formation of insoluble, cross-linked copolymers. The copolymerization with maleic anhydride was rapid and quite exothermic.

Discussion of Results.—The infrared absorption data presented in this paper is the first conclusive evidence that these two-stage polymerizations proceed through a course involving only the vinyloxy group in the first stage, and the resulting linear polymer, which possesses the allyl-type double bond, is then cross-linked or thermoset through this system. Previous evidence was based on the known preferential reactivity of vinyloxy compounds toward cationic reagents, and the failure of this group, when present as the only unsaturated system in the compound, to lend itself to free radical catalyzed polymerization. The absence of the 8.32-μ band and the pronounced diminished intensity of the 6.08–6.18 μ region in the polymers represents quite a marked change in absorption.

The linear copolymers resulting from cationic catalyzed copolymerization of compounds described in this paper with vinyl alkyl ethers, and subsequent cross-linking with free radical producing catalysts, either alone or through copolymerization with other monomers, suggests their use in coatings, elastomers or castings. The pronounced reactivity of the unsaturated linear polymers with maleic anhydride suggests the use of maleic anhydride as a cross-linking agent or vulcanizing agent for other unsaturated polymers of the hydrocarbon type, such as polybutadiene, polycyclopentadiene, the copolymer of styrene and butadiene, or natural rubber latex.

Acknowledgment.—The author is indebted to Miss Mary L. Van Natta and Dr. A. H. Gropp of this department for the infrared curves used in this investigation.

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Alkaloid Studies. V.[1] Synthesis of 1-Isopropyl and 1-Isobutyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline

BY CARL DJERASSI, J. J. BEEREBOOM,[2a] S. P. MARFEY AND S. K. FIGDOR[2b]

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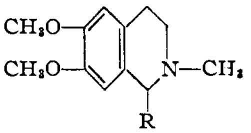
In connection with the characterization of certain cactus alkaloid degradation products, it was necessary to have available for comparison the previously unknown 1-isobutyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (I) and to know the composition of the acids arising from the oxidation of this substance.

N-Isovaleryl homoveratryl amide was subjected to the conventional Bischler–Napieralski reaction[3] using phosphorus pentoxide[4] as the cyclization agent. The resulting 1-isobutyl-6,7-dimethoxy-3,4-dihydroisoquinoline, obtained in 90% yield, was converted to the methiodide and reduced with sodium borohydride[5] to furnish the desired tetrahydroisoquinoline (I) in 85% yield The homogeneity of the product was demonstrated by chromatography and preparation of solid derivatives from the various eluates; the alternate cyclization structure (1-isobutyl-2-methyl-7,8-dimethoxy-1,2,-3,4-tetrahydroisoquinoline) was excluded by permanganate oxidation to N-methyl-3,4-dimethoxyphthalimide[6] (N-methyl imide of *m*-hemipinic acid) and direct comparison with an authentic sample[7] of the derived dimethyl ester.

Of particular interest for our purposes was the identification of the volatile "stench acids" produced in the oxidation As demonstrated first by paper chromatography and subsequently by actual isolation of the anilides, the main product isobutyric acid always was accompanied by a small amount of isovaleric acid arising from ring opening.

For reference purposes, the above sequence of steps was carried out also with N-isobutyryl homoveratryl amide leading ultimately to 1-isopropyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (II)



I, R = $CH_2CH(CH_3)_2$
II, R = $CH(CH_3)_2$

Acknowledgment.—We are indebted to the American Heart Association for financial assistance which enabled S.K.F. to participate in this investigation as a postdoctorate fellow.

Experimental[8]

1-Isobutyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (I).—Homoveratrylamine[9] was treated with isovaleryl chloride in benzene solution to yield the corresponding **amide** in 88% yield, m.p. 64–65.5°.

Anal. Calcd. for $C_{15}H_{23}NO_3$: C, 67.89; H, 8.74. Found: C, 67.75; H, 8.97.

Phosphorus pentoxide (50 g.) was added rapidly to a solution of 20 g. of the amide in 300 cc. of dry toluene and the mixture was refluxed for 15 minutes. An additional 30 g. of the pentoxide was added and refluxing was continued for 1 hour. The excess reagent was decomposed by the cautious addition of water and the resulting **1-isobutyl-6,7-dimethoxy-3,4-dihydroisoquinoline** isolated in the conventional manner, was distilled; yield 17 g., b.p. 136–139° at 1.2 mm., $n^{25}D$ 1.5536.

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56. Found: C, 73.15; H, 8.45.

The corresponding **methiodide** (prepared in benzene solution) was obtained in 96% yield after recrystallization from methanol–ether, m.p. 202–204°.

Anal. Calcd. for $C_{16}H_{24}NIO_2$: C, 49.36; H, 6.21. Found: C, 49.42; H, 6.15.

