[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH LABORATORY]

1,2,3,4-Dibenzphenanthrene and its Derivatives. I. Synthesis with Chrysene as Starting Material

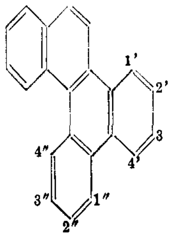
BY FELIX BERGMANN AND H. EMILE ESCHINAZI

1,2,3,4-Dibenzphenanthrene (I) is a carcinogen of special interest. Its strong activity was predicted by Hewett[1] from the behavior of 1- and 2-methyl-3,4-benzphenanthrene and serves as an excellent example for the correlation that exists between the spatial form of a molecule and its blastogenic properties. Additional rings or methyl groups, when attached to the same point of the basal skeleton, influence its carcinogenic activity in the same direction. On the other hand, the hydrocarbon I forms a bridge between the 3,4-benzphenanthrene and the 1,2-benzanthracene series, which, at first sight, are of entirely different character. If, however, carbon atoms 4′ and 1″ are connected by a two-carbon bridge, as in IIa (dotted line), a derivative of the strong carcinogen 9,10-dimethyl-1,2-benzanthracene is obtained.[2] In a similar way, by a bridge between carbon atoms 1′ and 10 the very potent carcinogen 1,2,3,4-dibenzpyrene (IIb) is formed.

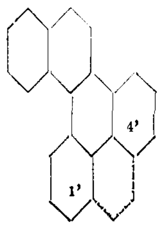
As an approach to the synthesis of IIa we have tried to prepare 1″-methyl-1,2,3,4-dibenzphenanthrene (III) and wish to describe here some observations on the different stages of the synthesis which, however, was not accomplished.

Beyer[3] has used chrysene for a synthesis, on which the preparation of I could be based, namely, condensation with succinic anhydride, reduction and cyclization of the corresponding butyric acid, but the cyclic ketone IV could not be reduced, and this method failed. Because of the similarity of 6-vinylchrysene to α-vinylnaphthalene, we have used this hydrocarbon and its derivatives for the Diels–Alder reaction.

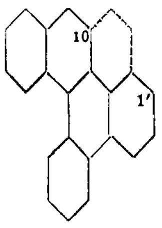
(a) From the Friedel–Crafts reaction of chrysene with acetyl chloride, Funke[4] isolated two isomeric methyl ketones, which he describes as the respective 5- and 6-derivatives, in analogy with the α- and β-substitution of naphthalene in the same type of reaction. Newman,[5] however, found authentic 5-ethylchrysene to be different from the reduction product of Funke's "5-acetylchrysene." We have now succeeded in isolating in addition to the two monoacetyl chrysenes, a diacetyl derivative of m. p. 296°.



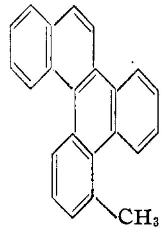
I



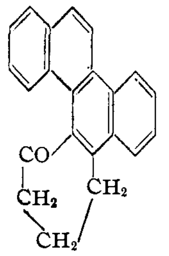
IIa



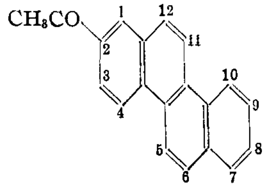
IIb



III



IV



V

In view of the high m. p. of the second acetyl derivative obtained (254°) and of the corresponding ethyl and isopropenyl compound (236 and 288°, respectively), it is inferred that substitution occurred in the 1- or 2-position because among the methyl derivatives of chrysene the 1- and 2-compound have a remarkably high melting point, namely, 250°[6] and 225°[7] as contrasted with 170°[6], 151°[6,7], 118°[5], and 161°[8] for the 3-, 4-, 5- and 6-methyl derivatives, respectively.

As the reduction product of the acetylchrysene m. p. 254° is different from the 1-ethyl compound, we ascribe to it tentatively formula V of 2-acetylchrysene. It will be of interest to see whether the diacetyl derivative has a symmetrical structure,

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(1) Hewett, *J. Chem. Soc.*, 193 (1938).

