations refer to independent samples.

Carbon and Hydrogen.—Calcd. for $C_{40}H_{64}$: C, 88.15; H, 11.85. Found: C, 88.66; H, 12.07; and in a distilled sample: C, 87.24; H, 12.06; after a correction for 0.7% oxygen, the latter analysis would indicate for the oxygen-free substance: C, 87.85; H, 12.14.

Molecular Weight.—(a) Rast micromethod: 0.291 mg. of substance in 2.539 mg. of exaltone (k = 21.3): Δ = 4.7°; 0.630 mg. in 3.441 mg.: Δ = 7.7°; 0.774 mg. in 4.115 mg.: Δ = 8.0°. (b) Cryoscopic macromethod: 47.1 mg. of substance in 6.121 g. of benzene (k = 5.1): Δ = 0.078°; 104.9 mg. in 6.121 g.: Δ = 0.175°. Calcd. for $C_{40}H_{64}$: mol. wt. 544.5. Found: mol. wt. 520, 506, 501, 503 and 500.

Hydrogenated samples: (a) 0.315 mg. in 1.730 mg. of exaltone: Δ = 7.6°; (b) 35.2 mg. in 6.121 g. of benzene: Δ = 0.057°. Found: mol. wt. 510 and 515.

C-Methyl Groups.[14]—15.23 mg. of substance required for the neutralization of the acetic acid formed 14.22 ml. of 0.01 N sodium hydroxide, and after the subtraction of the blank value, 13.5 ml.; 17.83 mg. required 16.3 ml. Found: 4.8 and 5.0 C-methyls.

Double Bonds.—In the apparatus devised by Prater and Haagen-Smit[15] 46.27 mg. of substance has added, in the presence of 21.2 mg. of platinum oxide catalyst and glacial acetic acid, 12.70 ml. of hydrogen (0°, 760 mm.); 44.5 mg. with 17.8 mg. platinum oxide added 12.41 ml. Found: 6.7 and 6.8 double bonds.

Properties and Adsorption Behavior of Phytofluene.—The compound forms a viscous oil which solidifies upon cooling to a glassy mass which apparently is without a crystalline structure. The oil is pale orange but 1% solutions appear colorless to the eye. Even much more dilute pure solutions in petroleum ether show a bluish-green fluorescence in diffuse daylight. Phytofluene is insoluble in methanol or ethanol but easily soluble in petroleum ether, ether or benzene. Upon shaking with equal volumes of petroleum ether and 83% ethanol the ratio of the material in the epiphasic fraction to that in the hypophasic fraction was 100:0 while in parallel tests the following ratios were obtained: anhydrovitamin A or isoanhydrovitamin A, 99:1; and vitamin A, 62:38.

No observable rotatory power was revealed in benzene or petroleum ether. The characteristic extinction values are listed in Table I. Some data concerning the air- and light-sensitivity are given in Table II.

TABLE I

EXTINCTION COEFFICIENTS OF PHYTOFLUENE AT THE MAXIMA (*italicized*) AND MINIMA

In hexane		In benzene	
mμ	$E^{1\%}_{1\,cm.} \times 10^{-3}$	mμ	$E^{1\%}_{1\,cm.} \times 10^{-3}$
332	0.78(7)	*338*	0.69(6)
338	.66(7)	344	.61(2)
348	1.21	*355*	1.06
358	0.61(0)	365	0.57(7)
367	1.13	*374*	.97(2)

TABLE II

DEGREE OF STABILITY OF A PURE SAMPLE OF PHYTOFLUENE AS MEASURED BY THE EXTINCTION VALUES AT 348 mμ

	Extinction in % of that of the starting material (= 100%)
Without solvent	
Exposure to air in a thin layer, in darkness, for 2 hours	18
Same in diffuse daylight	1.5
Kept in a slow stream of CO_2 (Kipp), in darkness, for 2 hours	92
Same in diffuse daylight	42
In petroleum ether solution (b. p. 60–70°)	
Kept under CO_2, in darkness, for 24 hours	99
Same in daylight, in amber glass	99
Same without CO_2	99
In a white flask, under CO_2, illuminated with a fluorescent Mazda lamp, 3500°, at 60 cm. distance, for 7 hours	82
Air slowly bubbled through solution in an Erlenmeyer flask in diffuse daylight for 1 hour	99
Exposed to air, in a flat glass dish for 24 hours (only partial evaporation occurred)	16
Refluxed in diffuse daylight for 30 min.	100
Kept over 20% methanolic KOH for a night	97

A very dilute solution of crude phytofluene in absolute alcohol which contained 0.02% hydrochloric acid and was permitted to stand in the cell of the spectrophotometer diminished rapidly in extinction, *e. g.*, by 20% within ten minutes. After ninety minutes the maximum at 348 mμ was absent. In a parallel experiment with vitamin A the rapid formation of the anhydrovitamin A spectrum with a sharp fine structure took place, in conformity with the data given by other authors.[7,16]

When developed with petroleum ether, phytofluene is only a little more weakly adsorbed than α-carotene on calcium hydroxide, alumina, magnesium oxide or magnesium hydroxide. On silicic acid (Merck, reagent, with 33% Celite) this sequence is inverted and the α-carotene zone appears directly below that of phytofluene. On activated alumina (150–200 mesh), phytofluene when developed with petroleum ether containing 0.25% acetone, forms a sharply defined narrow zone which in the presence of α-

(14) R. Kuhn and H. Roth, *Ber.*, **66**, 1274 (1933).

