

PHYTOCHEMICAL TERMINOLOGY.\*<sup>1</sup>

BY EDWARD KREMERS AND COLABORERS.

The lumber chamber of phytochemistry is replete with terms the significance of which is not fully understood. Such common words as plant acids and alkaloids have given rise to much misunderstanding. It is easy enough to give a definition that represents a certain viewpoint during a given period of phytochemical development. It is rarely that we find in the literature even a brief account of the origin and changed usage of expressions employed, frequently with but little reflection, by most students of science.

Certain terms reflect the name of the plant from which the substance was first isolated or prepared. Thus thymol, which has been found in numerous plants, is named after thyme, but does not reveal either its physical or chemical nature any more than its wide distribution in the vegetable kingdom. Others, though representing identical substances, have been named after a variety of plant sources. Thus the hydrocarbon now known as limonene was formerly designated by twenty different plant sources, such as citrene, carvene, etc.

While many of these substances have found their places in the drawing room of structural chemistry, they are still known by their former names. Thus, for the sake of convenience, we use the simple word limonene rather than the structural designation  $\Delta^1$ <sup>(8,9)</sup> Terpadiene; or the word citronellal rather than Dimethyl-2,6-octadiene-2,6- al-8. Numerous other words, however, have not been interpreted by structural designations, as e. g., podophyllic acid, podophyllotoxin, etc.

In presenting this glossary of phytochemical terms, generic as well as specific, no attempt is going to be made to follow any order, not even an alphabetical order for the present, but to offer such material as happens to be available. The writer will be grateful to all who discover errors, or omissions, or misinterpretations if they will kindly bring them to his attention.

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*Paraffin.* From Lat. *parum*, little, and *affinis*, affinity.<sup>2</sup> A name applied in 1830 by

\* Section on Historical Pharmacy, A. Ph. A., Miami meeting, 1931.

<sup>1</sup> An account of the development of phytochemical terminology would, no doubt, afford interesting reading. Those who are interested in this subject may read to advantage Runge's attempt, made in 1820, and based on the dualistic chemistry of oxygen of that period. (*Neueste Phytochemische Entdeckungen zur Begründung einer wissenschaftlichen Phytochemie: Kritische Bemerkungen über die jetzt herrschende Namenmacherei in der Phytochemie*, Chap. 4.) It reveals in striking manner the danger of forcing the growth of a language, even if the underlying principles are thought to be highly scientific. Should the present study develop far enough, the writer may, at some future date, attempt an account of this sort.

<sup>2</sup> The discovery of paraffin was announced in 1830 (*Schweizer-Seidel's Journal für Chemie und Physik*, 59, page 436) in an article bearing the title "Beiträge zur näheren Kenntnis der trockenen Destillation organischer Körper." (The editor refers to Dr. Reichenbach, in Blansko, Moravia, as the manager of a series of mines, iron furnaces, chemical and other factories in the territory of Count Salm.) From the heavy tar oil of the red beach he obtained upon fractional distillation, an oil from which crystals separated upon cooling. Neither filtration nor strong alcohol effected a separation, but dilute alcohol did. Recrystallized from hot, dilute alcohol they were colorless, odorless and tasteless; sp. gr. 0.8701; they did not react with red oxide of lead, manganese dioxide, sulphur, phosphorus, nitric acid, sulphuric acid, potassium hydroxide, potassium, and a number of other reagents. Hence he suggested the name paraffin (page 455).

Reichenbach<sup>1</sup> to a substance found in wood tar. Because it was not attacked by concentrated nitric acid, or other powerful chemical agents, he named it paraffin in order to designate "its most striking property, its few and weak affinities."<sup>2</sup> Reichenbach apparently supposed this substance to be a definite compound (Comp. Watt). Liebig,<sup>3</sup> in 1843, quotes two formulas, *viz.*  $C_1H_2$  (Gay-Lussac) and  $C_{10}H_{12}$  (Lewy). Writing about Chinese wax, Brodie in 1848 refers to the confusion that had already crept into the usage of this term.<sup>4</sup> Since the lower members of the series to which the hydrocarbons of this "paraffin" belong behave in the same way, Henry Watt<sup>5</sup> proposed to call the whole series the paraffins, better known as the methane series.