(2) A similar idea has recently been expressed by Bachmann and Safir, THIS JOURNAL, **63**, 2601 (1941); compare also Hewett, *J. Chem. Soc.*, 293 (1940).

(3) Beyer, *Ber.*, **71**, 915 (1938).

(4) Funke and Müller, *J. prakt. Chem.*, **144**, 242 (1936).

(5) Newman, THIS JOURNAL, **62**, 870 (1940).

(6) Bachmann and Struve, *J. Org. Chem.*, **5**, 416 (1940).

(7) Bachmann and Struve, *ibid.*, **4**, 456 (1939).

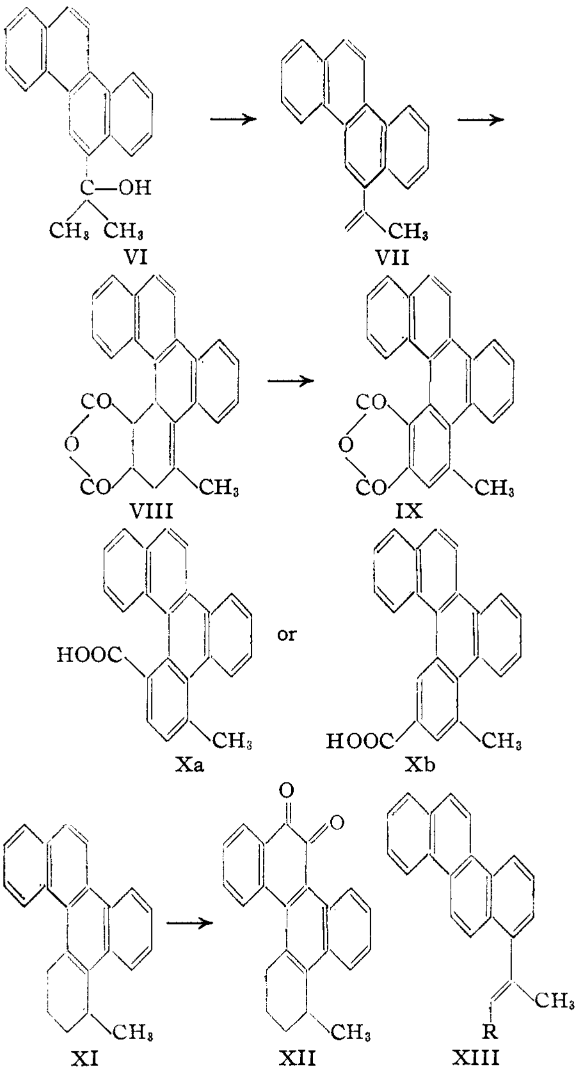
(8) Newman, THIS JOURNAL, **60**, 2947 (1938).

like, *e. g.*, the disubstitution products of pyrene and perylene in Friedel–Crafts reactions, or represents a combination of the two monosubstituted derivatives.

(b) Grignard reaction of 6-acetylchrysene with methylmagnesium iodide gave a mixture of the carbinol (VI) and the diene (VII). Conversion of VI into VII must be carried out with great care, because gentle heating with acids causes poly(di-?)merization. The best method for dehydration consists in adding a few drops of concentrated sulfuric acid to a solution of VI in cold acetic acid. If this reaction is carried out at 100°, a hydrocarbon of m. p. 307° is obtained, which results also from heating VII with stannic chloride.[9]

(c) Diels–Alder reaction of 6-isopropenylchrysene (VII) with maleic anhydride was tried under a variety of conditions, until the most suitable method was found. When the diene was heated with five equivalents of the anhydride on a steam-bath, the polymer of m. p. 307° was the only reaction product. Xylene as solvent yielded the desired adduct (VIII) in unsatisfactory yield. In view of the easy dehydration of VI, we then tried to melt it together directly with the anhydride at 120°, and, indeed, obtained VIII in 40% yield. Finally, it was found that in boiling acetic anhydride the diene condensed to 75%. The simplest method consists in heating directly, in the same solvent, the carbinol VI with maleic anhydride; the adduct results in 80% yield. VIII exists in two polymorphic modifications of identical m. p. and mixed m. p., but of different solubility. From saturated solutions in the hot, prisms are obtained, whereas dilute solutions deposit needles. Formula VIII, which we ascribe to the adduct, contains the double bond in its "original" position, although a shift of this bond to restore the disturbed aromatic chrysene skeleton could be expected. However, only form VIII explains the easy redissociation into the components, when heated above the m. p., especially in the presence of zinc dust.