The above methiodide (12.2 g.) in 400 cc. of methanol was refluxed for one hour with 7 g. of sodium borohydride and then concentrated to near dryness. After addition of 10% hydrochloric acid, the solution was made basic with potassium hydroxide and extracted with ether. Evaporation of the ether and distillation of the residue furnished 7.2

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(1) Paper IV, C. Djerassi, M. Gorman, A. L. Nussbaum and J. Reynoso, THIS JOURNAL, **76**, 4463 (1954).

(2) (a) Department of Chemistry, University of Manchester, Manchester 13, England; (b) Research Laboratories, Chas. Pfizer & Co., Brooklyn 6, N. Y.

(3) W. M. Whaley and T. R. Govindachari, *Org. Reactions*, **6**, 74 (1951).

(4) E. Spaeth and N. Polgar, *Monatsh.*, **51**, 190 (1929).

(5) B. Witkop and J. B. Patrick, THIS JOURNAL, **75**, 4474 (1953).

(6) R. A. Labriola, V. Deulofeu and B. Berinzaghi (*J. Org. Chem.*, **16**, 90 (1951)) isolated this imide directly in the permanganate oxidation of erysotrine methohydroxide.

(7) H. Richtzenhain, *Acta. Chem. Scand.*, **4**, 206 (1950). We are indebted to Dr. Richtzenhain for sending us a sample of this substance.

(8) Melting points are uncorrected. The microanalyses were carried out by Miss Phyllis Tocco and Mr. Robert French.

(9) We are indebted to Dr. F. B. Zienty, Monsanto Chemical Company, St. Louis, Mo., for a supply of this amine.

g. (88%) of the desired **tetrahydroisoquinoline I**, b.p. 137–139° at 0.5 mm., n^{25}_D 1.5283, λ^{EtOH}_{max} 285 mμ (log ϵ 3.59), λ^{EtOH}_{min} 254 mμ (log ϵ 2.75).

Anal. Calcd. for $C_{16}H_{25}NO_2$: C, 72.96; H, 9.57. Found: C, 72.75; H, 9.62.

The styphnate exhibited m.p. 212–214° after recrystallization from ethanol.

Anal. Calcd. for $C_{22}H_{28}N_4O_{10}$: C, 51.96; H, 5.55. Found: C, 52.23; H, 5.65.

The picrate melted at 185–187°.

Anal. Calcd. for $C_{22}H_{28}N_4O_9$: C, 53.65; H, 5.73. Found: C, 53.81; H, 6.07.

In another experiment, the base, prior to distillation, was chromatographed on alumina and the individual fractions (eluted with benzene) were converted to the picrate. In each instance the same picrate was obtained, an observation which was considered further evidence for the homogeneity of the Bischler–Napieralski cyclization product.

1-Isopropyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (II).—This substance was prepared exactly as the higher homolog and only the physical constants of the intermediates are listed:

N-isobutyl homoveratryl amide, m.p. 102.5–103.5°. *Anal.* Calcd. for $C_{14}H_{21}NO_3$: C, 66.90; H, 8.42. Found: C, 67.18; H, 8.74.

1-Isopropyl-6,7-dimethoxy-3,4-dihydroisoquinoline, b.p. 128–129° at 1.2 mm., n^{25}_D 1.5606. *Anal.* Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21. Found: C, 72.14; H, 8.36.

The methiodide possessed nearly the same m.p. (200–202°) as the higher homolog described above. *Anal.* Calcd. for $C_{15}H_{22}NIO_2$: C, 48.01; H, 5.91. Found: C, 47.88; H, 6.17.

1-Isopropyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (II), b.p. 128–129° at 1.0 mm., n^{25}_D 1.5357, λ^{EtOH}_{max} 285 mμ (log ϵ 3.60), λ^{EtOH}_{min} 254 mμ (log ϵ 2.77). *Anal.* Calcd. for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30. Found: C, 72.17; H, 9.31.

The picrate was recrystallized from methanol, m.p. 155.5–157°. *Anal.* Calcd. for $C_{21}H_{26}N_4O_9$: C, 52.71; H, 5.48. Found: C, 52.65; H, 5.61.

Permanganate Oxidation of 1-Isobutyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (I).—A solution of 22.8 g. of the base I in 100 cc. of 10% sulfuric acid was made just alkaline with solid potassium hydroxide and then treated at room temperature in short intervals with a 15% solution of potassium permanganate. After 120 g. of permanganate had been added, the reaction mixture was heated on the steam-bath and an additional 34 g. of the oxidizing agent was added over a period of two hours; the oxidation was then permitted to continue at room temperature overnight. The excess permanganate was decomposed with sulfur dioxide, the clear solution was acidified with concentrated sulfuric acid and extracted continuously with ether for four days. During the extraction, a crystalline precipitate separated at the interface which was filtered and recrystallized from methanol to yield 1.3 g. of colorless needles of the **N-methyl imide of 3,4-dimethoxyphthalic acid (*m*-hemipinic acid)**,[10] m.p. 269–270° (sublimation starting at *ca.* 225°).