(15) A. N. Prater and A. J. Haagen-Smit, *Ind. Eng. Chem., Anal. Ed.*, **12**, 704 (1940).

(16) E. M. Shantz, J. D. Cawley and N. D. Embree, THIS JOURNAL, **65**, 901 (1943).

carotene has the tendency to partially overlap with the pigment. (About 200 mg. of phytofluene may be handled on a 24 × 4.8 cm. alumina column.) Somewhat greater becomes the difference in the adsorbabilities of phytofluene and α-carotene when alumina–calcium hydroxide mixtures are used. The phytofluene zone is then markedly broader and the overlapping is of lesser extent. Phytofluene spreads out still more on pure calcium hydroxide and at the same time a differentiation of some stereoisomers may be observed. (We recommend that not more than 100 mg. of substance be placed on a 28 × 8 cm. calcium hydroxide column.) The separation of phytofluene from some members of the stereoisomeric α-carotene set is difficult.

In mixed chromatograms, using calcium hydroxide and petroleum ether, the following sequence was observed from top to bottom: vitamin A, phytofluene, anhydrovitamin A, and isoanhydrovitamin A; the phytofluene zone was flanked by broad, non-fluorescing interzones. Compared with the bluish-white fluorescence of the vitamin A section and with the orange-yellow fluorescence of the anhydro compounds, the phytofluene zone appeared definitely greenish in ultraviolet light.

Summary

The isolation of an oily, colorless, in ultraviolet light strongly fluorescing polyene hydrocarbon (possibly $C_{40}H_{64}$) from commercial tomato paste is described. The compound is photo- and air-sensitive and shows an unusually high adsorption affinity. Some of its spectral and structural characteristics are discussed as well as its role in the bio-synthesis of carotenoid pigments.

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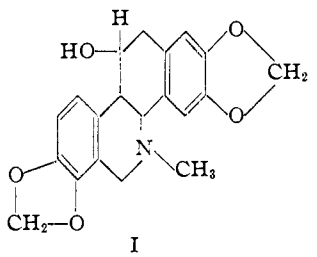
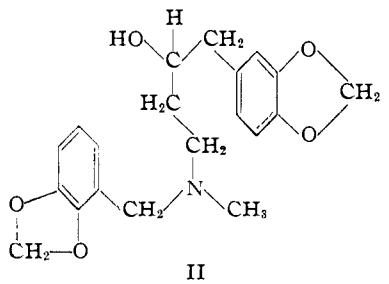
The Synthesis of Some Tertiary Amino Alcohols Related to Chelidonine

BY C. R. NOLLER AND P. D. KNEELAND

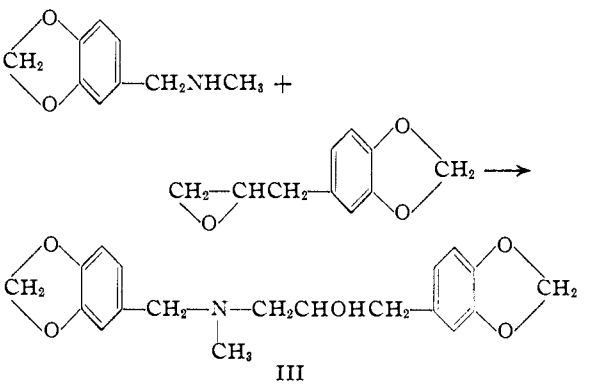
Chelidonine is an alkaloid occurring in celandine (*Chelidonium majus*),[1] and has pharmacological properties resembling those of papaverine.[2] The currently accepted structural formula for chelidonine (I) was proposed by Bruchausen and Bersch.[3] In view of the fact that compounds related to papaverine, but having the nitrogen in an acyclic portion of the molecule, may have antispasmodic properties less than, equal to, or greater than that of papaverine,[4] it was considered desirable to synthesize similar analogs of chelidonine and to determine their pharmacological action. Compound II can be thought of as arising from chelidonine by the breaking of two bonds of the alicyclic rings. Moreover, the product of reaction of safrole oxide with piperonylmethylamine, III, differs from II only in having one less methylene group between the amino group and the hydroxyl group, and a different linkage for one of the methylenedioxyphenyl groups.



I
Chelidonine



II



III

Accordingly the compounds listed in Table I were synthesized by analogous reactions. Their pharmacological action was tested in the laboratory of Dr. P. J. Hanzlik of the Department of Pharmacology, Stanford University Medical School, who states that they show no antispasmodic action, but instead a fairly consistent stimulating action on smooth muscle of different organs. Furthermore, the compounds on intravenous injection depressed the heart sufficiently to be practically useless for therapeutic purposes. The constitution assigned to the compounds is based on the constitution of the reaction product of benzylethylene oxide and ammonia.[5]

(1) Henry, "Plant Alkaloids," P. Blakiston's Son and Company, Philadelphia, Penn., 1939, p. 173.

(2) Hanzlik, *J. Pharmacol.*, **7**, 99 (1915); **18**, 63 (1921); **33**, 387 (1928).

(3) Bruchausen and Bersch, *Ber.*, **63**, 2520 (1930); **64**, 947 (1931).

(4) Rosenmund and co-workers, *ibid.*, **72**, 19, 2161 (1939); Wagner-Jauregg, Arnold and Born, *ibid.*, **72**, 1551 (1939).

(5) Castro and Noller, THIS JOURNAL, **68**, 203 (1946).