(d) Aromatization of VIII with lead tetraacetate gave a 20% yield of 1″-methyl-1,2,3,4-dibenzphenanthrene-3″,4″-dicarboxylic acid anhydride (IX), but this product could not be decarboxylated to the desired hydrocarbon (III). With basic copper carbonate in quinoline, partial decarboxylation occurred, leading to a monocarboxylic acid (Xa or b).[10] Aromatization of VIII with bromine gave IX in impure form. We now attempted to reverse the order of reactions, carrying out decarboxylation before aromatization. Potassium hydroxide or calcium oxide gave only intractable tars. When, however, the adduct was heated directly with selenium to 260°, decarboxylation took place prior to dehydrogenation, the product, obtained in 50% yield, being tetrahydromethyldibenzphenanthrene, probably (XI), which was characterized as its quinone (XII), but could not be aromatized with selenium at 360°. This observation is contrary to the behavior of the corresponding adducts of α- and β-vinylnaphthalene,[11] both of which yielded the aromatized anhydrides with dehydrogenating agents.



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[9] E. Bergmann, Taubadel and Weiss, *Ber.*, **64**, 1493 (1931); Staudinger and Breusch, *ibid.*, **62**, 442 (1929).

[10] Compare E. Bergmann and F. Bergmann, THIS JOURNAL, **60**, 1805 (1938).

[11] Cohen and Warren, *J. Chem. Soc.*, 1315 (1937).

The influence of aliphatic side chains on the blastogenic activity of aromatic hydrocarbons has been studied by several investigators.[12] It is generally known that in a homologous series the chemotherapeutical index reaches a maximum at a certain chain length because of the counter-effect of two (or more) opposing factors, on which pharmacological activity depends. Carcinogenic hydrocarbons as a class differ, however, fundamentally from all other kinds of biologically active substances by their lack of polar groups. It follows, therefore, that they act as such, in a state of adsorption to a cell acceptor, *i. e.*, the molecules remain in a two-dimensional phase during their action. We have to assume further, as mentioned above, that side-chains produce active compounds only if they imitate an active cyclic structure. It can now be seen immediately that in a plane a methyl group has only one position available, an ethyl group at 1–2, a *n*-propyl residue 2–4, a *n*-butyl group 4–8, etc.[13] The probability that a side-chain will occupy just the desired "pseudocyclic" position, thus decreases with increasing chain length. This conclusion is in agreement with the experiments of Cook[14] on 5-*n*-alkyl-1,2-benzanthracenes. Branching of the aliphatic chains modifies the described effect. An isopropyl group has only one possible position, the *s*-butyl group 2–4, the *s*-amyl group 6–8, etc. For unsaturated radicals the number of possibilities is still further reduced to half by the fixed arrangement about the double bond. To test this hypothesis, we have prepared, by means of Grignard reactions with 6-acetylchrysene, a series of homologous hydrocarbons XII, where R = H, CH_3, C_2H_5, *n*-C_3H_7, and also the corresponding saturated compounds of the first two members. From Table I, it is seen that the m. p.'s fall very rapidly with increasing chain length, and it may be that the higher members of the series represent a mixture of *cis*- and *trans*-forms.

In accordance with the behavior of α,β-dimethylstyrene, the hydrocarbon XII (R = CH_3) did not suffer polymerization by hot mineral acids. On the other hand, it is also unreactive toward maleic anhydride under the conditions described above.

