From the heats of formation, an enthalpy change of 10 kcal. is predicted for the reaction

$$CrI_3(c) = CrI_2(c) + {}^1/_2I_2(c) \qquad (3)$$

3 kcal. less than previously estimated by extrapolation of thermal dissociation equilibrium data at 570°.[5] The heat of reaction (3) at 25° has been determined by comparison of the heats of solution of CrI_3 and CrI_2 with excess solid iodine in 750 ml. of 0.02 *N* HCl solution. Known mixtures of CrI_3 and CrI_2 were dissolved and iodine was subsequently introduced. The heat of solution of pure CrI_2 was determined under similar conditions and the contribution of each component in the mixtures calculated. Inasmuch as iodine readily oxidizes chromium(II) to chromium(III), the final state of chromium after dissolving CrI_2 is the same as that with CrI_3. The results for the mixtures are somewhat less consistent than those for the pure substances; however, the difference between the mean values, 11 kcal. (Table I), agrees with the predicted result within experimental uncertainty.

Experimental Procedure

A description of the simple adiabatic calorimeter and its operation[6] and the preparation of CrI_3[7] have been given previously. Heats of solution were measured at 25 ± 1°. CrI_2 was prepared by thermal decomposition of CrI_3 in vacuum (400–500°), followed by sublimation in vacuum at 700°. The chromium chlorides were also purified by sublimation. The composition of these substances was checked by analysis; deviation from theoretical values did not exceed 0.5%. Samples were introduced into the calorimeter in sealed thin glass capsules, previously filled in a dry-box.

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The Stability of Hydroxystreptomycin

BY IRVING R. HOOPER AND MURRAY A. KAPLAN

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An unknown antibiotic isolated in the antibiotic screening program carried out at these laboratories was found to be identical with hydroxystreptomycin.[1-4] In the course of our degradation studies, it was found remarkably resistant to hydrolytic inactivation, compared to streptomycin.[5]

The stability of hydroxystreptomycin in water and methanol solutions is shown in Table I. Solutions initially contained 10 mg./ml. of hydroxystreptomycin base and were followed by bioassays.

Hydroxystreptomycin is much more stable to acid hydrolysis under mild conditions than is streptomycin. Table II shows the results obtained from stability studies on streptomycin and hydroxystreptomycin in 2 *N* hydrochloric acid at 20°. Initial concentrations were 4 mg. of antibiotic base/ml. The figures are taken from the best line fitted to the plot of the logarithm of concentration against time.

TABLE I

Solvent	*p*H	Time, days	Temp., °C.	Activity remaining, %
Water	2	8	20	>95
Water	6.5	8	20	>95
Water	12	8	20	>95
Water	2	1	100	56
Water	6.5	1	100	58
Methanol	2	4	65	72
Methanol	6.5	1	65	83

TABLE II

	Activity remaining, %			
	1 day	2 days	7 days	21 days
Streptomycin	50	19	<1	
Hydroxystreptomycin	93	85	58	20

The hydrogenated derivatives are very similar to the unreduced compounds with respect to stability in hydrochloric acid.

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The Reaction of Esters with Phenylhydrazine in the Presence of Phosphoric Acid[1]

BY T. O. JONES, R. E. HALTER AND W. L. MYERS

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The reactions of esters with ammonia, hydroxylamine and hydrazine to produce the corresponding amide, hydroxamic acid or hydrazide are well known. Cohn[2] and Meyer[3] reported a reaction between methyl salicylate and phenylhydrazine to produce the corresponding phenylhydrazide, and Baidakowski, Reformatski and Slepak[4] prepared a few phenylhydrazides by heating the ester and phenylhydrazine in a sealed tube at 210°, but no other examples of this reaction have since been reported.

Various modifications and adaptations of earlier procedures for carrying out similar reactions were tried for the reaction

$$R{-}\overset{\overset{O}{\|}}{C}{-}OR' + C_6H_5NHNH_2 \rightleftharpoons R{-}\overset{\overset{O}{\|}}{C}{-}NHNHC_6H_5 + R'OH$$

using the ester and the free base in various solvents or using the ester and the hydrochloride or sulfate salts, all without results. It was noted that when the phenylhydrazine salts were used, they remained unchanged during the trials so the phenylhydrazine

(1) Supported in part by a grant from the Research Corporation, 405 Lexington Ave., New York 17, N. Y.

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salt of a weaker acid, phosphoric acid, was tried and found to be singularly effective for the formation of hydrazides.

Other acids, *e.g.*, sulfuric, hydrochloric, benzenesulfonic, dichloroacetic, potassium bisulfate and sodium dihydrogen phosphate made up to hydrogen ion concentrations comparable to that of the phosphoric acid used, gave no yield of the phenylhydrazide in any case. Sodium benzenesulfonate and other phosphate salts were tried with negative results.

It appears that the reaction proceeds by a base–acid-catalyzed mechanism in which the phosphoric acid is the acid and the $H_2PO_4^-$ is the base in as much as the amount of acid required to catalyze the reaction lies within a minimum and maximum limit. The effect of minimum and or excess amounts of phenylhydrazine on the yield also seems to support this view.

