$(C_2H_5)_3N < NH_3 < (C_2H_5)_2NH < C_2H_5NH_2$ (curve D); and tri-*t*-butylboron, a reference acid with a high F-strain factor, yields the order $(C_2H_5)_3N < (C_2H_5)_2NH < C_2H_5NH_2 < NH_3$ (curve F).[6]

TABLE IV

SUMMARY OF DATA ON RELATIVE STRENGTHS OF AMMONIA AND THE METHYL- AND THE ETHYLAMINES

Series	Reference acid	Order (Fig. 1)
Ammonia and methylamines	H^+ (aqueous)	B
	HCl (no solvent)	No data
	$B(CH_3)_3$	B
	$B[C(CH_3)_3]_3$	E
Ammonia and ethylamines	H^+ (aqueous)	B
	HCl (no solvent)	B
	$B(CH_3)_3$	D
	$B[C(CH_3)_3]_3$	F

These changes in the orders produced by a given reference acid in the ethylamine series as compared to the methylamine series are in complete agreement with the effect of the predicted increase in F-strain resulting from the replacement of the methyl by the larger ethyl group. The results thus offer strong support for the F-strain hypothesis.

Finally, it is noteworthy that the order yielded by tri-*t*-butylboron in the ethylamine series, $(C_2H_5)_3N < (C_2H_5)_2NH < C_2H_5NH_2 < NH_3$, is the exact opposite of the order which would be predicted if only the polar factor were considered, $NH_3 < C_2H_5NH_2 < (C_2H_5)_2NH < (C_2H_5)_3N$. The importance of considering both factors, polar and steric, is apparent.

Acknowledgment.—The purchase and construction of the apparatus used in this investigation was made possible by a grant from the Penrose Fund of the American Philosophical Society. This assistance is gratefully acknowledged.

Summary

1. The relative order of base strength, $NH_3 < (C_2H_5)_3N < C_2H_5NH_2 < (C_2H_5)_2NH$, observed with hydrogen chloride as the reference acid is altered to $(C_2H_5)_3N < NH_3 < (C_2H_5)_2NH < C_2H_5NH_2$ with trimethylboron as the reference acid. Tri-*t*-butylboron causes a further change in the order of the amines to $(C_2H_5)_3N < (C_2H_5)_2NH < C_2H_5NH_2 < NH_3$.

2. These changes in orders are in accord with the predicted effect of F-strain on the relative strengths of these bases. In particular, the relatively greater changes in the orders brought about by a given reference acid in the ethylamine series as compared with the methylamine series, strongly support the F-strain hypothesis.

3. In the course of this investigation, the addition compounds ethylamine-trimethylboron, diethylamine-trimethylboron, triethylamine-trimethylboron, and ethylamine-tri-*t*-butylboron were prepared and characterized. Diethylamine and triethylamine do not combine with tri-*t*-butylboron at 0°.

DETROIT, MICHIGAN RECEIVED MARCH 2, 1945

[6] It should be pointed out that the present study merely establishes the order as $(C_2H_5)_3N$, $(C_2H_5)_2NH < C_2H_5NH_2 < NH_3$ with tri-*t*-butylboron as the reference acid. However, in view of the results obtained with hydrogen chloride and trimethylboron, there is little reason to doubt that triethylamine lies below diethylamine, as indicated above.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH, AND MELLON INSTITUTE]

The Cyclic Dimerization of Isobutylene[1]

BY JOSEPH B. MCKINLEY,[2] DONALD R. STEVENS AND WILMER E. BALDWIN

The authors had previously found that isobutylene polymerized at high temperatures and pressures to give a cyclic dimer as the main product. This fact was never noticed before, although Ipatieff[3] recognized that isobutylene reacted at 380–390° and 70 atmospheres pressure to give an unresolved complex of paraffins, naphthenes and olefins. The hydrocarbon was isolated, and, from a study of its properties and possible modes of formation, it was concluded that it might be 1,1,3-trimethylcyclopentane. The present study had as its main aims, therefore, the confirmation of the structure postulated for the dimer, and the determination of the effect of reaction variables on its formation.