TABLE I

Compound	Formula	M. p., °C.	M. p. of picrate, °C.	M. p. of corresponding dihydro compound, °C.	Picrate, °C.
XII, R = H(= VII)	$C_{21}H_{16}$	161	144	137	144
R = CH_3	$C_{22}H_{18}$	160	132–133	100	133
R = C_2H_5	$C_{23}H_{20}$	102	138-140		
R = *n*-C_3H_7	$C_{24}H_{22}$	40?	129-130		

Experimental Part

1. **6-Acetylchrysene.**—After many trials the best method found was the following: In a three-necked flask, fitted with an efficient stirrer and reflux condenser, are mixed chrysene (40 g.) and acetyl chloride (75 cc.) with carbon disulfide (500 cc.). Aluminum chloride (35 g.) is added at room temperature within five minutes. Stirring is continued for eight hours at room temperature and the temperature then raised to 60° very slowly (during about six hours). The solvent is now distilled off, and the residue decomposed with ice-cold hydrochloric acid. Traces of solvent are removed by steam-distillation, and the remaining black cake is pounded in a mortar and dried on a water-bath. The dry powder is now extracted two or three times with boiling benzene and this solution distilled *in vacuo*, b. p. 251° (0.1 mm.). The distillate solidified on trituration with methanol. Recrystallization from petroleum ether (130°) gave yellowish rods, m. p. 145°, yield 35 g. The black residue, after extraction with benzene, is treated several times with boiling xylene and the extracted material again distilled. After a small head of 6-acetylchrysene, two fractions can be isolated: (a) b. p. 255–260° (0.05 mm.); from glacial acetic acid needles, m. p. 254° (V); with concd. sulfuric acid cherry-red color.

Anal. Calcd. for $C_{20}H_{14}O$: C, 88.9; H, 5.2. Found: C, 88.8; H, 5.1.

(b) B. p. 270–280° (0.05 mm.); from much butanol as microcrystalline needles, m. p. 296°.

Anal. Calcd. for $C_{22}H_{16}O_2$: C, 84.6; H, 5.1. Found: C, 84.3; H, 5.5.

2. **Grignard Reactions.**—These were carried out with three equivalents of the magnesium compound and the second component was added either as powder or suspended in xylene. The ether was then removed and the xylene solution boiled for four hours.

(a) With methylmagnesium iodide: on decomposition of the reaction mixture from 14 g. of 6-acetylchrysene, a white precipitate settled down immediately. It was carefully washed free from traces of acid and recrystallized from petroleum ether (130°) (the solution has usually a faintly violet color) as rods, m. p. 172° (VI); with concd. sulfuric acid, deep violet color; yield, 9 g. or 60%.

Anal. Calcd. for $C_{21}H_{18}O$: C, 88.1; H, 6.3. Found: C, 87.8; H, 6.4.

On preparation of the picrate of VI dehydration occurs so that the product is identical with the picrate of the diene (VII); red needles (from glacial acetic acid), m. p. 144°.[15]

Anal. Calcd. for $C_{21}H_{19}O_7N_3$: N, 8.5. Found: N, 8.9.

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(12) For a comprehensive review of this subject see Fieser, *Am. J. Canc.*, **XXXIV**, 37 (1938).

(13) The maximal number of possibilities depends not only on the length of the side-chain, but also on the structure of the substituted cyclic compound and on the point of substitution. Therefore a maximal and minimal number is given in every case.

(14) Cook and Robinson, *J. Chem. Soc.*, 303 (1940).

(15) All the picrates in this series showed a strong tendency to dissociate and could not be entirely freed from picric acid. Therefore, their nitrogen analyses gave usually too high values.

The soluble part from the Grignard mixture was purified by distillation, b. p. 220° (2 mm.); white plates (from glacial acetic acid), m. p. 161° (VII), yield 3.5 g. or 25%.

Anal. Calcd. for $C_{21}H_{16}$: C, 94.0; H, 6.0. Found: C, 94.2; H, 5.9.