Experimental

In a typical experiment to prepare the β-acetylphenylhydrazine, 8.8 g. (0.1 mole) of ethyl acetate, 43 g. (0.4 mole) of phenylhydrazine, 5.4 g. (0.3 mole) of water and 1.2 g. (0.01 mole) of sirupy phosphoric acid (85%) were placed in a 100-ml. round-bottom flask and refluxed gently for 1 hour. The water, unreacted ester, and excess phenylhydrazine were then removed by distillation at reduced pressure (*ca.* 20 mm.), the distillation being stopped when the temperature rose above 100° to prevent decomposition of the residue. The material remaining in the flask was then extracted with 100 ml. of hot benzene, from which on cooling, about 9 g. (60% yield) of the phenylhydrazide crystallized out. A single recrystallization from hot benzene produced the silvery platelets characteristic of the phenylhydrazides, m.p. 128° (uncor.), reported 129°.[5] The solubility of the phenylhydrazides in benzene is greatly increased by small amounts of ester or phenylhydrazine. Failure to obtain a solid product on extraction of the residue from the vacuum distillation was usually due to incomplete removal of these reactants.

The same general procedure was suitable for preparing other phenylhydrazides except for the length of time of refluxing. For formates, 0.5 hour was sufficient while for the higher aliphatic esters and benzoates, up to 3 hours were required. For esters of the higher dibasic acids such as ethyl adipate and for methyl salicylate, up to 5 hours of reflux time were needed. The reaction has been tried on all the aliphatic esters through the caprylates, giving yields from 60% for the lower members of the series to as low as 20% for the higher members. For esters of the dibasic acids the yields were about 20%.

When moderate amounts of phenylhydrazides of acids were desired as derivatives for identification purposes,[6] it was found that an adequate yield was produced by heating together under reflux for 1 hour a mixture containing 1 g. of an ester, *e.g.*, ethyl propionate, 4 g. of phenylhydrazine, 0.3 g. of water and 1 drop of phosphoric acid. The hot solution after refluxing was poured into about 75 ml. of 1.4 *N* hydrochloric acid at 30° and stirred until the phosphate salt of the unreacted phenylhydrazine and phenylhydrazine dissolved (*ca.* 5 min.). It was found necessary to maintain these conditions closely because an increase in the temperature or the concentration of the acid caused hydrolysis of the product while a decrease in the temperature or acid concentration extended unnecessarily the time required to dissolve the phenylhydrazine and its salts. After filtering, the crystals were washed free of the ester and other adsorbed impurities with cold cyclohexane or ligroin (b.p. 75–110°), and recrystallized from benzene.

The effect of varying the amount of phenylhydrazine used while holding the quantities of the other reactants and conditions constant was tried. The maximum yields were obtained using 4 equivalents of phenylhydrazine. When the amount of phenylhydrazine was reduced to 2.8 equivalents or increased to 5.6 equivalents the yield was about half of the maximum. If the amount of phenylhydrazine was increased to 8 equivalents or reduced to 1 equivalent, the yield dropped to 5–10%.

The effect of varying the amount of phosphoric acid used while holding the amounts of the other reactants and conditions constant was tried with similar results. The maximum yield was produced with 0.1 molar equivalent of phosphoric acid with little or no yield resulting if the amount of the acid was reduced to 0.025 or increased as high as 0.3 molar equivalent. Decreasing the amount of water to 1 molar equivalent or increasing to 8 molar equivalents cut the yield to about 10%. No yield was obtained in trials when no water was present or when the water was increased to 15 molar equivalents or more.

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The Structure of Di-(methylcyclohexyl)-benzenes from the Cycloalkylation of 4-Methylcyclohexene with Benzene in the Presence of Hydrogen Fluoride[1]

BY V. N. IPATIEFF,[2] J. E. GERMAIN AND HERMAN PINES

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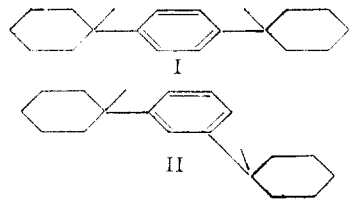
It was reported[3] that 4-methylcyclohexene reacts with benzene in the presence of hydrogen fluoride to form 1-methyl-1-phenylcyclohexane in about 75% yield. The remainder of the product consisted of dicycloalkylated benzene from which a solid was separated which melted at 70–71° and to which the structure of *p*-di-(methylcyclohexyl)-benzene (I) was assigned. In order to determine



I

II

the composition of the dicycloalkylated benzene the higher boiling fractions from several experiments were combined and redistilled on a 30-plate, 26-mm. Oldershaw column.[4] The various cuts were further redistilled using a spinning band Piros–Glover column having an efficiency at a total reflux and at atmospheric pressure of about 60 theoretical plates. Two main fractions were separated: A and B.

A: b.p. 163.5° at 3.0 mm., $n^{20}D$ 1.5340, d^{20}_4 0.9688. *Anal.* Calcd. for $C_{20}H_{30}$: C, 88.82; H, 11.18; Mr_D, 86.56. Found: C, 89.32; H, 11.18; Mr_D, 86.75.

B: b.p. 181.5° at 3.7 mm., $n^{60}D$ 1.5238, m.p. 70–71° after crystallization from ethanol. *Anal.* Calcd. for $C_{20}H_{30}$: C, 88.82; H, 11.18. Found: C, 88.74; H, 11.17.

Based on spectrographic analyses and boiling point the polycycloalkylated benzene consisted of 23% compound II, most probably *m*-di-(1-methylcyclohexyl)-benzene, and 64% compound

(1) This work was made possible in part through the financial assistance of the Universal Oil Products Company, Des Plaines, Illinois.

(2) Deceased, November 29, 1952.

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