method is both qualitative and quantitative. The yields, which in some cases would be greater than 100% if calculation were made on the basis of substrate actually oxidized can be explained by the differences in temperature of the oxidizing solutions resulting from the addition of the dimethyldihydroresorcinol in hot water (see below). Only one serious difficulty was experienced. In the cases in which both ammonia and formaldehyde were produced, only small yields of either could be obtained because of the formation of hexamethylenetetramine. This difficulty was partially overcome in the case of formaldehyde by an earlier addition of dimethyldihydroresorcinol, with which the formaldehyde apparently reacts preferentially. The compounds used for the reactions were selected because of availability and as examples of each type of product. Formaldehyde was isolated in each case, while acid or ammonia were titrated if the theoretical equation required their formation. If the equation and a qualitative test (for ammonia)[5] indicated the formation of an amide (II and IV), the solution was treated under hydrolytic conditions, and the acid formed was distilled and titrated.

TABLE I

Compound	% oxidized	% of theoretical amount of products isolated (based on substrate taken) HCHO	NH_3	HCOOH	CH_3COOH
$CH_2OH—CHOH—CH_2OH$	94.2	91.7		93.7	
$CH_2OH—CH_2NH_2$	84.4	69.2	59.0		
$CH_2OH—C(CH_3)NH_2—CH_3$	88.0	91.2	84.0		
$CH_2OH—C(CH_3)NH_2—CH_2OH$	89.2	92.6			73.5
$CH_2OH—CHOH—CH_2NH_2$	82.2	82.1		90.8	

Experimental

Determination of Completeness of Oxidation.—The substrate, about 10^{-4} mole, in water solution or emulsion was treated with a 10% excess over the theoretical amount of a saturated solution of potassium metaperiodate (1.66×10^{-2} mole per liter) for twenty minutes. To the resulting solution was added borax–boric acid buffer solution, and potassium iodide, and the liberated iodine was titrated with standard arsenite solution.

Determination of Formaldehyde.—In the absence of ammonia, the oxidation mixture, after standing for twenty minutes, was treated with a 10% excess over the theoretical amount of dimethyldihydroresorcinol[6] in alcohol solution, brought to *p*H 4, warmed to 60°, and allowed to stand in the ice-box until precipitation was complete. The formaldehyde dimethone was collected and weighed, and the melting point taken to determine the purity of the sample.

In case ammonia was formed in the reaction, the following procedure was adopted. The substrate and periodate solutions were mixed, and dimethyldihydroresorcinol in hot water solution was added after about three minutes. After twenty minutes, the solution was brought to *p*H 4 and treated as before.

Determination of Acid.—If no ammonia was formed in the reaction, the oxidation mixture, after twenty minutes, was titrated with standard alkali. If ammonia was formed, the solution was acidified with sulfuric acid and about three-fourths of it distilled. Water was added, and the distillation repeated. The distillate was then titrated with standard alkali.

(5) J. A. Sanchez, *Anales asoc. quim. argentina*, **24**, 366 (1926).

(6) E. C. Horning and M. G. Horning, *J. Org. Chem.*, **11**, 95 (1946).

Determination of Ammonia.—If no acid was formed in the reaction, the oxidation mixture, after twenty minutes, was titrated with standard acid.

Determination of Amides.—If the formation of amide was indicated (see above), the solution, after completion of the oxidation, was made strongly acidic with sulfuric acid, refluxed for two hours and then distilled to about one-fourth volume. Water was added, and the solution was again distilled to one-fourth volume, and the distillate titrated with standard alkali. If the acid formed was known, it was necessary to distill and titrate only 10% of the solution, and calculate the total amount originally present.[7]

(7) L. J. Gillespie and E. H. Walters, THIS JOURNAL, **39**, 2027 (1917).

CHEMICAL LABORATORY
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LOS ANGELES, CALIF. RECEIVED SEPTEMBER 24, 1947

Crystalline Procaine Penicillins

BY CHARLES J. SALIVAR, F. HOWARD HEDGER AND ELLIS V. BROWN

There is an urgent need for a penicillin dosage form which will give prolonged penicillin blood levels with more certainty and without the objectionable features of the currently available preparations.