The same diene was obtained in quantitative yield from the carbinol VI in acetic acid solution, when cold concd. sulfuric acid was added dropwise. If the reaction was, however, carried out above 100°, and also in numerous other experiments with the diene VII, *e. g.*, on boiling its solution in stannic chloride, a high-melting dimer was obtained. It was recrystallized from ethyl benzoate–acetic anhydride or from nitrobenzene, m. p. 307°.

Anal. Calcd. for $(C_{21}H_{16})_2$: C, 94.0; H, 6.0. Found: C, 93.7; H, 6.3.

The isomeric acetylchrysene of m. p. 254° yielded in the same way an isopropenyl compound, m. p. 288° (leaflets from glacial acetic acid).

Anal. Calcd. for $(C_{21}H_{16})_k$: C, 94.0; H, 6.0. Found: C, 94.3; H, 6.0.

(b) With ethylmagnesium bromide: the reaction yielded 26% of carbinol, m. p. 119° (rods, from high-boiling petroleum ether), and 68% of the diene (XII, R = CH_3), m. p. 159–160° (leaflets, from glacial acetic acid). The carbinol was dehydrated quantitatively by the method just described. Both compounds were found to be inert toward maleic anhydride and to yield the same picrate of m. p. 132–133° (red needles, from glacial acetic acid).

Anal. (a) of the carbinol. Calcd. for $C_{22}H_{20}O$: C, 88.0; H, 6.7. Found: C, 87.8; H, 6.5. (b) of the diene. Calcd. for $C_{22}H_{18}$: C, 93.6; H, 6.4. Found: C, 93.3; H, 6.3. (c) of the picrate. Calcd. for $C_{28}H_{21}O_7N_3$: N, 8.2. Found: N, 8.5.

(c) With *n*-propylmagnesium bromide: in this case, only the diene was obtained as a yellow oil, b. p. 210–215° (0.1 mm.); yield, 67%. After some months microcrystalline needles appeared (XII, R = C_2H_5), m. p. 102° (from ethanol).

Anal. Calcd. for $C_{23}H_{20}$: C, 93.2; H, 6.8. Found: C, 93.2; H, 6.6.

The picrate had m. p. 138–140° (red needles, from glacial acetic acid).

Anal. Calcd. for $C_{29}H_{23}O_7N_3$: N, 8.0. Found: N, 8.3.

(d) With *n*-butylmagnesium bromide: only the diene is obtained, as a yellow oil, b. p. 230–235° (0.1 mm.). After six months, it crystallized partially, but the solid had a low m. p. (about 40°) and could not be purified in crystalline state.

Anal. (of the oil) Calcd. for $C_{24}H_{22}$: C, 92.9; H, 7.1. Found: C, 93.1; H, 7.0.

The picrate was made as above, m. p. 129–130°.

Anal. Calcd. for $C_{30}H_{25}O_7N_3$: N, 7.8. Found: N, 8.2.

3. **Catalytic Reductions.**—(a) of VII: 6-isopropenylchrysene (2.7 g.) in ethyl acetate (150 cc.) in the presence of a Pd–$BaSO_4$ catalyst absorbed 220 cc. of hydrogen at room temperature in three hours (calcd. 220 cc.). The 6-isopropylchrysene was recrystallized from petroleum ether (130°) as needles, m. p. 137°, yield 2.4 g.

Anal. Calcd. for $C_{21}H_{18}$: C, 93.3; H, 6.7. Found: C, 93.1; H, 6.5.

The picrate had m. p. 144–145° (needles, from glacial acetic acid); mixed m. p. with the picrate of the unsaturated analog VII, 138–140°.

Anal. Calcd. for $C_{27}H_{21}O_7N_3$: N, 8.3. Found: N, 8.7.

(b) of XII (R = CH_3): 1.6 g. of this hydrocarbon absorbed the required amount of hydrogen only during twenty-four hours. From petroleum ether (80°) it gave sharp-edged plates, m. p. 100°.

Anal. Calcd. for $C_{22}H_{20}$: C, 93.0; H, 7.0. Found: C, 93.1; H, 6.8.

