ride (1 g.), sodium acetate (1.5 g.) and some alcohol was refluxed for four hours. The product gave colorless prisms from alcohol, m. p. 184°; yield, 2 g.

Anal. Calcd. for $C_{16}H_{18}O_2N_2$: N, 10.37. Found: N, 10.21.

Beckmann Change with the Oxime.—Thionyl chloride (11 g.) was added dropwise into the ice cold suspension of the oxime (1 g.) in chloroform (50 cc.). The resulting solution, after standing, was shaken with ice water. Subsequent to removal of chloroform the residual yellow oil (1 g.) was dissolved in ether and treated with concd. sodium bisulfite. After being dried with potassium carbonate, and removal of ether, 0.5 g. of oil which soon turned to colorless prisms was obtained. It was pressed on a tone plate and crystallized from ether, m. p. 75–76°. Folin found the same m. p. for his specimen of *p*-dimethylaminobenzonitrile.[2]

(2) Folin, *Am. Chem. J.*, **19**, 333 (1897).

Anal. Calcd. for $C_9H_{10}N_2$: C, 73.97; H, 6.85; N, 19.18 Found: C, 74.23; H, 6.78; N, 19.26.

On working up the bisulfite solution, 0.4 g. of benzaldehyde was obtained. It was identified by converting it into phenylhydrazone which alone or mixed with a known specimen melted at 155–156°.

Anal. Calcd. for $C_{13}H_{12}N_2$: N, 14.29. Found: N, 14.28.

***p*-Dimethylaminobenzoic Acid.**—A solution of the nitrile (0.2 g.) and potassium hydroxide (1 g.) in alcohol (9 cc.) and water (1 cc.) was refluxed for eight hours until liberation of ammonia had ceased. The product gave colorless prismatic needles from alcohol, m. p. 235° (dec.).

Anal. Calcd. for $C_9H_{11}O_2N$: N, 8.48. Found: N, 8.64.

CHEMICAL LABORATORY OF
KITASATO INSTITUTE
TOKYO, JAPAN

RECEIVED SEPTEMBER 17, 1934

COMMUNICATIONS TO THE EDITOR

THE ISOMERIZATION OF NORMAL HEPTANE

Sir:

C. D. Nenitzescu and A. Dragan have reported [*Ber.*, **66**, 1892 (1933)] that *n*-hexane and *n*-heptane heated on a water-bath in the presence of aluminum chloride yield a large amount of isohexane and isoheptane, respectively. The data presented by these authors do not substantiate these statements with great certainty: the starting materials were not very pure, the products obtained boiled over wide ranges, and the assertion regarding the compounds formed is based only on these boiling ranges, without the corroborating evidence of other physical properties. A. D. Petrow, A. P. Meschtscherjakow and D. N. Andrejew [*ibid.*, **68**, 1 (1935)] state that *n*-heptane is isomerized in 25% yield by heating for six hours at 300–400° in the presence of zinc chloride. In this case the density of the fractions obtained is obviously too high to correspond to any of the branched-chain heptanes. We have repeated the work of Nenitzescu and Dragan, using 2650 g. of pure *n*-heptane from Jeffrey pine. The product boiling from 50 to 98.4° was carefully fractionated, and the following properties determined for the fractions: $n^{20}D$, average molecular weight (by vapor density), and critical temperature of solution in aniline. A comparison of these data with the properties of *n*-hexane and all the heptanes indicates the presence of *n*-hexane and 2-methylhexane, and of no other isomeric heptane.

We estimate that the *n*-hexane found represents about 1% and the 2-methylhexane about 4% of the *n*-heptane consumed in the reaction.

A further investigation of this reaction is in progress.

RESEARCH LABORATORIES
ETHYL GASOLINE CORPORATION
DETROIT, MICHIGAN
GEORGE CALINGAERT
DONAL T. FLOOD

RECEIVED JANUARY 18, 1935

ERGOTOCIN: THE ACTIVE PRINCIPLE OF ERGOT RESPONSIBLE FOR THE ORAL EFFECTIVENESS OF SOME ERGOT PREPARATIONS ON HUMAN UTERI

Sir:

It has been found by the authors, working in conjunction with Drs. Davis, Adair and Rogers of the Department of Obstetrics and Gynecology of The University of Chicago, that the alkaloids ergotoxine, ergotamine and sensibamine are uniformly ineffective when administered orally to human mothers in doses of 2 mg. Larger doses (2-4 mg.) often induce unpleasant side reactions such as nausea, vomiting, increase in blood pressure, diarrhea, etc. However, even

these large and dangerous doses do not induce contractions in the eighth-day postpartum uterus, in all mothers. While the number of cases studied by us is relatively small (15 cases) these large doses of the alkaloids were found effective only in about 30% of the cases.

