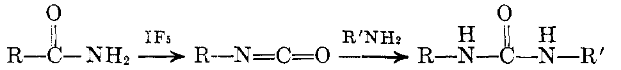
exposed to iodine pentafluoride in pyridine solution, have been found to undergo rearrangement to give products similar to those obtained under Hofmann conditions.[4]



$$R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}NH_2 \xrightarrow{IF_5} R{-}N{=}C{=}O \xrightarrow{R'NH_2} R{-}\overset{H}{N}{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}\overset{H}{N}{-}R'$$

The *t*-butyl isocyanate produced from pivalamide after 2 hr at 110° in pyridine–iodine pentafluoride, was isolated as di-*t*-butylurea (78%). Hexanamide and octanamide rearranged readily under similar conditions, and after aqueous work-up the product was a mixture of isocyanate and carbamoyl fluoride. Reaction with *t*-butylamine converted both products to the urea (57% from hexanamide, 41% from octanamide).[5]

Some iodination of benzamide, or its rearranged product, was observed in 1 hr at 93°; an iodinated carbanilide was isolated upon hydrolysis of the reaction mixture.[5]

Because of the complex nature of the reagent used here, it has not been possible to determine if an N-halogenated amide is an intermediate here,[4] or if dehydrogenation of the amide leads to a nitrene directly.[5]

It is worth noting that benzophenone hydrazone was converted to a mixture of benzophenone azine and benzophenone (after aqueous work-up) by iodine pentafluoride in methylene chloride alone. There was no evidence for the formation of a C–F bond. When the hydrazone was oxidized in pyridine solution, only a small amount of the same two products were obtained; the major products were water soluble.

Experimental Section

Reaction of Pivalamide, Iodine Pentafluoride, and Pyridine.—A mixture of 4.0 g of pivalamide, 3 ml of iodine pentafluoride, and 25 ml of pyridine was heated at 110° for 2 hr. The reaction mixture was cooled, poured into water, and extracted with methylene chloride. The extract was washed with water, 10% aqueous hydrochloric acid, and water, and dried over magnesium sulfate. The infrared spectrum and vpc trace of a portion of this that had been concentrated by distillation indicated only *t*-butyl isocyanate. The methylene chloride solution was treated with 10 ml of *t*-butylamine. Removal of the methylene chloride left 1,3-di-*t*-butylurea, 5.4 g, subliming at 240°, lit.[5] mp 242–243°.

Anal. Calcd for $C_9H_{20}N_2O$: C, 62.74; H, 11.70; N, 16.26. Found: C, 62.79; H, 11.62; N, 15.93.

Rearrangement of Hexanamide with Iodine Pentafluoride.—A 4.6-g sample of hexanamide was treated with iodine pentafluoride (3 ml)–pyridine as described above. The organic product extracted into methylene chloride was, by infrared spectrum, a mixture of isocyanate (4.4 μ) and carbamoyl fluoride (5.6 μ). The ^{19}F nmr spectrum exhibited the carbamoyl fluoride peaks at ϕ +15.5, J_{HF} = 8 cps.[6] The methylene chloride solution was treated with *t*-butylamine (10 ml) and gave N-*n*-pentyl-N'-*t*-butylurea, 4.19 g, mp 59–61°.

Anal. Calcd for $C_{10}H_{22}N_2O$: C, 64.47; H, 11.90; N, 15.04. Found: C, 64.23; H, 11.95; N, 14.12.

Rearrangement of Benzamide with Iodine Pentafluoride.—A mixture of benzamide (5.3 g), iodine pentafluoride (3.0 ml), and pyridine (30 ml) was heated on a steam bath for 1 hr. The mixture was poured over ice and partitioned between methylene chloride and water. A solid, 3.5 g, was removed by filtration. This solid was an iodinated diphenyl urea, mp 243–245° dec.

Anal. Found: C, 41.10; H, 3.30; N, 7.46; I, 41.0.

Anal. Calcd for a monoiodocarbanilide ($C_{13}H_{11}N_2OI$): C, 46.17; H, 3.28; N, 8.38; I, 37.5.