With the discovery of other substances like the original paraffin, but different in degree of saturation, the use of the term was extended to include unsaturated chain hydrocarbons<sup>6</sup> as well as cyclic hydrocarbons.<sup>7</sup>

In plant chemistry the term paraffin is applied to either chemical units or to mixtures consisting of solid members of the methane or related series.<sup>8</sup> Sometimes the word paraffin is compounded with the plant name, its source, as, *e. g.*, Aurade-paraffin.<sup>9</sup> Wherever the chemical identity is known, or supposed to be known, the specific names are preferably used.<sup>10</sup>

Whether a phytoparaffin belongs to the methane or ethene series is revealed by its capacity to decolorize bromine. Members of the several polymethylene series do not seem to have been found in plants thus far. For isolation of the paraffin and the identification of the individual hydrocarbons, also for their origin in plants, see hydrocarbons of the methane series, also hydrocarbons of the ethene series.<sup>11</sup>

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He refers to it as a stearoptene (page 457) and calls attention to its possible technical application (candles, lubricant, acid-proof coating, etc.). He reports having obtained it likewise from the white pine and supposes that it may be obtained by the destructive distillation of all woods (page 459).

No elementary analysis is recorded.

According to *Penny Cycl.* XII, 396 of 1838 the substance under consideration was discovered almost simultaneously by Dr. Christison in England and by Reichenbach in Moravia. However, the former named his product petrolin (*Murray's Engl. Dict.* 1).

<sup>1</sup> "Sollte sich auf diese Weise meine Meinung, dass der hier abgehandelte Koerpere in bis jetzt unbekannter, fuer die Wissenschaft neuer sey, bewaehren: so wuerde ich mir eriauben, fuer ihn die Benennung *Paraffin* vorzuschlagen, das Auffallendste in seinem Verhalten, seine wenigen und schwachen Verwandtschaften, bezeichnend, und abgeleitet von den Worten *parum* und *affinis*, welche sich, den Gesetzen der lateinischen Versification zufolge, die vor einem Vocale die Elision der Sylbe *um* erheischt, sprachrichtig zu dem Worte *Paraffinin* zusammen siehen lassen, und durch Abkuerzung *Paraffin* geben, wobei der Accent auf das zweite a faellt." (*Journal fuer Chemie und Physik*, 59 (1830), 455.)

<sup>2</sup> Quotation from Schorlemmer, *Rise and Development of Organic Chemistry*, page 93.

<sup>3</sup> *Handb. d. Chemie*, page 1287.

<sup>4</sup> Ceroten "...besteht....aus einem festen Kohlenwasserstoffe, eine von jenen Substanzen, die unter dem allgemeinen Namen Paraffin umfasst und verwechselt worden sind." (*Annalen*, 67, page 210).

<sup>5</sup> "This substance is a hydrocarbon or a mixture of hydrocarbons of the series  $C_nH_{2n+2}$ ... the name paraffin may therefore be conveniently used as a generic term for the whole series." (Watt's, *Dict. Chem.*, VI, page 705.) (Comp. also Schorlemmer's, *Rise and Development of Org. Chem.* (1894), page 92. See also *Murray's New Engl. Dict.* Paraffin. 3.)

<sup>6</sup> "Das Stearopten des Rosenoels gehoert, wie Flueckiger dargetan hat, zu den Kohlenwasserstoffen der Paraffinreihe  $C_nH_{2n}$ ." (Gildemeister, *Die aeth. Oele*, 2te Aufl., Bd. 2, page 591.)

<sup>7</sup> "Cyclo Paraffins or Polymethylenes." (C. O. Johns, *History of Chem. of Petrol. Research*, page 7; also *Bulletin Am. Petrol. Institute*, June 30, 1926, page 7.)

<sup>8</sup> "The paraffins thus far isolated...." (Gildemeister-Kremers, "The Volatile Oils," 2nd Edition, Vol. I, page 278.)

<sup>9</sup> "Aurade-paraffin od. Neroli camphor," Gild., *Die aeth. Oele*, 2te Aufl., Bd. III, page 101.

<sup>10</sup> *E. g.*, Triacontane, etc.

<sup>11</sup> An enumeration of these will be found in Gildemeister, *Die aeth. Oele*, 3te Aufl., Bd. I, page 302.