We have found, however, that *some* fluid extracts of ergot prepared in accordance with U. S. P. method, were effective in doses corresponding to 3–4 g. of ergot. The activity of these extracts could of course not be due to the known alkaloids (the amounts of these alkaloids as assayed by us were too small to account for the activity), and we undertook the problem of the isolation of the principle responsible for the efficacy of oral ergot dosage. While preparations containing 60–80% of this principle were obtained by us over a year and one-half ago, the isolation of the pure crystalline substance was made only Dec. 12, 1934. We have called this principle ergotocin. In human mothers this substance is uniformly effective when administered orally in doses of 0.3 mg. and intravenously in doses as low as 0.1 mg. The yield of 0.3 mg. of ergotocin is roughly equal to 3–4 g. of crude defatted ergot. This principle thus accounts for the activity of the fluid extracts.

Ergotocin has now been used on over 150 patients and no unpleasant symptoms have been observed with it. It controls uterine hemorrhage instantly. Intravenously the effect is noticed within fifteen seconds after administration. In the first stages the action of ergotocin resembles that of pituitary extracts, except that its effect lasts for three or four hours, in marked contrast to the transient effect usually obtained with pituitary extract. In its low toxicity, small dosage, prompt action in uterine hemorrhage, prolonged effect on the uterine muscles, ergotocin is unique among oxytocic principles.

Ergotocin salts, as well as the free base, are white, well-defined crystalline substances. The base melts with decomposition at 155°. The picrate, which is red, melts at 195–197°, with decomposition. When heated with alkali, ergotocin (or its salts) does not liberate any ammonia. Under the same experimental conditions, however, the known alkaloids (ergotoxine, ergotamine, sensibamine) eliminate quantitatively one mole of ammonia. The free base is somewhat soluble in water, and the salts are readily soluble. One may obtain even a 10% aqueous solution of some salts of ergotocin, a unique property among the alkaloids isolated from ergot. Ergotocin differs from the known ergot alkaloids (ergotoxine, ergotamine, sensibamine) in that it is not precipitated by Meyers' reagent in dilutions greater than 1 part in 7500, while the other alkaloids are precipitated in dilutions of 1:200,000 to 1:2,000,000. The optical rotation of the salts of ergotocin so far investigated is positive. The chemistry of ergotocin as well as some of the attempts to synthesize it will be reported as soon as the work now under way is complete.

We believe that with the isolation of this principle ergot therapy can now be put on a rational basis. If one bears in mind that many ergots do not contain this principle (and yet are acceptable on the basis of the U. S. P. assays), the cause of the difference of opinion among obstetricians regarding the value of ergot in obstetrics becomes evident.

The authors wish to take this opportunity to thank most sincerely the Research Corporation, Inc., for a grant which made this work possible and the Eli Lilly Co. for generously aiding us in this investigation.

Needless to say, without the coöperation and constant guidance of Drs. Davis, Adair and Rogers, on the clinical and pharmacological evaluation of this principle, this work would not have been brought to a successful conclusion.

GEORGE HERBERT JONES CHEMICAL LABORATORY
THE UNIVERSITY OF CHICAGO M. S. KHARASCH
CHICAGO, ILLINOIS R. R. LEGAULT

RECEIVED MARCH 30, 1935

THE SURFACE TENSION OF SOLUTIONS

Sir:

It has long been known that aqueous solutions of most salts have a slightly greater surface tension than water throughout the range of concentrations hitherto investigated and must, therefore, according to the Gibbs Theorem, be negatively adsorbed in the surface layer. According to Freundlich and earlier authors such "capillary inactive substances" give surface tension–concentration (σ–c) curves which are approximately straight lines with a gentle positive slope. Wagner [*Physik. Z.*, **25**, 47 (1924)] and later Onsager and Samaras [*J. Chem. Phys.*, **2**, 528 (1934)] have applied the Debye–Hückel theory of interionic attraction to the problem and derived an equation

$$\frac{\sigma}{\sigma_0} = 1 + \frac{79.517}{D\sigma_0} c \log \frac{1.143 \times 10^{-13} (DT)^3}{c}$$

for dilute aqueous solutions of all uni-univalent salts (D = dielectric constant; T = absolute temperature).