Identification of the Cyclic Dimer.—The cyclic dimer was identified by synthesizing it in a conventional manner. For the synthesis, 1,3-dimethylcyclopentanol was treated with hydrogen chloride to form 1-chloro-1,3-dimethylcyclopentane, a new substance.[4] The chlorocyclopentane was converted to 1,1,3-trimethylcyclopentane by methylation with both zinc dimethyl and methylmagnesium iodide. The comparison of the properties of the cyclic dimer with those of the conventionally synthesized 1,1,3-trimethylcyclopentane given in Table I establishes the two as identical.

[1] An abstract of a thesis presented by Joseph B. McKinley to the graduate school of the University of Pittsburgh in August, 1943, in partial fulfillment of requirements for the degree of Doctor of Philosophy. Contribution No. 545 from the University of Pittsburgh.

[2] Present address: Gulf Research and Development Co., P. O. Box 2038, Pittsburgh 30, Pa.

[3] Ipatieff, *Ber.*, **44**, 2978 (1911).

[4] The synthesis involved optically inactive substances. The formation of inadequately characterized optically active 1-chloro-1,3-dimethylcyclopentane is reported by Zelinsky and Rjachina, *Ber.*, **57**, 1931 (1924).

TABLE I

1,1,3-TRIMETHYLCYCLOPENTANE AND THE CYCLIC DIMER COMPARISON[a]

	1,1,3-Trimethylcyclopentane	Cyclic dimer
Mol. wt.	112.2[b]	113
B. p., °C. at 760 mm.[c]	105.0	105.0
d^{20}_4	0.7481	0.7480
n^{20}_D	1.4109	1.4108
Aniline point, °C.[d]	59.7	59.8
Mol. refraction	37.22	37.22
Viscosity at 20°C.[e] Centistokes	0.827	0.828
Viscosity at 20°C.[e] Centipoise	0.619	0.619
% Carbon	85.63[b]	85.82[f]
% Hydrogen	14.37[b]	14.51[f]
Atomic carbon to hydrogen ratio	0.5:1[b]	0.497:1

[a] The estimated accuracy of the physical constants given for the preparations is ±2 units in the last place reported. [b] Theoretical values. [c] Employing the percolator method given in Shriner and Fuson "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, 1940, pp. 92–93. [d] Using aniline and method which gave a value of 69.9° for *n*-heptane. [e] Employing viscometer of Cannon and Fenske, *Ind. Eng. Chem., Anal. Ed.*, **10**, 297 (1938). [f] See ref. 13.

The proof of structure outlined above assumes that no structural rearrangements occurred during the conventional synthesis of the naphthene. The assumption is justified, however, because Chavanne and co-workers[5] have shown that a *gem*-dimethyl group can be substituted on a cyclopentane ring by treating a 1-chloro-1-methylcyclopentane with methylmagnesium iodide. Furthermore, that the chloro group substitutes the hydroxyl group of the cyclopentanol without rearrangement is indicated by the ease with which the chlorocyclopentane could be methylated with zinc dimethyl, for Noller[6] found that, under the approximate experimental conditions which we employed (see details below), zinc alkyls alkylate only tertiary chlorides.

TABLE II

DIMERIZATION OF ISOBUTYLENE[a]

	Time series[b]			Pressure series			Temp. series		
Isobutylene charged to bomb, g.	323	321	323	70	180	645	338	304	285
Temp., °C.	400	400	400	400	400	400	370	430	460
Time at temp., hr.	½	1	4	1	1	1	2	1	1
Press., max. lb./sq. in.	2160	2050	2200	540	1280	5350	2120	2025	2025
Yield based on isobutylene charged:									
Total liquid, wt. %	45.4	57.7	77.5	22.5	42.9	80.8	34.2	72.9	51.7
Crude dimer (95–128°), wt. %	18.7	23.6	29.9	15.1	22.3	22.6	11.0	33.4	21.7
Cyclic dimer, wt. %	11.2	15.3	20.6	10.3	14.5	14.5	6.0	23.4	16.1
Liquid product:									
Crude dimer, wt. %	41.3	40.9	38.6	67.1	52.0	28.0	32.2	45.9	42.0
Cyclic dimer, wt. %	24.8	26.6	26.6	45.9	33.8	17.9	17.4	32.1	31.0

[a] At 460° coke and carbon formation amounted to 4.7 wt. % of the isobutylene charged; at the lower temperatures such formation was negligible. [b] Results of the dimerization at 400° for one hour under 2050 maximum lb./sq. in. form part of the other series but are omitted from them.