We have prepared procaine salts of two penicillins and have milled them in vegetable oil to give injectable mixtures. Preliminary animal and clinical trials have indicated that significant and prolonged penicillin blood levels are obtainable with these preparations. These data will be published later.

For the preparation of procaine benzylpenicillin, 10 g. of sodium benzylpenicillin dissolved in 10 ml. of water is treated with a solution of 7.6 g. of procaine hydrochloride in 10 ml. of water and the reaction product is allowed to crystallize slowly. After crystallization is completed, the product is filtered, washed with water and dried in a vacuum drier at 50°.

The practically colorless crystalline procaine salt of benzylpenicillin melts (capillary) at 129–130°. *Anal.* Calcd. for $C_{29}H_{38}N_4O_6S \cdot H_2O$: N, 9.52; S, 5.44. Found: N, 9.78; S, 5.35.

The biological potency obtained by the Oxford plate method[1] against *S. aureus* is 1020 U./mg. The potency as determined iodometrically[2] is 1007 U./mg. The calculated value based on 1667 U./mg. for sodium benzylpenicillin is 1008 U./mg. The optical rotation is $[\alpha]^{25}D$ +173° (1% in 50% aqueous acetone).

Procaine *n*-amylpenicillin was also prepared in the same manner from sodium *n*-amylpenicillin.[3] It melts at 113–115°. *Anal.* Calcd. for $C_{27}H_{42}N_4O_6S \cdot H_2O$: N, 9.86; S, 5.63. Found: N, 9.79; S, 5.97.

(1) W. H. Schmidt and A. J. Moyer, *J. Bact.*, **47**, 199 (1944).

(2) J. F. Alicino, *Ind. Eng. Chem., Anal. Ed.*, **18**, 619 (1946).

(3) Report presented by C. J. Salivar, V. V. Bogert and E. V. Brown at the Conference on Antibiotic Research held in Washington, D. C., January 31, 1947, under the auspices of the Antibiotics Study Section of the National Institute of Health.

The biological potency against *S. aureus* is 983 U./mg. and as determined iodometrically is 986 U./mg. The calculated potency is 955 U./mg. and the optical rotation is $[\alpha]^{25}D$ +175° (1% in 50% aqueous acetone).

RESEARCH LABORATORY
CHAS. PFIZER AND CO., INC.
BROOKLYN, NEW YORK RECEIVED SEPTEMBER 20, 1947

The Friedel–Crafts Reaction of Benzene and 3,4-Dichlorohexane

BY KEIITI SISIDO AND HITOSI NOZAKI

The condensation of benzene with 3,4-dichlorohexane has been studied. The dichlorohexane was prepared from divinylacetylene by catalytic hydrogenation followed by chlorination.[1] The reaction product obtained by the usual procedure was composed of two fractions.

The analysis and molecular weight determination of the first fraction agreed with the formula $C_{12}H_{16}$, showing that it was a mono-cyclialkylated benzene. The dehydrogenation of this hydrocarbon with sulfur or with selenium under the condition not to be accompanied with anomalies[2] gave an oily product, whose picrate formed orange needles melting at 144–144.5°, alone or admixed with an authentic specimen of 1,4-dimethylnaphthalene picrate. It has often been observed, however, in the case of the picrates of naphthalene derivatives, that a mixture of two different isomers shows no depression of the melting point. But as all of the isomers of dimethylnaphthalene are already known, an examination of the literature about the characteristic data of the hydrocarbons and their picrates made it clear that the dehydrogenation product above mentioned was nothing else but 1,4-dimethylnaphthalene. From these observations, we concluded that the hydrocarbon $C_{12}H_{16}$ was a new compound, 1,4-dimethyltetralin.

In the alkylation of benzene with alkyl halogenides catalyzed by aluminum chloride, the isomerizations of the alkyl radicals are often observed. The mechanism of the present condensation is explained from this view-point that the chlorine atoms of the 3,4-positions migrate to the 2,5-positions and the resulting dichloride cyclialkylates benzene to form a six-membered carbon ring.

The second reaction product formed colorless liquid. Several attempts to crystallize it were unsuccessful. The results of its analysis and molecular weight determination gave a formula $C_{18}H_{26}$, showing that it was not 3,4-diphenylhexane[3] as expected at first, but a di-cyclialkylated benzene, *i. e.*, 1,4,5,8-tetramethyl-1,2,3,4,5,6,7,8-octahydroanthracene, -phenanthrene or a mixture of them.