Oxidation of Benzophenone Hydrazone with Iodine Pentafluoride.—A solution of 2.0 ml (0.029 mole) of iodine pentafluoride in 100 ml of methylene chloride was stirred at 15° while 2.9 g (0.015 mole) of benzophenone hydrazone in 50 ml of methylene chloride was added over a 3-hr period. The solution was stirred at 15° for 30 min; then water was added and the methylene chloride solution was washed with water and dilute sodium thiosulfate solution. A residue of 2.78 g was obtained from the methylene chloride extract. This residue was recrystallized from hexane; the first crop was benzophenone azine, 0.81 g, mp 160–161°, identified by infrared spectrum and mixture melting point.[7] The solution was chilled and benzophenone, 0.62 g, mp 47–48°, was obtained.

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[4] P. A. S. Smith, *Org. Reactions*, **3**, 267 (1946); P. A. S. Smith, "Molecular Rearrangement," Part I, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1964.

[5] Similar isolation methods were used by others studying the rearrangement of primary amides with lead tetraacetate. See H. E. Baumgarten and A. Staklis, *J. Am. Chem. Soc.*, **87**, 1141 (1965), and B. Acott and A. L. J. Beckwith, *Chem. Commun.*, 161 (1965).

[6] R. F. Merritt, unpublished results, found the ^{19}F peak in *n*-propyl carbamoyl fluoride (from hydrogen fluoride and *n*-propyl isocyanate) at ϕ +15.9.

[7] T. Curtius and F. Rauterberg, *J. Prakt. Chem.*, **44**, 192 (1891).

The Synthesis of Piperitenone *via* Mesityl Oxide and Methyl Vinyl Ketone

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The monoterpenoid, piperitenone (IV), is of interest because it can be converted to a wide variety of important monoterpenoids. It has been obtained by several chemical routes[1a,b] as well as from essential oils.[1c,d] The most practical synthesis[1b] from geranic acid has been shown to give almost equal yields of IV and a bicyclic cyclobutanone.[2] Recently, Bergmann and Bracha[3] have described the synthesis of piperitenone in 41% yield by the condensation of mesityl oxide with methyl vinyl ketone using sodium *t*-pentoxide in toluene. However, this work has been refuted by Naves[4] who claimed that the product of the reaction was isoxylitone (VI), the self-condensation product of mesityl oxide. The reaction has been studied in considerable detail by several groups[5-7] and the general consensus is that under the Bergmann reaction conditions the principal product is isoxylitone, and piperitenone is formed in only 8% yield. Moreover, the mixture is almost impossible to separate by distillation. We also have repeated Bergmann's work and obtained only a low yield of piperitenone contaminated with isoxylitone and several other products as well as polymeric material due to the self-condensation of methyl vinyl ketone. More recently, Wiemann[8] has obtained piperitenone

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[1] (a) A. A. Penfold, G. R. Ranage, and J. L. Simonson, *J. Chem. Soc.*, 1496 (1939); (b) C. Balant, C. A. Vodoz, H. Kappeler, and H. Schinz, *Helv. Chim. Acta*, **34**, 722 (1951); (c) Y. R. Naves, *ibid.*, **25**, 732 (1942); (d) S. Shimizu, N. Ikeda, and H. Ueda, *Bull. Agr. Chem. Soc. Japan*, **24**, 324 (1960).

[2] J. J. Beereboom, *J. Am. Chem. Soc.*, **85**, 3525 (1963).

[3] E. D. Bergmann and P. Bracha, *J. Org. Chem.*, **24**, 994 (1959).

[4] Y. R. Naves and J. M. Conia, *Bull. Soc. Chim. France*, 378 (1960).

[5] Y. R. Naves and J. M. Conia, *Compt. Rend.*, **251**, 1130 (1960).

[6] H. Ueda, *Bull. Agr. Chem. Soc. Japan*, **24**, 601 (1960).