Previous attempts to synthesize the naphthene have been reported in the literature. Zelinsky and Uspensky[7] treated 3,3-dimethylbicyclo(0,1,3)-hexane with hydrogen iodide to obtain what they assumed to be either 1-iodo-2,4,4-trimethylcyclopentane or 1-iodo-3,3-dimethylcyclohexane. Reduction of the iodo product gave a hydrocarbon which they thought was 1,1,3-trimethylcyclopentane, the expected reduction product of the iodocyclopentane, because its properties differed from those known for 1,1-dimethylcyclohexane, the expected reduction product of the iodocyclohexane. Dey and Linstead[8] believed they might have prepared the trimethylcyclopentane by subjecting 5,5-dimethylcyclohexane-1,3-dione to Clemmensen reduction, inasmuch as their main reaction product was proved to be 2,4,4-trimethylcyclopentanone, which has the same carbon skeleton as the naphthene. The properties[9] of these other preparations do not agree with those of our 1,1,3-trimethylcyclopentane and were of no help for the identification of the cyclic dimer.

The Dimerization.—In the study of the dimerization, reaction times, temperatures, and maximum pressures[10] ranged between one-half and four hours, 370 and 460°, and 540 and 5350 lb./sq. in., respectively. The exact conditions and summarized results of the treatments completed are given in Table II. All of the total liquid products contained the same main components regardless of the conditions under which they were prepared. Typical detailed results of the examination of one liquid are shown in Table III and Fig. 1. In general, the product of the boiling range of fraction 4, the crude dimeric fraction, was made up largely of the cyclic dimer, but it contained a lesser amount of unsaturates and a small quantity of paraffins. Product of the boiling range of fraction 2 was mainly paraffinic, al-

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(5) Chavanne, Miller and Cornet, *Bull. soc. chim. Belg.*, **40**, 673 (1931).

(6) Noller, THIS JOURNAL, **51**, 594 (1929).

(7) Zelinsky and Uspensky, *Ber.*, **46**, 1466 (1913).

(8) Dey and Linstead, *J. Chem. Soc.*, 1063 (1935).

(9) Zelinsky and Uspensky's preparation had a b. p. of 115–116° at 760 mm., a d^{20}_4 of 0.7703, and a n^{20}_D of 1.4223. Dey and Linstead's product had a b. p. of 106–107° at 767 mm., a d^{18}_4 of 0.7764, and a n^{18}_D of 1.4240.

(10) In the bomb technique employed, the pressure rose to a maximum and then fell because of reaction.

though a substantial amount of acyclic olefins was present. Material in the boiling range of fraction 5 contained mainly cyclic unsaturates, and that in the boiling range of fraction 7 was made up largely of cyclic saturates and acyclic unsaturates, which were, most probably, trimers.

TABLE III

EXAMINATION OF LIQUID PRODUCED IN ONE HOUR AT 400° UNDER 2050 LB. MAXIMUM PRESSURE[a]

Fraction	B. p., °C., at 740 mm.	Wt., %	n^{20}_D	d^{20}_4	Br. no.
1	to 75	0.9	1.3799	0.6672	54
2	75-85	5.4	1.3846	.6780	34
3	85-95	1.7	1.3919	.6949	23
4	95-128	40.9	1.4101	.7389	38
5	128-150	3.6	1.4322	.7711	121
6	150-175	2.6	1.4376	.7789	104
7	175-195	14.3	1.4365	.7839	52
8	>195	30.6	1.4609	.8292	...

[a] Gaseous product and experimental loss were 39.8 wt. % and 2.5 wt. %, respectively, of the isobutylene reacted. The analysis of the gas in wt. % was methane, trace; propylene, 0.4; propane, 3.1; isobutylene, 91.2; isobutane, 2.7; C_5 and higher (unsaturates), 2.3; C_5 and higher (saturates), 0.3. Analysis by E. H. Epprecht of Gulf Research and Development Co.

The effect (Table II) of increasing either reaction time or maximum pressure was to increase the yield of total liquid product. The liquid yield also increased with increased temperatures up to 430°, but, when a substantially higher temperature (460°) was employed, it decreased because of excessive cracking of the product. The yield of cyclic dimer showed the same general time and temperature dependence as did the total liquid; however, it was relatively independent of maximum reaction pressure above 1280 lb./sq. in. The maximum yield of 23.4% resulted when the reaction was carried out under a maximum pressure of 2025 lb./sq. in. at 430° for one hour. The percentage of cyclic dimer found in the various liquid products was independent of reaction time. This percentage decreased as the maximum reaction pressure was increased, but increased to a constant value of about 32% as the reaction temperature was increased. The highest percentage of cyclic dimer found in any liquid product was 45.9%, resulting when the reaction was carried out under a maximum pressure of 540 lb./sq. in. at 400° for one hour.