In chemical and pharmaceutical technology, hence in commerce, the word paraffin has been used to designate a number of petroleum products. Originally employed as a name for a solid, it has been used for liquids and semi-solids as well. Thus, *e. g.*, in England the word is used to designate benzin, etc., the "gas" of our automotive language.<sup>1</sup> The pharmaceutical usage of the terms liquid paraffin<sup>2</sup> (*Paraffinum liquidum*),<sup>3</sup> soft paraffin<sup>4</sup> (*P. molle*),<sup>5</sup> and solid or hard paraffin<sup>6</sup> (*P. durum*)<sup>7</sup> is well known. The same designations are employed irrespective of whether the hydrocarbons involved are members of the methane series, of the olefene series, or of the several polymethylene series, or whether they are mixtures of two or more series. In order to differentiate its use from that employed for technological or motive purposes it is named "Medicinal Paraffin."<sup>8</sup> Its therapeutic action is indicated in such words as *Laxoparaffin*.<sup>9</sup> Assuming its medicinal use to be understood by all, the geographic source is indicated in such terms as *Russolax*<sup>10</sup> in which any reference to the word paraffin was evidently regarded as superfluous. When paraffin has been employed in place of other unctuous substances, such as fats or fatty oils, its presence may be indicated as in "Paraffin Cold Cream;"<sup>11</sup> also *Paraffitoria*,<sup>12</sup> suppositories made with paraffin.

Other compounded forms are common, such as paraffin candle, paraffin wax, paraffin paper, etc.<sup>13</sup>

Adjective forms are found, *e. g.*, in paraffined (paper), paraffinic (nitrites), paraffinized (preparation) and paraffinoid (as opposed to benzinoid tars).<sup>14</sup>

The German language, which lends itself most readily to compounding of words, records the following: *Paraffinabscheidung*<sup>15</sup> and *Paraffinfilter*<sup>16</sup> (with reference to the form in which the paraffin separates from volatile oils).

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#### PODOPHYLLIC<sup>17</sup> ACID.

Podophyllum acid was first isolated and so called by Podwissotski<sup>18</sup> in 1882. He was unable to obtain it in a crystalline condition and believed it to be physiologically inert. Kuersten,<sup>19</sup> in 1891, showed that it is simultaneously produced with picropodophyllin,<sup>20</sup> from podophyllotoxin, *q. v.* He obtained it in a crystalline condition and expressed its composition by the formula  $C_{20}H_{24}O_9$ . Dunstan and Henry,<sup>21</sup> in 1898, prepared a gelatinous acid  $C_{15}H_{16}O_7$  corresponding to the lactone picropodophyllin  $C_{15}H_{14}O_6$  *q. v.* and showed that it was not an oxidation product as Kuersten had supposed. These relationships, ascertained by Dunstan and Henry, find partial expression in the following empirical formulas:

<sup>1</sup> *Pharm. Journ.*, 57 (1896), 557.

<sup>2</sup> *C. & D.*, Mch. 1, 1919, adv. page 18; see also *Liquid Paraffin*, B. P. 1914, *Ph. Journ.*, July 26, 1919, page 64 of ads; see also *Russolax*.

<sup>3</sup> *Paraffinum liquidum*. See also *Petrolatum liquidum*, U. S. P. X.

<sup>4</sup> Soft paraffin.

<sup>5</sup> *P. molle*. *Am. Dr. & Ph. Rec.*, 23, page 190; from *C. & D.*; Comp. also *P. molle alb.* and *P. m. flav.* *Ph. Journ.*, July 26, 1919, first cover page.

<sup>6</sup> Solid or hard paraffin, also "Paraffin Wax" (*C. & D.*, Mch. 1, 1919, page 18 of ads).

<sup>7</sup> "Paraffin Dur.", B. P." *Pharm. Journ.*, July 26, 1919, page 64 of ads.

<sup>8</sup> *C. & D.*, June 30, 1928, page 119 of ads.

<sup>9</sup> *Arch. d. Pharm.*, 265, page 659.

<sup>10</sup> *Russolax* (see Card Index).

<sup>11</sup> *Ph. Zentrh.*, 65, page 34.

<sup>12</sup> *Paraffitoria* (*Ph. Zentrh.*, 66, page 835); also *Paraffitoria Belladonnae* (*D. Med. Woch.*), Jan. 19, 1922, No. 3, page 11 of adv.

<sup>13</sup> See Murray's *New English Dictionary* for additional illustrations and quotations.

<sup>14</sup> *Ibid.*

<sup>15</sup> Gild., *Die aeth. Oele*, 2te Aufl. Bd. III, pages 491 and 616.

<sup>16</sup> *Ibid.*, Bd. II, page 640.

