introducing a significant change in the group bonded to the axis carbon. Thus, the conformational preference of the hydroxyl group on the 4-*t*-butyl-substituted ring should be similar to the hydroxyl group on the nonsubstituted cycloheptanol, which would account for the physically indistinguishable *cis* and *trans* isomers.

### Experimental Section[13]

**4-*t*-Butylcyclohexanone** (1) was prepared in 82% yield by chromic acid oxidation of commercial 4-*t*-butylcyclohexanol, m.p. 48–49°, lit.[14] m.p. 49–50°.

**4-*t*-Butylcycloheptanone** (2).—A mixture of 4-*t*-butylcyclohexanone (72 g., 0.5 mole) and *p*-tolylsulfonylmethylnitrosamide (125 g., 0.58 mole) in 160 ml. of 89 vol. % aqueous ethanol was cooled to 0°, and a solution of 15 g. of potassium hydroxide in 50 ml. of 50% aqueous ethanol was added dropwise with stirring over 2 hr. The addition rate was such as to maintain the temperature at 15–20°. Work-up according to the procedure of deBoer and Backer[15] gave the the ketone in 49% yield, b.p. 68° (0.2 mm.).

*Anal.* Calcd. for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.58; H, 11.90.

**4-*t*-Butylcycloheptanol** (4). **A. By Reduction of 4-*t*-Butylcycloheptanone with Lithium Aluminum Hydride.**—A solution of 4-*t*-butylcycloheptanone (11.0 g., 65 moles) in 20 ml. of anhydrous ether was added dropwise over a 30-min. period[16] to a stirred suspension of lithium aluminum hydride (1.2 g., 30 mmoles) in 100 ml. of anhydrous ether cooled by means of an ice–water bath. After stirring an additional 18 hr. (3 hr. for one run), the excess hydride and alcoholate were destroyed with 20 ml. of water, and the precipitate formed was dissolved in 80 ml. of 10% aqueous sulfuric acid. Extraction with ether, drying over anhydrous sodium sulfate and distillation gave the alcohol in 85% yield, b.p. 72° (0.2 mm.), $n^{25}D$ 1.4751.

*Anal.* Calcd. for $C_{11}H_{20}O$: C, 77.58; H, 13.03. Found: C, 77.52; H, 12.98.

**B. By Reduction of 4-*t*-Butylcycloheptanone with Hydrogen over Platinum Oxide.**—A solution of 4-*t*-butylcycloheptanone (6.6 g., 40 mmoles) in 50 ml. of glacial acetic acid containing 6 drops of concentrated hydrochloric acid was shaken with 400 mg. of platinum oxide (Englehard Industries, 82.3%) under 30 p.s.i. of initial hydrogen pressure for 15 min. The uptake of hydrogen was in good agreement with the theoretical amount. After removal of the spent catalyst, the reaction mixture was diluted with 5 vol. of water and continuously extracted with ether for 24 hr. The ether phase was separated, neutralized with aqueous sodium bicarbonate, and dried over anhydrous sodium sulfate. Distillation gave the alcohol in 95% yield. Identity with the alcohol obtained by procedure A was established by n.m.r. spectroscopy and capillary column gas chromatography.

**C. By Reduction of 4-*t*-Butylcycloheptanone with Sodium Borohydride.**—A mixture of sodium borohydride (0.35 g., 9 mmoles) in 8 ml. of water was added dropwise over a 10-min. period to a stirred solution of 4-*t*-butylcycloheptanone (4.0 g., 24 mmoles) in 20 ml. of methanol. After stirring at reflux temperature for 1 hr. and at room temperature for 2.5 hr., the salt was decomposed by the addition of 80 ml. of 10% sodium hydroxide. Extraction with ether, washing with saline solution, drying over anhydrous sodium sulfate, and distillation gave the alcohol in 92% yield. Identity with the alcohol obtained by procedure A was established by n.m.r. spectroscopy and capillary column gas chromatography.

**Cycloheptanol** (5).—Reduction of cycloheptanone with lithium aluminum hydride gave the alcohol in 85% yield: b.p. 42° (0.4 mm.), $n^{25}D$ 1.4750; lit.[17] b.p. 88° (18 mm.), $n^{20}D$ 1.4747.

**Cycloheptyl acid Phthalate** (6) was prepared by the conventional procedure yielding white needles, m.p. 100–101°, after two recrystallizations from petroleum ether (b.p. 30–60°), lit.[18] m.p. 100–102°.

**4-*t*-Butylcycloheptyl Acid Phthalate** (7).—In a typical preparation, a solution of 2.5 g. of 4-*t*-butylcycloheptanol and 2.3 g. of phthalic anhydride in 10 ml. of dry pyridine was kept at 100° for 20 hr. Working up in the usual way gave an oil which was crystallized from petroleum ether. The first crop, m.p. 79–81°, yielded 2.7 g. of material. After two additional crystallizations, the melting point was 83–85°.

*Anal.* Calcd. for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.44; H, 8.28.

**Kinetic Measurements on Saponification of Acid Phthalates.**—The measurements were carried out with samples of cycloheptyl (6) and 4-*t*-butylcycloheptyl (7) acid phthalates purified by four recrystallizations from petroleum ether.