The picrate had m. p. 133° (beautiful red slender needles, from glacial acetic acid); mixed m. p. with the picrate of XII, 129–130°.

Anal. Calcd. for $C_{28}H_{23}O_7N_3$: N, 8.2. Found: N, 8.45.

Neither of the two higher homologs of XII was reduced at room temperature or at 80°.

4. **Condensation with Maleic Anhydride.**—Carefully crystallized dimethyl-6-chrysenylcarbinol (VI) (8.5 g.), free from traces of acid, was boiled for two hours with maleic anhydride (17 g., 5 equiv.) in acetic anhydride (30 cc.). On cooling, 9 g. of adduct VIII was obtained. The mother liquor yields an additional crop of 1 g. by cautious addition of water. Recrystallization from acetic anhydride yielded either prismatic blocks (from concentrated solutions) or white needles (from dilute solutions), m. p. 262°.

Anal. Calcd. for $C_{25}H_{18}O_3$: C, 82.0; H, 4.9. Found: C, 82.4; H, 5.0.

Aromatization with Lead Tetraacetate.—A hot solution of VIII (5 g.) in acetic anhydride (100 cc.) was added to a hot solution of lead tetraacetate (17 g.) in acetic acid (100 cc.), and the mixture boiled for two hours. On cooling, yellow rods were deposited, m. p. 325° (from ethyl benzoate) (IX), yield 5 g., 20%.

Anal. Calcd. for $C_{25}H_{14}O_3$: C, 82.9; H, 3.9. Found: C, 83.0; H, 3.9.

Dehydrogenation of VIII in acetic acid solution with bromine, in the presence of sodium acetate,[16] gave the compound IX in about 30% yield, but in a form which could not be purified satisfactorily from contaminations.

Decarboxylation.—(a) When the adduct VIII (1.2 g.) was heated with zinc dust (0.5 g.) in a low vacuum (100 mm.), a yellow liquid distilled off at 280–300°. It was triturated with acetic acid and identified as the diene VII, m. p. 160°.

(b) VIII (5 g.) and selenium (2.5 g.) were heated slowly to 270–310° (bath temperature) during four hours. A small amount of crystalline material (150 mg.) sublimed at normal pressure. The reaction mixture was extracted with ethyl acetate, and the extracted material distilled, b. p. *ca.* 250° (0.5 mm.); 2.2 g. of a yellow sirup was obtained, which solidified after treatment with acetone–isopropanol; from isopropanol as yellowish rods, m. p. 139° (XI), which were identical with the sublimed portion.

Anal. Calcd. for $C_{23}H_{20}$: C, 93.2; H, 6.8. Found: C, 93.1; H, 6.8.

The picrate crystallized from acetic acid in red rods, m. p. 140°.

Anal. Calcd. for $C_{29}H_{23}O_7N_3$: N, 8.0. Found: N, 8.55.

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[16] Adams and Geissman, THIS JOURNAL, **61**, 2088 (1939).

The hydrocarbon XI (50 mg.) was oxidized with potassium dichromate (60 mg.) in acetic acid (2 cc.) by boiling for ten minutes. The quinone was precipitated by water, then treated with ethanol and recrystallized from high-boiling petroleum ether as short red rods, m. p. 178° (XII).

Anal. Calcd. for $C_{23}H_{18}O_2$: C, 84.7; H, 5.5. Found: C, 84.4; H, 5.7.

When the hydrocarbon XI (0.8 g.) was heated with selenium (0.4 g.) to 310–320° for twelve hours, and the mass extracted with boiling xylene, an oil, b. p. 260–265° (0.02 mm.), was obtained, which on recrystallization from isopropanol yielded yellowish rods, m. p. 137–138°, identical with the starting material, and a minute amount of small blocks, which adhered to the wall. This second substance was separated and yielded from an acetic acid solution a picrate of m. p. 165° (red rods). Its amount, however, was not sufficient for analysis.