Mechanisms of Dimerization.—The mechanism by which the cyclic dimer forms is not known. It was found, however, that the compound could not be formed from the commonly occurring diisobutylene,[11] an expected intermediate, under conditions suitable for the formation of the naphthene from isobutylene. The hydrocarbon could form, however, in several other ways which are shown in the accompanying schematic diagram. For example, it is possible that two molecules of isobutylene (I) might polymerize to 1,1,3,3-tetramethylcyclobutane (II). If (II) is formed, thermal stress would be expected to rupture one

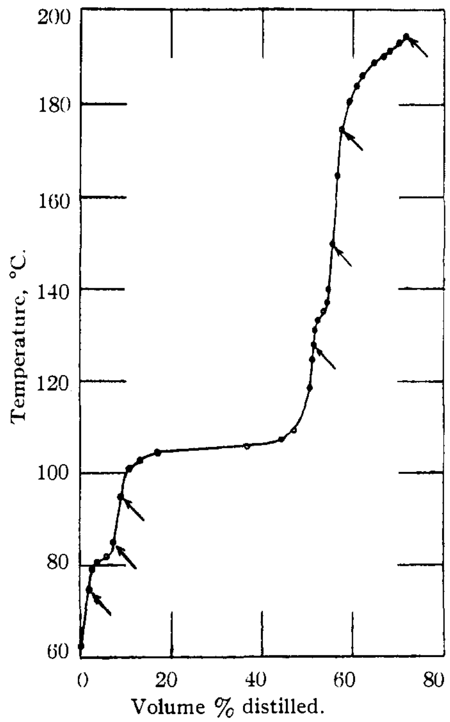
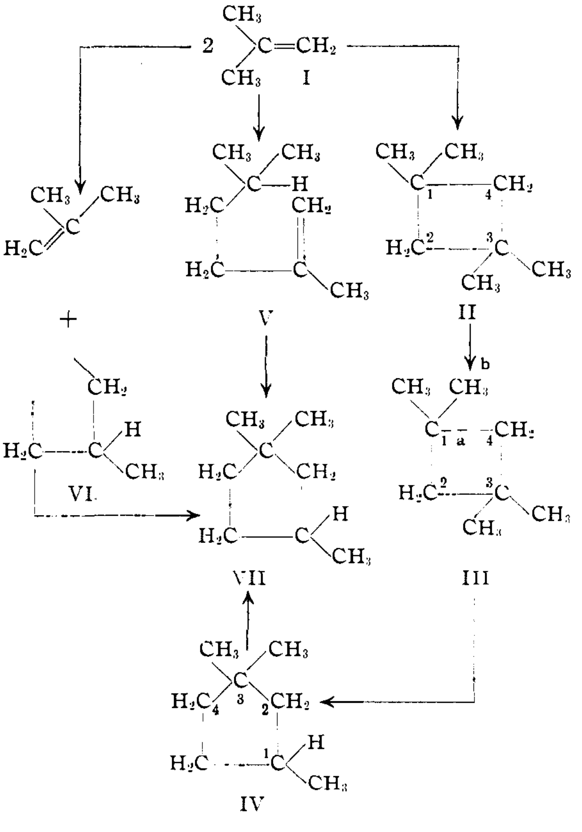


Fig. 1.—Distillation curve of the product described in Table III. Arrows define fractions taken.



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[11] A mixture of four parts of 2,4,4-trimethylpentene-1 and one part of 2,4,4-trimethylpentene-2.

of the carbon–carbon bonds of the ring to give the bivalent radical (III) which could isomerize to another bivalent radical (IV). The latter radical might then cyclicize to form the cyclic dimer (VII).