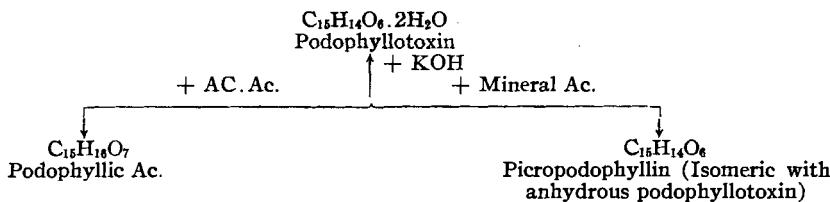
<sup>17</sup> For the etymological derivation see *Picropodophyllin*.

<sup>18</sup> *Pharm. Journ.* (3rd series), 12, pages 217 and 1011.

<sup>19</sup> See footnote <sup>2</sup> on page 255.

<sup>20</sup> See *Podophyllotoxin*.

<sup>21</sup> See footnote <sup>3</sup> on page 255.



*Preparation.*—Podwissotski<sup>1</sup> obtained the resinous podophyllic acid during the preparation of podophyllotoxin, when ether was added to the chloroformic solution of the impure product. Kuersten<sup>2</sup> isolated crystalline podophyllic acid by treating an alkaline solution of podophyllotoxin with potassium permanganate. Dunstan and Henry<sup>3</sup> prepared a substance, which, they suggested, was the same as Podwissotski's picropodophyllic acid and Kuersten's podophyllic acid, by boiling podophyllotoxin with alkali, cooling carefully and acidifying with dilute acetic acid. After a few hours the whole mass solidified to a transparent jelly. Every attempt to isolate the gelatin-like solid from the gel failed. The various salts prepared therefrom were used as a means of identification.

*Properties.*—The acid  $\text{C}_{15}\text{H}_{14}\text{O}_7$  analyzed in the form of its salts is considered to result from the addition of the elements of a molecule of water to the lactone picropodophyllin  $\text{C}_{15}\text{H}_{14}\text{O}_8$ . From the aqueous solutions, well-formed crystals were obtained of the sodium, silver and copper salts.<sup>4</sup>

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#### PICROPODOPHYLLIN.

This crystalline substance was first prepared from *Podophyllum* and named by Podwissotski<sup>5</sup> in 1882. (From Gr. *πυκνός* bitter, and Gr. *πόδος*, foot + Gr. *φύλλον*, leaf.) He found it to possess the medicinal properties of the "resin" (Podophyllin, *q.v.*), but much more pronounced. Kuersten,<sup>6</sup> in 1891, obtained the same substance and suggested that it is an isomer of podophyllotoxin.<sup>7</sup> Dunstan and Henry,<sup>8</sup> in 1898, isolated a substance which had all the properties of Podwissotski's picropodophyllin and assigned to it the formula  $\text{C}_{15}\text{H}_{14}\text{O}_8$ . They regarded it as the lactone of podophyllic acid, also as isomeric with podophyllotoxin (see Podophyllic Acid). When treated with various reagents it yielded similar results to those obtained from podophyllotoxin.<sup>7</sup>

*Preparation.*—Podwissotski<sup>9</sup> obtained picropodophyllin by treating the alcoholic solution of podophyllotoxin, *q.v.* with slaked lime, drying thoroughly and extracting with alcohol. From the sufficiently concentrated alcoholic solution picropodophyllin crystallized in long, silky crystals. Kuersten,<sup>6</sup> prepared it by treating podophyllotoxin with alkalies. Thus, on heating podophyllotoxin with aqueous ammonia he obtained the crystalline product. Dunstan and Henry<sup>8</sup> boiled podophyllotoxin with alkali and obtained a white precipitate which was soluble in hot alcohol. On cooling, this solution deposited crystals in the form of a silky mass. These were purified by recrystallization from hot alcohol.

*Properties.*—This lactone which crystallizes in colorless, silky crystals melts at 227°. It is easily soluble in chloroform, acetone and hot alcohol, but nearly insoluble in cold water and cold alcohol. The taste is very bitter. It is optically inactive.<sup>8</sup>

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#### PODOPHYLLOTOXIN.

This substance was first isolated in an amorphous condition from *Podophyllum peltatum* and so named by Podwissotski<sup>10</sup> in 1882. It was regarded by him as the bearer of the cathartic

<sup>1</sup> See footnote <sup>18</sup> on page 254.