This equation predicts that the curve should be nearly straight in moderate concentrations, but that the limiting slope at extreme dilutions should be plus infinity.

We have devised a modification of the capillary rise method which has enabled us to measure the surface tension of solutions relative to that of water with greater precision than has hitherto been possible. The data for potassium chloride solutions are shown in the accompanying figure, together with a plot of the Onsager and Samaras equation. At extreme dilutions (less than 0.006 N) the surface tension is less than that of water, whereas above 0.006 N the surface tension is increased and is approximately a linear function of the concentration. These results are not in accord with the Onsager and Samaras equation, especially as to the sign of the limiting slope at extreme dilutions. Similar results have been obtained with potassium sulfate and cesium nitrate solutions. On the other hand, sucrose solutions from 0.0005 to 0.005 mole per liter, inclusive, when measured in the same apparatus, gave an increased surface tension. The effect which causes the diminution of surface tension and therefore, according to the Gibbs Theorem, also causes positive adsorption in the surface layer, is presumably due to an interaction between the polarized water molecules and the ions, which at extreme dilutions tends to force the ions into the surface layer. At higher concentrations the interionic forces predominate and cause negative adsorption and increased surface tension.

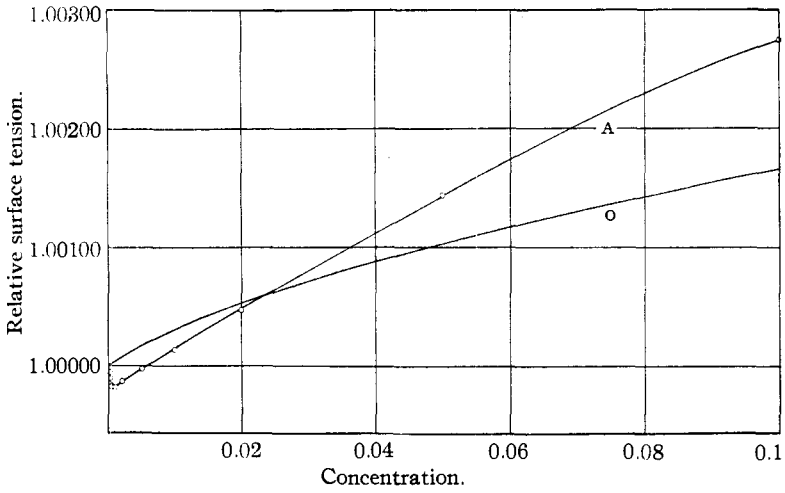

Fig. 1.—A, KCl at 25°; O, Onsager equation for uni-univalent salts.

The work is being continued both experimentally and theoretically to determine the general validity of the phenomenon and the factors which influence it.

MALLINCKRODT LABORATORY
HARVARD UNIVERSITY
CAMBRIDGE, MASS.
GRINNELL JONES
WENDELL A. RAY

RECEIVED APRIL 18, 1935

THE MOLECULAR STRUCTURE OF GERMANIUM TETRACHLORIDE

Sir:

The electron diffraction investigation of the chlorides of the fourth group elements [L. Brockway and F. T. Wall, THIS JOURNAL, **56**, 2373 (1934)] has been extended by the study of germanium tetrachloride. Professor L. M. Dennis of Cornell University very kindly supplied a sample of the compound.

The photographs show two distinctive qualitative features: the little hump on the inner edge of the first strong maximum and the sloping shelf on the outside of the second maximum. Both of these characteristics appear in the theoretical intensity curve based upon a regular tetrahedral model included in Fig. 1 of the previous report. Two maxima were observed beyond the limit of the published curve.

The quantitative comparison is given in Table I. The third column gives the indicated values for the observed maxima and minima; the fourth gives the corresponding points on the theoretical curve and the fifth column shows the Ge–Cl interatomic distance. The first two points give values much lower than the average as has always been observed in the case of short distance (about ten centimeters) photographs of relatively large molecules [Ref. 1]. The value which Wierl [*Ann. Physik.*, [5] **8**, 548 (1931)] obtained with photographs covering only half of the present angular range is not altered by this more complete investigation.