It is also conceivable that the dimerization involves the isomerization of isobutylene to the bivalent radical (VI), and the addition of (VI) to a normal isobutylene molecule. Alternatively, isobutylene might first form 2,5-dimethylhexene-1 (V), which is postulated by McCubbin and Adkins[12] as a possible acyclic dimer of isobutylene. This olefin, if formed, might cyclicize by a process of intramolecular alkylation, involving the tertiary hydrogen, to give (VII). These mechanisms support the structure assigned to the cyclic dimer, which is otherwise confirmed by the conventional synthesis.

Experimental Details[13]

1-Chloro-1,3-dimethylcyclopentane.—A method which is essentially that of Chavanne[14] was used to prepare a stock of 1,3-dimethylcyclopentanol (b. p. 59.8–60.0° at 20 mm., d^{20}_4 0.8903, n^{20}_D 1.4420). In a sample experiment, the cyclopentanol (132.4 g.) reacted with 57.6 g. of dry hydrogen chloride at 2°. The crude product was washed with water, then with saturated sodium bicarbonate solution, again with water, and finally dried with calcium chloride. The preparation was fractionated through a 20-plate column at 15 mm. pressure using a reflux ratio of 20:1. Superheating and decomposition during fractionation were avoided by immersing the still pot in a water bath at 45–50°. The constant boiling product (b. p. 33.2° at 15 mm., d^{20}_4 0.9347, n^{20}_D 1.4406) weighed 128.9 g.; yield, 83.8%.

Anal. Calcd. for $C_7H_{13}Cl$: C, 63.39; H, 9.88; Cl, 26.73. Found: C, 63.46; H, 10.09; Cl, 26.57.

1,1,3-Trimethylcyclopentane. A. By Zinc Dimethyl Methylation.—A solution of 53 g. of 1-chloro-1,3-dimethylcyclopentane in 53 g. of dry xylene was added, in one hour, to a stirred solution of 20 g. of zinc dimethyl (Eastman Kodak Co.) in 150 g. of dry xylene, keeping the temperature at 25°.[15] The reaction mixture was slowly heated to and maintained at 40° for one-half hour. The cooled product was treated with 20 ml. of concentrated hydrochloric acid in 80 ml. of water to decompose zinc dimethyl. It was washed with saturated sodium bicarbonate solution and with water, dried over calcium chloride, and finally refluxed over sodium. The product was combined with other similarly prepared material and the composite was fractionated to obtain 90 g. of product, boiling from 90.5 to 139.5° at 760 mm., which was free from the bulk of the solvent xylene. Fractionation of this concentrate at 735 mm. through a 62-plate column using a reflux ratio of 30:1 with determination of the bromine numbers[16] of the fractions, showed that it consisted of unsaturates (b. p. 91–92°, d^{20}_4 0.7696, bromine number 149), a solvent and saturated product. Except for the small amount (10 ml.) contained in transition fractions, all of this saturated product (50 ml.) boiled at 103.7 ± 0.1°, showing the isolation of a pure compound. A 10-ml. middle fraction was filtered through silica gel[17] to remove traces of lower-boiling unsaturates and solvent xylene. Properties of the purified product are given in Table I. The total yield of the naphthene was 34.7% of the theoretical, based on the chloride reacted.

Anal. Calcd. for C_8H_{16}: C, 85.63; H, 14.37; mol. wt., 112.2. Found: C, 85.55; H, 14.44; mol. wt., 112.

B. By Methylmagnesium Iodide Methylation.—Methylmagnesium iodide was prepared in 1030 ml. of dibutyl ether at 35–39° from 60.9 g. of magnesium and 356 g. of methyl iodide. Three hundred and eight grams of 1-chloro-1,3-dimethylcyclopentane was added to the stirred Grignard reagent in forty minutes. The temperature was not controlled during this operation; the heat generated caused it to rise gradually to 70°. Stirring was continued for an additional one hundred and thirty-five minutes while the reaction mixture cooled to 25°. The Grignard reagent was decomposed with water and 35% acetic acid. The oily layer was washed with 10% sodium hydroxide solution and with water and finally dried with anhydrous potassium carbonate. It was fractionated through a 15-plate column to obtain 100 ml. of product boiling from 90.8–129.0° (740 mm.). This fraction was combined with 50 ml. of xylene, refluxed over sodium, and refractionated (reflux ratio 30:1) through a 62-plate column. The data showed the production of 50.3 g. (19.3% yield) of the desired naphthene. A 15-ml. middle fraction of the naphthenic material (b. p. 104.0–104.1° at 745 mm.) was further purified by filtration through silica gel. Its properties were identical with those of the 1,1,3-trimethylcyclopentane prepared using zinc dimethyl.