<sup>2</sup> *Arch. d. Pharm.*, 229, page 220.

<sup>3</sup> *Journ. Chem. Soc.*, 73, page 209.

<sup>4</sup> *Ibid.*, page 216.

<sup>5</sup> *Pharm. Journ.* (3rd series), 12, pages 217 and 1011.

<sup>6</sup> *Arch. d. Pharm.*, 229, page 220.

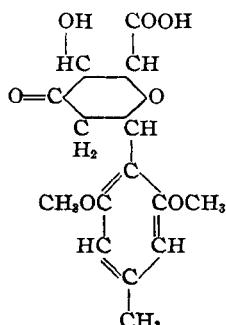
<sup>7</sup> See under Podophyllotoxin.

<sup>8</sup> *Journ. Chem. Soc.*, 73, page 209.

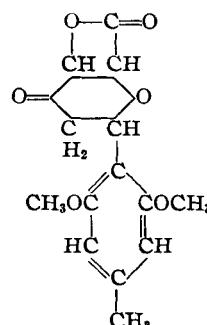
<sup>9</sup> *Pharm. Journ.* (3rd series), 12, pages 217 and 1011.

properties of the drug. Kuersten,<sup>1</sup> in 1891, obtained it in crystalline condition and assigned to it the formula  $C_{20}H_{24}O_6 \cdot 2H_2O$ . Dunstan and Henry,<sup>2</sup> in 1898, isolated what they regarded as the same substance from *P. emodi*, but assigned to their crystalline product the formula  $C_{16}H_{14}O_6 \cdot 2H_2O$ . Like its isomer, picropodophyllin  $C_{18}H_{14}O_6$ , it contains two methoxy groups. Both yield monobrom derivatives. When fused with potassa, they yield orcinol and acetic acid. When distilled with zinc dust, both yield dimethyl naphthalene.

When acted upon with aqueous alkali, podophyllotoxin yields, on the one hand, the isomeric crystalline lactone picropodophyllin  $C_{18}H_{14}O_6$ ; and, on the other hand, a gelatinous acid  $C_{16}H_{16}O_7$  of which picropodophyllin is assumed to be the lactone (see Podophyllic Acid).<sup>2</sup> This is regarded as identical with the picropodophyllic acid of Podwissotski (which Kuersten<sup>1</sup> looked upon as an oxidation product of podophyllotoxin). These related substances are regarded as derivatives of a substituted phenylated hydropyronine, *viz.*:



Podophyllic Acid<sup>3</sup>  
(Dimethoxy, methyl-phenyl hydropyronine  
carboxylic ac.)



Picropodophyllin<sup>4</sup>  
(Lactone thereof)

No structural expression is given to the isomerism of podophyllotoxin and picropodophyllin.

*Preparation.*—Podwissotski obtained podophyllotoxin (amorphous) by precipitating the chloroform extract of the rhizome with light petroleum<sup>5</sup> and Kuersten showed that by fractionally precipitating a chloroform solution of this crude podophyllotoxin the crystalline product can be obtained.<sup>1</sup> Dunstan and Henry extracted the official podophyllin, prepared, however, from *P. emodi*, with chloroform. The dark brown extract was boiled with benzene, and the hot benzene solution filtered into a cold flask and allowed to cool somewhat. By this means a good deal of resin was removed. The solution was then poured from the deposited resin, boiled for some time with animal charcoal, filtered, and set aside for several days, when almost colorless crystals of podophyllotoxin were obtained. These were purified by recrystallization either from a mixture of chloroform and light petroleum or from alcohol and water.

*Properties.*—The colorless crystals thus obtained with two molecules of water of crystallization  $C_{18}H_{14}O_6 \cdot 2H_2O$  melt at 117° and are readily soluble in alcohol, acetone, chloroform and hot benzene, but only slightly in water. Its taste is very bitter.  $[\alpha]_D = -94^\circ 48'$ . Anhydrous podophyllotoxin, obtained by crystallization from absolute alcohol, melts at 157°. The anhydrous product may also be obtained by heating the hydrate for a few minutes to 117°, dissolving the dried product in chloroform and adding dry light petroleum until the mixture becomes slightly turbid. After standing a few hours, the anhydrous substance crystallizes out.  $[\alpha]_D = -78^\circ 4'$ .