Germanium tetrachloride shows about the same deviation (Table II) from additivity of the radii that the silicon and tin chlorides do. The sharp

TABLE I

GERMANIUM TETRACHLORIDE

Three photographs; camera distance, 10.43 cm.; $\lambda = 0.0606$ Å.

Max.	Min.	$\frac{4\pi \sin \theta/2}{\lambda}$	x	a = Ge–Cl
1		4.088	8.17	(2.000)
	2	5.305	10.65	(2.008)
2		6.273	13.22	2.108
	3	8.598	17.82	2.074
3		9.750	20.29	2.080
	4	11.07	22.76	2.056
4		12.75	27.33	2.143
	5	14.24	29.82	2.094
5		15.46	32.20	2.082
	6	17.02	36.86	2.164
6		18.51	39.35	2.123
			Average	2.103

Ge–Cl = 2.10 ± 0.03 Å.
(Wierl, 2.10 ± 0.05 Å.)

TABLE II

Bond	Observed distance	Radius sum	Difference
C–Cl	1.76	1.76	0.00
Si–Cl	2.02	2.16	.14
Ge–Cl	2.10	2.21	.11
Sn–Cl	2.29	2.39	.10

distinction between these three and carbon tetrachloride can scarcely be explained on the basis of gradations in electronegativity of the central atoms. It seems probable that there is some essential difference in the character of the bond, such as the formation of double electron pair bonds as discussed in the previous report.

Studies of the tetramethyl compound are being made in the further investigation of this point.

GATES CHEMICAL LABORATORY L. BROCKWAY
CALIFORNIA INSTITUTE OF TECHNOLOGY
PASADENA, CALIFORNIA

RECEIVED APRIL 1, 1935

OCCURRENCE OF ANABASINE IN NICOTIANA GLAUCA R. GRAH. (SOLANACEAE)

Sir:

Beta-pyridyl-α'-piperidine, $C_{10}H_{14}N_2$, isomeric with nicotine, was shown by Orechoff and Menschikoff [*Ber.*, **64**, 266 (1931)] to be present in the plant *Anabasis aphylla* L. (Chenopodiaceae) and was named "anabasine." Pictet and Rotschy had previously [*ibid.*, **34**, 696 (1901)] reported β-pyridyl-α'-piperidine, which they called "nicotimine," to be present in tobacco in a ratio of 1 part of nicotimine to 200 parts of nicotine. Later work has shown that Pictet and Rotschy did not isolate the proper compound, but recently Ehrenstein [*Arch. Pharm.*, **269**, 627 (1931)] has apparently isolated the alkaloid anabasine from tobacco.

Schmuck [Krasnodar (U. S. S. R.) State Inst. Tobacco Invest., *Bull.* **109**, 24 (1934)] stated that the alkaloid of *Nicotiana glauca* R. Grah. was not nicotine, but no identification was made. A sample of *Nicotiana glauca* roots was sent to this Laboratory by Mr. B. McKinney of the Tempe, Ariz., station of the Division of Truck Crop and Garden Insect Investigations of this Bureau. When examined it was found to contain about 1% of anabasine. A sample of the whole plant was later received from the same source and the identity confirmed by botanists of this Department. Further examination of samples of dried leaves from plants grown from seeds on the Arlington Experiment Farm by the Bureau of Plant Industry showed that they also contained anabasine. It is doubtful that nicotine is present except possibly in a trace.

The anabasine isolated was a liquid alkaloid boiling at 281° (537.8°F.) (corr.), which was soluble in water in all proportions and formed a picrate whose melting point of 212–213° (413.6–415.4°F.) was unchanged by admixture with picrate of anabasine prepared from commercial anabasine sulfate. The optical rotation $[\alpha]^{20}D$ was −9.1°, instead of −82.2° reported by Orechoff and Menschikoff, or −59.66° reported by Nelson [THIS JOURNAL, **56**, 1989 (1934)]. Dehydrogenation by palladium black produced α,β-dipyridyl, which was formed into the dipicrate and the monopicrate, comparing closely with known samples of these picrates in appearance and melting points.

The principal method used to extract the anabasine was to digest the material with warm 1% hydrochloric acid, filter, make alkaline and extract with ether. When the alkaline solution was distilled, ammonia and pyridine were found in the first part of the distillate but nicotine was not detected. The removal of the anabasine by further distillation was incomplete.