Anal. Calcd. for C_8H_{16}: C, 85.63; H, 14.37; mol. wt., 112.2. Found: C, 85.81; H, 14.49; mol. wt., 113.

Preparation and General Examination of Dimerization Products.—A typical preparation (Table II) involved charging a weighed quantity of pure isobutylene (b. p. −6.7° at 760 mm.) to an evacuated 1715-ml. S. A. E. 4140 steel rotating bomb. The vessel was introduced into a preheated electric furnace, heated at a rate of 7°/minute to the desired reaction temperature, and maintained at this temperature for the predetermined reaction time. The bomb was then cooled at a rate of 10°/minute to room temperature in a strong air blast. It was placed in a bath at 50° and the gas content was released through a trap at 0°. After cooling the bomb to room temperature, the liquid product was recovered and combined with that collected in the trap; the combined product was degassed completely, employing an efficient fractionating column. Sufficient runs were made under each set of reaction conditions to supply at least 400 ml. of liquid for examination. When an analysis of a gaseous product was desired, the condensable portion was condensed in traps at −78 and −195°, and the non-condensable part was collected in a gas-holder over salt water.

Gaseous products were analyzed by low-temperature fractionation, bromination, and refractionation. In addition, the isobutylene content was determined by absorption in 63% sulfuric acid; the hydrogen content was estimated by contacting with a nickel catalyst, under such conditions that any hydrogen present would combine with the olefins contained, and then noting the volume contraction. The various liquid products were fractionated (reflux ratio 20:1) at atmospheric pressure through a 16-plate column (see Table III) and the densities, refractive indices, and bromine numbers of the fractions were determined. Study of the properties of the fractions in relation to average values for the different types of hydrocarbons expected permitted the estimation of the general nature of the total liquids. This method was amplified for crude dimeric fractions by refractionating representative cuts and by a similar study of the properties of the fractions obtained before and after removal of unsaturates. Olefin removal was accomplished by treatment with 83% sulfuric acid followed by redistillation, by silica gel filtration, or by the thioglycolic acid method described below. The method of Hoog and Eichwald[18] gave no indication for the presence of toluene in the crude dimeric

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(12) McCubbin and Adkins, This Journal, **52**, 2547 (1930).

(13) Microanalyses by Ralph O. Clark and Lincoln T. Jenkins of Gulf Research and Development Co.

(14) Chavanne, *Bull. soc. chim. Belg.*, **35**, 283 (1926).

(15) The zinc dimethyl solution was made up in an atmosphere of dry carbon dioxide and the reaction was carried out in such an atmosphere.

(16) Mulliken and Wakeman, *Ind. Eng. Chem., Anal. Ed.*, **7**, 59 (1935).

(17) Mair and White, *J. Research Natl. Bur. Standards*, **15**, 51 (1935).

(18) Hoog and Eichwald, *Rec. trav. chim.*, **58**, 481 (1939).

fractions except possibly a small amount in that prepared at the extreme temperature of 460°.

Isolation of the Cyclic Dimer.—For the precise isolation of the cyclic dimer, liquid reaction product (909 g.) made from isobutylene in the presence of added nitrogen at 430–440° under 4700 maximum lb./sq. in. for one hour[19] was fractionated through a 45-plate column to obtain a 100-ml. middle fraction from the plateau material boiling at 105° (760 mm.). This fraction was filtered through silica gel several times to remove unsaturated components. The saturated product obtained (54 ml.) was further purified by fractionating it through a 62-plate column at 740 mm. (reflux ratio 40:1) to obtain ten 5-ml. fractions and a residue. All of the fractions, except the first two and last, boiled at the same temperature and had the same refractive index, indicating the isolation of a pure compound. The sixth and seventh fractions were combined and taken as the isolated compound. The properties of this composite are shown in Table I for the cyclic dimer.