Anhydrous podophyllotoxin, when exposed to air and light for several weeks, acquires a purple color; the hydrated substance, however, appears to be quite stable under these conditions.

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<sup>1</sup> *Arch. d. Pharm.*, 229, page 220.

<sup>2</sup> *Journ. Chem. Soc.*, 73, page 209.

<sup>3</sup> *Ibid.*, page 223.

<sup>4</sup> *Do.*, page 223.

<sup>5</sup> See footnote <sup>3</sup> on page 255.

## PODOPHYLLO-RESIN.

This amorphous, physiologically active compound was first isolated and named by Dunstan and Henry<sup>1</sup> in 1898. All attempts to crystallize the compound were unsuccessful. However, a crystalline acetyl derivative was obtained from which the authors concluded that it probably had the formula  $C_{12}H_{12}O_4$ . They assumed that the physiological activity of the drug is partly due to this compound.

*Preparation.*—After the removal of podophyllotoxin and quercetin from the resin of *Podophyllum* there remained a dark colored amorphous mass partly soluble in alcohol. After the purification of the alcohol-soluble portion, it is obtained as a reddish brown transparent substance softening and becoming semi-liquid a few degrees above ordinary temperature.

*Properties.*—An amorphous, reddish brown, transparent substance, soluble in alcohol but insoluble in petroleum ether, ether, chloroform, etc. It yields a crystalline acetyl derivative, and has a suggested formula of  $C_{12}H_{12}O_4$ .

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## PODOPHYLLOQUERCETIN.

This yellow coloring material was first isolated by Podwissotski<sup>2</sup> in 1882, who obtained it in a crystalline form by sublimation. He found it to be without emetic or aperient action, but perhaps the cause of some intestinal pain which accompanies the administration of *Podophyllum*, Kuersten,<sup>3</sup> in 1891, concluded that it probably was not identical with quercetin, and assigned to it the formula  $C_{23}H_{16}O_{11}$ . Dunstan and Henry,<sup>4</sup> in 1898, considered it to be identical with the quercetin of quercitron bark.

*Preparation.*—Podwissotski<sup>2</sup> prepared podophylloquercetin from podophyllin. After extracting the resin with petroleum ether and chloroform, it was dried and exhausted with ether which removes this substance in a pure form. The ether was recovered and the residue treated with lead acetate, which forms a compound soluble in acetic acid. The lead compound was decomposed in the usual way and the reaction product exhausted with ether. On recovering the ether, podophylloquercetin appears as a yellow powder which may be obtained in a crystalline form by sublimation or by precipitation from an ammoniacal solution with ether. Kuersten<sup>3</sup> obtained it in much the same way, *viz.*, after the resin had been exhausted with petroleum ether and chloroform, it was extracted with ether. The ether being recovered, the residue was dissolved in cold glacial acetic acid. On standing crystals of podophylloquercetin appeared. Dunstan and Henry<sup>4</sup> prepared this coloring material by dissolving the residue from the ethereal solution of the resin which had been previously extracted with chloroform, in hot glacial acetic acid. On cooling crystals were obtained which had the properties of ordinary quercetin.

*Properties.*—Podophylloquercetin crystallizes in short needles of a yellow color and metallic luster. It melts at 247° to 250° at which temperature it decomposes, partially subliming to minute yellow crystals. It is soluble in alcohol and ether, sparingly soluble in chloroform and insoluble in water. With aqueous ammonia, potassa and caustic soda it forms bright yellow solutions. Its combinations with alkaline earths are insoluble. Continued action of alkalies decompose it. Exposure to air changes the color to green. Alkaline copper solution is easily reduced when warm, as well as ammoniacal silver solution. Kuersten<sup>3</sup> records its melting point as being 257° to 277°.

A. H. UHL.

## SOME ASPECTS OF PROFESSIONAL PHARMACY.\*

BY DEAN CHARLES B. JORDAN.

About five years ago Dean Spease told me of what, at that time, was probably a dream and now it has reached its fruition. He said that he hoped to form an

<sup>1</sup> *Jour. Chem. Soc.*, 73, page 209.<sup>2</sup> *Pharm. Jour.* (3rd series), 12, pages 217 and 1011.<sup>3</sup> *Arch. d. Pharm.*, 229, page 220.<sup>4</sup> *Jour. Chem. Soc.*, 73, page 209.

\* Address before Academy of Pharmacy and Northern Ohio Branch, January 12, 1932.  
See page 86.