Nicotiana glauca grows wild in various parts of the Southwest, particularly in California. It is the first species of plant in this country found to contain anabasine as the principal alkaloid. A study of certain other species of *Nicotiana* should prove of interest as their alkaloids have not been definitely determined.

Anabasine is a promising contact insecticide,

comparing favorably with nicotine for use against aphids.

INSECTICIDE DIVISION C. R. SMITH
BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE
U. S. DEPARTMENT OF AGRICULTURE
WASHINGTON, D. C.

RECEIVED APRIL 20, 1935

THE PREPARATION AND PROPERTIES OF BENZENE-d_6

Sir:

We have developed a technique for the exchange reaction between deuterium oxide and benzene, discovered by Horiuti and Polanyi [*Nature*, **134**, 377 (1934); *Trans. Faraday Soc.*, **30**, 1164 (1934)] which permits the ready production of benzene-d_6. Two cylindrical Pyrex vessels of about 50-cc. capacity are connected by a Pyrex U-tube containing an active nickel catalyst supported on kieselguhr. The catalyst tube is heated externally by a closely fitting electric furnace, and the catalyst reduced (in our case with deuterium) at 420°. After the system is thoroughly evacuated and sealed a sample of 5 cc. of benzene and 10–20 cc. of heavy water is introduced *in vacuo* through a special breakable seal. By means of an electric furnace, which closely fits either cylinder, the water is brought to ebullition and, carrying with it a proportion of benzene vapor, is driven over the catalyst, heated to 200°, where some exchange occurs, the product condensing in the second cylinder appropriately cooled. By reversing the procedure the benzene–water mixture can then be passed once more through the catalyst. Frequent repetition of the process ultimately establishes an equilibrium partition of deuterium between water and benzene. By replacing the hydrogen-diluted deuterium oxide with fresh pure deuterium oxide and continuing the passage over the catalyst, further conversion toward benzene-d_6 can be obtained.

We traced the progress of the exchange by attaching to the reaction system via a quartz-Pyrex seal a cylindrical quartz absorption cell 30 mm. thick. Benzene vapor at room temperatures gives a series of sharply defined ultraviolet absorption bands. Each of the substituted benzenes, C_6H_5D, $C_6H_4D_2$, etc., shows similar bands, displaced toward the ultraviolet by frequency differences varying for each band but roughly constant for each additional D atom. As exchange occurs forming an equilibrium among the 13 benzenes this results in a considerable overlapping and complication of the spectrum. With continued progress toward the final state, the overlapping disappears, the sharply defined bands of C_6D_6 only remaining.

In four successive equilibrations with 5 cc. of benzene using an initial 10 cc. of 95% D_2O and then successively 10, 20 and 20 cc. of 100% D_2O a product containing 55, 85, 97 and >99% of the hydrogen as deuterium has been prepared. The deuterium contents have been *estimated* from the absorption spectra. For example, in the 97% product, the bands corresponding to C_6D_5H and C_6D_6 were the only ones visible, the former with about one-fifth the intensity of the latter. Densities of the carefully purified and redistilled samples at the first two stages were, 55%, d^{25}_4 0.9146; 85%, d^{25}_4 0.9349; and the final product had a density of 0.9417. After four separate processes of purification we received approximately 3.5 cc. of final product. Measurements are being made of the Raman spectra, infra-red and ultraviolet absorptions and other physical properties. We are continuing our study of the variables in the preparation and also extending the procedure to other compounds.

FRICK CHEMICAL LABORATORY P. I. BOWMAN
PRINCETON UNIVERSITY W. S. BENEDICT*
PRINCETON, N. J. H. S. TAYLOR

RECEIVED APRIL 22, 1935

(*) National Research Fellow.

THE HYDROLYSIS OF ERGOTININE AND ERGOCLAVINE

Sir:

Following our preliminary communications [*J. Biol. Chem.*, **104**, 547 (1934); THIS JOURNAL, **57**, 383 (1935); *Science*, **81**, 256 (1935)] regarding the cleavage of ergotinine by alkali to lysergic acid, isobutyrylformic acid, ammonia and a polypeptide which on further hydrolysis with acid yielded proline and phenylalanine, we have made a logical extension of the investigations to the study of the cleavage of ergotinine by acid. Heating with hydrochloric acid resulted in the destruction of the lysergic acid portion of the molecule with the formation of obscure amorphous material. On the other hand, *l*-phenylalanine, $[\alpha]^{20}D$ −28° (c = 0.39 in H_2O), was obtained as such while proline was isolated as the methyl ester (*Anal.* C, 55.70; H, 8.81), $[\alpha]^{25}D$ +33° (c = 0.65 in CH_3OH), which was further characterized by the gold salt (*Anal.* C, 15.70; H, 2.62; Au, 41.83).