Estimation of Cyclic Dimer Formation.—For the routine estimation of cyclic dimer formation under any particular set of reaction conditions employed, the crude dimeric fraction of the liquid was analyzed. The analysis consisted of estimating the saturates present from the bromine number, assuming that the unsaturates contained had a molecular weight of 112. The unsaturates were then removed from the crude dimer and the cyclic dimer content of the saturated product obtained was determined by comparing its density (d^{20}_4) with that of 1,1,3-trimethylcyclopentane and an average value (0.7051) for octanes. Olefin removal was accomplished by treating the crude dimeric product with thioglycolic acid,[18] and filtering the acid-treated product (*ca.* 35 ml.), which still contained traces of unsaturates, through a column (diameter 15 mm.) of 20 g. of 100–200 mesh silica gel, and recovering as much saturated product as possible by displacing it from the gel with water.[17] Some separation of mixtures of paraffins and naphthenes is caused by silica gel filtration; however, by refiltering the saturated products obtained, it was determined that the amount of such separation was not sufficient to affect the essential validity of the analytical results given.

Acknowledgment.—The authors wish to thank Dr. W. A. Gruse and Dr. R. L. Wakeman of the Mellon Institute for suggestions made relative to this investigation and for their interest in it.

Summary

1. A study of the thermal polymerization of isobutylene was made at temperatures of from 370 to 460°, maximum pressures of from 540 to 5350 lb./sq. in., and times of from one-half to four hours. Under these conditions a cyclic dimer, 1,1,3-trimethylcyclopentane, is the main reaction product. It amounts to as much as 45.9% of the total liquid product when the reaction is carried out at 400° under 540 maximum lb./sq. in. for one hour.

2. Mechanisms are proposed to explain the formation of 1,1,3-trimethylcyclopentane from isobutylene.

3. A conventional synthesis of the trimethylcyclopentane, which resulted in the identification of the cyclic dimer, is described. During the synthesis, a new substance, optically inactive 1-chloro-1,3-dimethylcyclopentane, was prepared.

PITTSBURGH, PA. RECEIVED FEBRUARY 12, 1945

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[19] This product is not described in the text, but a large amount was available as a result of preliminary work. Its distillation curve and properties indicated that it was substantially identical to the product, described in Table II, made at 430° under 2025 maximum lb./sq. in. in one hour. In the two reactions virtually the same amount of isobutylene reacted; the extra pressure of nitrogen apparently had little effect.

[CONTRIBUTION NO. 568 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Furan and Tetrahydrofuran Derivatives. VI. The Total Synthesis of *dl*-Oxybiotin[1]

BY KLAUS HOFMANN

Although a number of biological studies[2,3,4] of biotin derivatives have been described and have led to most interesting results, further progress in this field depends largely on the synthesis of new biotin analogs. It seemed of interest to prepare a number of such analogs in order to investigate further the relationships of chemical structure to biotin activity.

In a recent communication[5] the synthesis of hexahydro-2-oxo-1-furo[3,4]imidazole-4-valeric acid, an oxygen analog of biotin, was announced, and microbiological studies[6] have demonstrated a high degree of biotin activity for this compound. In view of this comparable biological activity, as well as the close structural similarity to biotin, we have proposed the name *dl*-oxybiotin for this new compound.

The present report describes in detail the final phases of the oxybiotin synthesis. The different steps of the complete synthesis may be summarized as follows: 2-furanpentanol (I), the starting material, was prepared from furfural by conventional methods, and was condensed with diethyl acetylene-dicarboxylate according to the Alder–Rickert procedure. Saponification of the resulting 3,4-dicarbethoxy-2-furanpentanol gave 3,4-dicarboxy-2-furanpentanol (II) which was acetylated and transformed into the acid chloride (III).[7] Compound (III) was subjected to a modified Curtius degradation and the resulting 3,4-diaminocarbethoxy-2-furanpentanol acetate was partially hydrolyzed to give 3,4-diaminocarbeth-

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[1] The author wishes to express his appreciation to Ciba Pharmaceutical Products, Inc., and to the Buhl Foundation for their generous support of this study.

[2] du Vigneaud, Dittmer, Hofmann and Melville, *Proc. Soc. Exptl. Biol. Med.*, **50**, 374 (1942).

[3] Melville, Dittmer, Brown and du Vigneaud, *Science*, **98**, 497 (1943).

[4] Dittmer, du Vigneaud, György and Rose, *Arch. Biochem.*, **4**, 229 (1944).

[5] Hofmann, THIS JOURNAL, **67**, 694 (1945).

[6] Pilgrim, Axelrod, Winnick and Hofmann, *Science*, **102**, 35 (1945).

[7] Hofmann, THIS JOURNAL, **67**, 421 (1945).