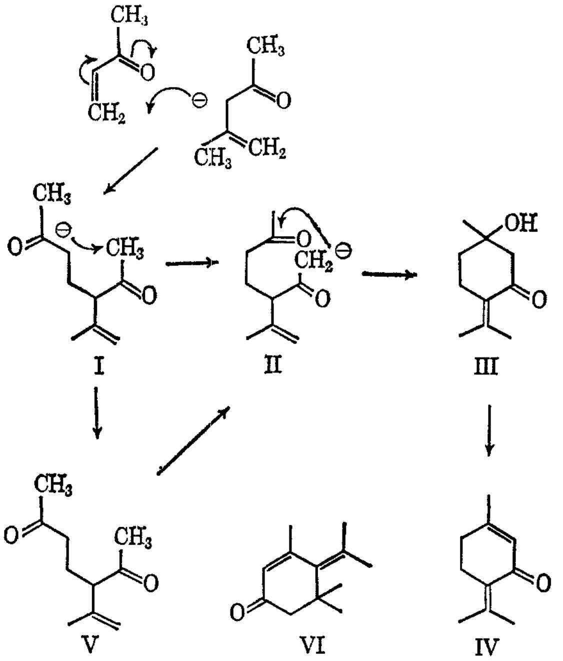
[7] E. D. Bergmann and P. Bracha, *J. Org. Chem.*, **26**, 4685 (1961).

[8] J. Wiemann and Y. Dubois, *Compt. Rend.*, **253**, 1109 (1961); J. Wiemann and Y. Dubois, *Bull. Soc. Chim. France*, 1813 (1962).

along with the corresponding ketol III in 15% yield by condensing mesityl oxide with methyl vinyl ketone in the presence of barium oxide and benzene.

Despite these rather unsuccessful attempts[9] the condensation route to IV remains attractive and we would like to record our own attempts to prepare piperitenone (IV) and, more importantly, a simple method of securing IV from the variety of other products that are usually formed in the reaction.

SCHEME I



We found that the heterogeneous system of potassium hydroxide and tetrahydrofuran restricts the formation of isoxylitone considerably. With equal molar quantities of mesityl oxide and methyl vinyl ketone, IV could be prepared in 25% yield. With an excess of mesityl oxide the yield was raised to 54% based on methyl vinyl ketone. The principal by-product was still isoxylitone which is very difficult to remove by a fractional distillation. Fortunately Naves[10] has reported that piperitenone is capable of forming a water-soluble sodium bisulfite addition compound. Treatment of the reaction mixture from the condensation reaction with bisulfite followed by ether extraction gave an aqueous solution from which piperitenone could be regenerated and isolated in 54% over-all yield.

Using sodium hydride as the catalyst, the methyl vinyl ketone and mesityl oxide condensation yields a variety of products, the principal one being isoxylitone (VI). At low temperatures and with potassium *t*-butoxide as the catalyst the same mixture of products is formed but the one formed in highest yield is the primary Michael condensation product, the diketone V. Wiemann[8] has proposed that piperitenone is formed by an aldol reaction between mesityl oxide and methyl vinyl ketone followed by a Michael reaction. In view of the isolation of V, we believe that the opposite course may take place. Isomesityl oxide anion initiates a Michael reaction with methyl vinyl ketone to give the anion I (Scheme I) which is either neutralized to form V or it abstracts the proton from the methyl group to form the anion II, which in turn attacks the carbonyl group to start the aldol reaction.

Experimental Section

Piperitenone.—To a suspension of 40 g (0.73 mole) of pulverized potassium hydroxide in 1 l. of tetrahydrofuran (stored over calcium hydride) was added with stirring 686 g of mesityl oxide. A solution of 178 g (2.5 moles) of methyl vinyl ketone in 196 g (total 9 moles) of mesityl oxide was added over 45 min with sufficient cooling to keep the temperature below 30°. The reaction was stirred at reflux temperature for 30 min and then cooled to 25°. Acetic acid (43 ml) was added and the solvent and mesityl oxide were removed by distillation. The residue was filtered and the precipitate was washed with 100 ml of ether. The filtrate was distilled and a fraction [90–125° (10 mm), 340 g] was collected. Gas-liquid partition chromatography[11] (glpc) indicated that the material contained 63% IV, 5% of V, and 22% of VI.