The investigation was extended to a preliminary study of ergoclavine [W. Küssner, *E. Merck's Jahresbericht. Original Mitteil.*, **47**, 5 (1933)]. On alkaline hydrolysis ammonia, lysergic acid (*Anal.* C, 71.37; H, 6.25), and isobutyrylformic acid were obtained. The latter was isolated as the phenylhydrazone which melted at 148° (*Anal.* C, 63.77; H, 6.64) (G. Barger has reported [*E. Merck's Jahresbericht. Original Mitteil.*, **47**, 12 (1933)] that a base similar to ergine and isobutyrylformamide can be obtained from ergoclavine). From the amino acid fraction only one substance was isolated which from the analysis appeared to be leucine (*Anal.* C, 54.92; H, 9.77).

Ergoclavine was then hydrolyzed by hydrochloric acid. This again resulted in the destruction of the lysergic acid portion of the molecule. From the amino acid fraction a substance was isolated which agreed in properties with partly racemized *l*-leucine (*Anal.* C, 55.05; H, 10.04). The inversion of its rotation in aqueous solution $[\alpha]^{20}D$ −6°, to $[\alpha]^{20}D$ +6° in dilute hydrochloric acid solution appears to eliminate isoleucine. The mother liquor still contained an amino acid which from the strong pyrrole red test suggested proline. However, contrary to our experience with ergotinine, this fraction did not yield proline as the methyl ester. This coincides with our experience in the attempt to isolate proline from ergotamine. It is not excluded that hydroxyproline may be in question.

Our study of the degradation of lysergic acid itself has yielded among other substances, indole derivatives which will be a subject for a later communication.

LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH
NEW YORK, N. Y.
WALTER A. JACOBS
LYMAN C. CRAIG

RECEIVED APRIL 22, 1935

METHYLCHOLANTHRENE FROM CHOLIC ACID

Sir:

In view of the important biological implications of the chemical transformation of substances normally present in the body into cancer-producing agents, an extension of the observations of Wieland and Dane [*Z. physiol. Chem.*, **219**, 240 (1933)] to additional cases has been undertaken. In a four-step process the German investigators converted desoxycholic acid into the actively carcinogenic methylcholanthrene with an over-all yield of approximately 4.3%. We have obtained the same hydrocarbon in 5.4% yield from cholic acid, the most abundant acid constituent of the bile. Since the process is quite rapid and the starting material only one-tenth as expensive as desoxycholic acid, the new method provides a ready source of the hydrocarbon for experimental purposes.

Cholic acid (200 g.) was oxidized in glacial acetic acid solution (1700 cc.) with 150 g. of chromic anhydride in 150 cc. of water and 600 cc. of acetic acid at 30–40° (two and one-half to three hours), giving 140 g. of dehydrocholic acid, m. p. 237–238° [method of Hammarsten, *Ber.*, **14**, 71 (1881)]. The triketo acid (40 g.) was reduced to 3,7-dihydroxy-12-keto-cholanic acid according to Kawai [*Z. physiol. Chem.*, **214**, 71 (1933)], using Adams catalyst (2.5 g.), and the entire reduction product (from which the pure monoketone could be isolated in 30–40% yield) was subjected to pyrolysis at 260–280° for one hour and at 320–330° for eight to nine hours and distilled in vacuum. The very viscous distillate (14–18 g.), probably containing a mixture of norcholatrienes, was heated with 20–25 g. of selenium, added in several portions, at 320–330° for forty-eight hours. After extraction with benzene, distillation and purification through the picrate there was obtained 2.0–2.2 g. (5.2–5.7%, over-all) of orange-yellow methylcholanthrene, m. p. 177–178°, corr. After passing a benzene solution of the hydrocarbon through an adsorption tower of activated alumina, methylcholanthrene was obtained as pale yellow needles, m. p. 178.5–179°, corr.

CONVERSE MEMORIAL LABORATORY
HARVARD UNIVERSITY
CAMBRIDGE, MASSACHUSETTS
LOUIS F. FIESER
MELVIN S. NEWMAN

RECEIVED APRIL 24, 1935