Decarboxylation of IX with Copper.—Five grams of the aromatic anhydride IX and basic copper carbonate (5 g.) were heated in quinoline (35 cc.) for half an hour. Then benzene (100 cc.) was added and the solution washed with excess dilute sulfuric acid. On concentrating the benzene solution, a small amount of crystals separated; from butyl acetate as beautiful prisms, m. p. 292–293° (Xa or b).

Anal. Calcd. for $C_{24}H_{16}O_2$: C, 85.7; H, 4.8. Found: C, 85.4; H, 5.1.

Summary

1. The central position of 1,2,3,4-dibenzphenanthrene in the system of carcinogenic hydrocarbons is discussed.
2. 6-Isopropenylchrysene is used in the Diels–Alder reaction for the attempted synthesis of 1″-methyldibenzphenanthrene. This route led finally to the tetrahydro stage (XI) of the desired aromatic hydrocarbon.
3. An hypothesis has been advanced for the influence of aliphatic side-chains on the activity of carcinogenic hydrocarbons.
4. A series of 6-alkenyl- and 6-alkylchrysenes is synthesized, related to 1″-methyl-1,2,3,4-dibenzphenanthrene, for carcinogenic tests.

REHOVOTH, PALESTINE RECEIVED NOVEMBER 6, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, SCHOOL OF TROPICAL MEDICINE OF THE UNIVERSITY OF PUERTO RICO, UNDER THE AUSPICES OF COLUMBIA UNIVERSITY]

Puerto Rican Fatty Oils. IV. Expressed Tropical Almond (Talisay) Oil

BY CONRADO F. ASENJO AND JOSÉ A. GOYCO

The tropical almond tree (*Terminalia Catappa* L.) is indigenous to the East Indies but is also found widely distributed in Puerto Rico and many other tropical countries. The kernels of the fruit are edible and yield nearly 55% of a fixed oil by extraction; by expression the yield is only 35%. This oil is known in the Philippines as Talisay oil and in India it is called Indian almond oil.

Oudemans[1] reported that tropical almond oil consisted principally of olein, palmitin, and some traces of stearin. Grimme[2] gave the range of its characteristics. Cruz and West[3] examined a sample of ether extracted oil from Philippine kernels and found it to consist of the glycerides of oleic (40.85%), linoleic (22.91%), myristic (1.00%), palmitic (28.47%), stearic (3.99%), and arachidic (0.75%) acids. Except for this last study, no other quantitative studies of the composition of the oil seem to have been carried out.

The present investigation was undertaken to supply information with regard to the composition of the expressed almond oil from Puerto Rican kernels. The sample expressed in the laboratory of the School was used immediately in this investigation. It had a very light yellow color and an excellent odor and taste. It was found suitable for the manufacture of edible fats, cosmetics and pharmaceutical products.

Material.—Only ripe fruits were collected, either yellow or purple in color according to the degree of ripeness, and these came from trees in San Juan and in the neighboring town of Toa Baja. The fruit was ovoid in shape, measuring 5 to 6 cm. in length and 3 to 4 cm. in width at its axis. Their average weight per fruit, as collected, was 22.7 g. but, after drying out in a circulating air oven at a temperature of 50 to 60°, they weighed only 5.5 g. each. The dried fruit consisted of 50% fibrous covering, 42% husk, and 8% kernel. Upon analysis the dried kernel gave the following results:

Moisture, %	4.92
Fat (ether extract), %	54.60
Proteins (N × 6.25), %	27.87
Crude fiber, %	2.49
Ash, %	1.06
Nitrogen-free extract, %	9.06

Preparation of the Oil.—The oil was expressed from the dried kernels in a Carver press, using a maximum pressure of 15,000 lb. per sq. in. The oil yield was 35%. Filtration

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[1] Oudemans, *J. prakt. Chem.*, **100**, 409 (1867), through Wehmer, "Die Pflanzenstoffe," Gustav Fischer, Jena, 1931.

[2] Grimme, *Chem. Rev. Fett-Harz.-Ind.*, **17**, 233 (1910), through Wehmer, ref. 1.

[3] Cruz and West, *The Philippine J. Sci.*, **48**, 13–19 (1932).