The crude piperitenone was added to a stirred solution of 560 g of sodium sulfite and 2 l. of water at 80–90°. The suspension was stirred and acetic acid (200 ml) was added dropwise to maintain a pH of 8–9. When the pH of the reaction became steady after about 30 min the mixture was cooled to room temperature and extracted three times with 250 ml of ether. Evaporation of the ether gave 88 g of crude oil that contained very little piperitenone by glpc. The aqueous layer was cooled in an ice bath and the pH was adjusted to 12.0 with 50% sodium hydroxide. The suspension was stirred for 10 min and then extracted four times with 300 ml of ether. The ether was dried over anhydrous sodium sulfate and evaporated to give 203 g (54%) of piperitenone that showed a single peak on glpc assay; $\lambda_{\max}^{\mathrm{EtOH}}$ 243, 277 mμ (ϵ 9925, 7860) [lit.[5] $\lambda_{\max}^{\mathrm{EtOH}}$ 243, 278 mμ (ϵ 12,600, 7940)].

Use of Sodium Hydride as a Catalyst.—To a stirred suspension of 4 g of sodium hydride in 200 ml of tetrahydrofuran was added dropwise at 0° a solution of 36 g of methyl vinyl ketone and 196 g of mesityl oxide over a 1-hr period. The reaction was stirred at 25° for 1 hr and then refluxed for 30 min. After cooling, 10 ml of acetic acid was added and the solvent and excess mesityl oxide were removed by distillation. A mixture of products (70.4 g) was obtained by vacuum distillation, bp 90–115° at 3 mm (glpc showed 16% IV, 13% V, and 36% VI). A sample of VI was collected by preparative glpc: $\lambda^{\mathrm{CCl_4}}$ 5.99, 10.05 μ, $\lambda_{\max}^{\mathrm{MeOH}}$ 236, 298 mμ (ϵ 3500, 14,500) [lit.[4] $\lambda_{\max}^{\mathrm{EtOH}}$ 238.5, 297 mμ (ϵ 2160, 13,200)]; $\delta_{\mathrm{CDCl_3}}$ = 0.94 (6 H, singlet), 1.85 (3 H, broad singlet), 1.98 (3 H, broad singlet), 2.06 (2 H, doublet, J = 2 cps), 2.20 (3 H, singlet), and 5.82 (1 H, broad singlet) ppm.

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.61; H, 10.06.

Using Potassium *t*-Butoxide as a Catalyst.—A solution of 1.4 g of potassium *t*-butoxide in 200 ml of tetrahydrofuran (dried over calcium hydride) was treated with 6 g of mesityl oxide and cooled to −5°. Over 45 min a solution of 45.5 g (0.5 moles) of methyl vinyl ketone and 196 g (2 moles) of mesityl oxide was added while keeping the reaction mixture at 0° with an ice bath. After stirring for an additional 15 min, 1 ml of acetic acid was added and the solvent and the excess mesityl oxide were removed by distillation. The residue was filtered and washed with ether and the filtrate was distilled under vacuum. A fraction (17.6 g), bp 70–105° (0.5 mm), was collected and analyzed by glpc. Besides piperitenone (30%) and isoxylitone (14%) the fraction also contained V (40%) which was collected by preparative glpc: $\lambda^{\mathrm{CHCl_3}}$ 3.26, 5.82, 6.07, 11.1 μ, $\lambda^{\mathrm{CH_3OH}}$ 298 mμ (ϵ 410); $\delta_{\mathrm{CDCl_3}}$ = 1.64 (3 H, doublet, J = 1.2 cps), 2.12 (6 H, singlet), 1.7–2.8 (4 H, several multiplets), 3.20 (1 H, triplet, J = 7 cps), 4.92 (1 H, singlet), 5.02 (1 H, triplet, J = 1.2 cps) ppm.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.59; H, 9.57.

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(9) A recent report describes the preparation of piperitenone in 50% yield from the condensation of mesityl oxide and 4-diethylamino-2-butanone: H. Ueda, K. Takeo. P. Tsai, and C. Tatsumi, *Agr. Biol. Chem.* (Tokyo), **29**, 374 (1965).

(10) Y. R. Naves and G. Papazian, *Helv. Chim. Acta*, **25**, 1023 (1942).

(11) A 10 ft × 0.25 in. (i.d.) glass column filled with 20% Carbowax 20M on Gas-chrom P with a column temperature of 180° was used for this and subsequent assays and preparative separations.