Experimental

The Condensation of 3,4-Dichlorohexane with Benzene.—To a mixture of 105 g. of benzene and 24 g. of aluminum chloride was added 42 g. of 3,4-dichlorohexane in the course of about one hour under stirring, during which time the reaction temperature was maintained at 5–10°. After additional fifteen minutes the mixture was heated slowly so as to insure a uniform evolution of hydrogen chloride gas. Heating was continued for about two hours until the reaction temperature reached 25° and practically no more evolution of gas was observed. The reaction mixture was poured over crushed ice acidified with hydrochloric acid and treated as usual. The solvent was removed and the residue was distilled under reduced pressure. The following fractions were obtained.

Fraction	B. p., °C.	Pressure, mm.	Yield, g.	Appearance
I	107–131	37	11	Colorless liquid
II	79–110	9	5	Colorless liquid
III	112–140	9	1	Colorless liquid
IV	140–170	9	5	Colorless viscous oil
V	170–184	9	3	Viscous sirupy oil
VI	Residue	..	3	Viscous sirupy oil

The Mono-cyclialkylated Product: 1,4-Dimethyltetralin.—Fractions I and II were combined and the mixture was redistilled. The main fraction boiling at 216–227° under atmospheric pressure weighed 14 g. occupying 50% of the total condensate. It formed a colorless liquid with characteristic odor. The boiling point determined by the Emich method was 226°.

Anal. Calcd. for $C_{12}H_{16}$: C, 89.94; H, 10.06; mol. wt., 160. Found: C, 89.74; H, 10.21; mol. wt. (cryoscopy in benzene), 152.

The Dehydrogenation of 1,4-Dimethyltetralin with Sulfur.—A mixture of 2.4 g. of the hydrocarbon and 1.0 g. of sulfur was heated on a metal-bath at 180–250° for two and a half hours. The reaction product was immediately distilled and yellowish oil, boiling at 260–300° (bath temperature), was obtained. It was dissolved in hot alcohol and added a hot alcoholic solution of picric acid. On cooling, orange needles separated. After one recrystallization from alcohol, the picrate melted at 144–144.5° and repeated crystallizations changed the melting point no more. This fact showed that the material was already quite pure. When admixed with an authentic specimen of 1,4-dimethylnaphthalene picrate (m. p. 143–144°) it melted at 144–144.5°.

Anal. Calcd. for $C_{12}H_{12}\cdot C_6H_3O_7N_3$: C, 56.10; H, 3.92. Found: C, 55.39; H, 4.17.

The Dehydrogenation of the Dimethyltetralin with Selenium.—To 1.58 g. of the substance was added 1.62 g. of selenium and the mixture was heated on a metal-bath at 250–300° for one hour. The reaction product was shaken out and heated for additional six and a half hours at 300–350° (bath temperature). Distillation of the dehydrogenation product gave 0.57 g. of yellowish oil, which yielded the same picrate as described above.

The Di-cyclialkylated Product.—Fraction IV was redistilled under reduced pressure and the main fraction boiling at 145–160° at 9 mm. was subjected to the following experiments.

Anal. Calcd. for $C_{18}H_{26}$: C, 89.19; H, 10.81; mol. wt., 242. Found: C, 89.20; H, 10.81; mol. wt. (cryoscopy in benzene), 220.

A mixture of 4.5 g. of the substance and 2.3 g. of sulfur was heated for about three hours at 180–260°. The resulting black mass was distilled under reduced pressure. The red viscous oil, which distilled at 230–300° (bath temperature) at 5–6 mm., solidified immediately. On recrystallizations from alcohol, colorless prisms melting at 219–220°[4] separated. An analysis was impossible for lack of material.

Higher Boiling Fractions.—Fraction V and the residue separated a small quantity of crystals, melting at 197–

(1) Spiegler and Tinker, THIS JOURNAL, **61**, 940 (1940).
(2) Ruzicka and Peyer, *Helv. Chim. Acta*, **18**, 676 (1935).
(3) Lepin and Reich, *Chem. Zentr.*, **87**, I, 787 (1916).
(4) *Cf.* Ellison and Hey, *J. Chem. Soc.*, 1849 (1938).