Anal. Calcd. for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01. Found: C, 59.98; H, 5.19.

A 0.5-g. sample of the imide was cleaved by refluxing for one hour with 20% sodium hydroxide solution and furnished 0.4 g. of *m*-hemipinic acid, m.p. 201–202°; after solidification and remelting, m.p. 176–177° was observed.[11] Recrystallization from methanol–benzene changed the m.p. to 190–191° (m.p. 177° after resolidification); the variable melting points recorded[12] for *m*-hemipinic acid have been ascribed to solvation and/or rate of heating.

A more suitable derivative for characterization purposes is ***m*-hemipinic acid dimethyl ester** prepared in quantitative yield by diazomethane esterification of the acid; m.p. 88–89° (from ether), undepressed upon admixture with an authentic specimen.[7]

Anal. Calcd. for $C_{12}H_{14}O_6$: C, 56.69; H, 5.55. Found: C, 56.71; H, 5.84.

In another oxidation carried out as above but using only one-tenth the quantities listed, the residue from the ether extraction was steam distilled and the distillate, containing the volatile "stench acids," was again extracted continuously with ether. The resulting acid fraction was converted to the sodium salt and then by successive treatments with thionyl chloride and aniline into the anilide. Chromatography of the crude anilide fraction on 200 g. of neutral alumina (activity III) yielded four main fractions upon elution with hexane–benzene (1:1), benzene, ether and methanol. Recrystallization of the benzene fractions from hexane furnished 0.1 g. of **isobutyric acid anilide**, m.p. 101–102°, undepressed on admixture with authentic anilide (m.p. 101–102°) but depressed to 86–92° when mixed with isovaleric acid anilide. The ether and methanol eluates were rechromatographed and elution with benzene–ether mixtures gave 0.03 g. of **isovaleric acid anilide**, m.p. 106–107°. A mixture with authentic isovaleric acid anilide (m.p. 106.5–107.5°) showed the same melting point, while a 20° depression was observed on admixture with isobutyric acid anilide.

That the isobutyric acid was not formed to any appreciable extent by oxidation of isovaleric acid was demonstrated in appropriate blank experiments.

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(10) We are grateful to Prof. V. Deulofeu (Buenos Aires) and H. Schmid (Zürich) for samples of *m*-hemipinic acid.

(11) *m*-Hemipinic acid anhydride is reported to melt at 175° (Y. Hirshberg, D. Lavie and E. D. Bergmann, (*J. Chem. Soc.*, 1034 (1951)).

(12) M.p. 174–175° (G. Goldschmiedt, *Monatsh.*, **9**, 772 (1888)); m.p. 194–195° (A. W. Gilboy, W. H. Perkin and J. Yates, *J. Chem. Soc.*, 1405 (1901)); m.p. 203° (W. H. Perkin, Jr., G. A. Edwards and F. W. Stoyle, *ibid.*, 199 (1925)).

Reactions of Long-chain Amines. IV. Preparation of N-Alkylpyrrolidines, N,N-Dialkylpyrrolidinium Chlorides and N,N-Dialkylpiperidinium Chlorides[1]

BY JOHN G. ERICKSON AND JOAN S. KEPS

RECEIVED JULY 26, 1954

von Braun[2] has described the preparation of methyl-, ethyl-, propyl- and amylpyrrolidines by heating 1,4-dibromobutane or 1,4-diiodobutane with the corresponding amines. In each case an excess of amine was used as acid acceptor. We have found that long-chain alkylpyrrolidines may be prepared conveniently by heating the amines with a slight excess of the commercially available 1,4-dichlorobutane. Sodium carbonate or other inorganic bases may be used as acid acceptors. Despite the comparative unreactivity of both the amines and the dichlorobutane, good yields of product are obtained.

The preparation of long-chain N-alkyl-piperidines by reactions of primary amines with 1,5-dibromopentane has been studied already.[3] von Braun[4] heated 1,5-dibromopentane with several secondary amines and thereby obtained piperidinium bromides. He used piperidine, diethylamine, diisoamylamine and methylaniline. Two moles of amine were heated with one of dibromopentane. We have prepared long-chain N,N-dialkylpyrrolidinium chlorides and N,N-dialkylpiperidinium chlorides in good yield by heating secondary amines with 1,4-dichlorobutane and 1,5-dichloropentane, respectively. An excess of dichloro compound was used

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(1) Paper No. 168, Journal Series, General Mills, Inc., Research Department.

(2) J. von Braun, *Ber.*, **44**, 1252 (1911); **49**, 966, 2629 (1916).

(3) J. A. Goodson, L. J. Goodwin, J. H. Gorvin, M. D. Goss, K. S. Kirby, J. A. Lock, R. A. Neal, T. M. Sharp and W. Solomon, *Brit. J. Pharmacol.*, **3**, 49 (1948); through *C. A.*, **43**, 3380 (1949).

(4) J. von Braun, *Ber.*, **41**, 2156 (1908).