Standard aqueous sodium hydroxide was prepared using conductivity water. Frequent restandardization failed to reveal any significant variation in normality.

The acid phthalate was weighed out in a volumetric flask, brought up to volume with excess standard aqueous sodium hydroxide, and placed in a constant-temperature bath (accurate to ±0.1°). Aliquots were removed periodically, the reaction was quenched by chilling in ice–water, and the remaining sodium hydroxide was titrated with 0.05 *N* standard potassium acid phthalate to a cresol red end point.

The rate constants were calculated using the integrated form of equation for a second-order reaction.

The thermodynamic activation functions were obtained by IBM 1620 computer regression analysis of ln $k/T$ *vs.* $1/T$.

**Acknowledgment.**—The capillary column gas chromatographic and n.m.r. spectroscopic work were carried out at Louisiana State University with the gracious cooperation of Professor J. G. Traynham. The author is indebted to the Research Corporation for generous support of this research.

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[13] Analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. All boiling points and melting points are uncorrected.

[14] L. Schmerling, *J. Am. Chem. Soc.*, **69**, 1121 (1947).

[15] J. deBoer and H. J. Backer, *Org. Syn.*, **34**, 24 (1954).

[16] In one run where the quantity of reactants was reduced by one-half, the ketone was added all at once and hydrolyzed after 10 min. of reaction time.

[17] P. A. Smith and D. R. Baer, *J. Am. Chem. Soc.*, **74**, 6137 (1952).

[18] P. A. Smith, D. R. Baer, and S. N. Ege, *ibid.*, **76**, 4564 (1954).

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## Free-Radical Reactions of Diethylketene Acetal

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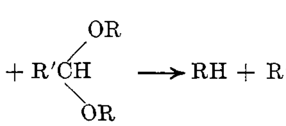
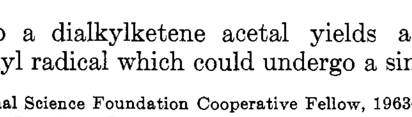
The major reaction products of the peroxide-induced reactions of acetals are alkanes and esters. A free-radical chain sequence involving the β elimination of an alkyl radical from an α,α-dialkoxyalkyl radical (reaction 1) which is produced by abstraction of the α-hydrogen from the parent acetal by the eliminated alkyl radical (reaction 2) has been proposed as the mechanism for these reactions.[3] Addition of a free radical to a dialkylketene acetal yields an α,α-dialkoxyalkyl radical which could undergo a similar frag-



$$R'\dot{C}(OR)_2 \longrightarrow R'C(=O)OR + R\cdot \qquad (1)$$



$$R\cdot + R'CH(OR)_2 \longrightarrow RH + R'\dot{C}(OR)_2 \qquad (2)$$

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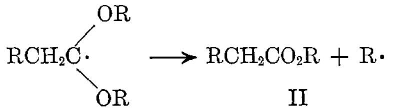
[1] National Science Foundation Cooperative Fellow, 1963–1965.

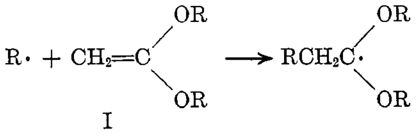
[2] Phillips Petroleum Research Fellow, 1963–1964.

[3] (a) L. P. Kuhn and C. Wellman, *J. Org. Chem.*, **22**, 774 (1957); (b) E. S. Huyser, *ibid.*, **25**, 1820 (1960); (c) E. S. Huyser and Z. Garcia, *ibid.*, **27**, 2716 (1962); (d) E. S. Huyser and D. T. Wang, *ibid.*, **29**, 2720 (1964).

mentation reaction yielding an ester and an alkyl radical. If the adding radical is the alkyl radical eliminated in the fragmentation of the α,α-dialkoxyalkyl radical, the over-all reaction would be the isomerization of dialkylketene acetal to an ester. We have found that diethylketene acetal (I, R = $C_2H_5$) undergoes rearrangement



$$\mathrm{RCH_2\dot{C}(OR)_2 \longrightarrow \underset{II}{RCH_2CO_2R} + R\cdot} \tag{3}$$



$$\mathrm{R\cdot + \underset{I}{CH_2{=}C(OR)_2} \longrightarrow RCH_2\dot{C}(OR)_2} \tag{4}$$

to ethyl *n*-butanoate (II) in a thermal reaction (125°) induced by *t*-butyl peroxide. Though our data indicate a short kinetic chain length[4] for sequence 3 and 4 (Table I), the observed increase in the kinetic chain length as the initiator concentration is diminished is consistent with the isomerization proceeding by such a chain reaction.

Peroxide-induced reactions of I with ethers yielded α-substituted ethyl acetates as the major reaction products. Thus, when I was heated with a large excess of tetrahydropyran in the presence of *t*-butyl peroxide, ethyl 2-tetrahydrofurylacetate was formed. Similarly, ethyl 1,4-dioxylacetate was obtained from the *t*-butyl peroxide induced reaction of I with 1,4-dioxane. These products most likely result from fragmentation of the adduct radical (reaction 5) produced by the addition of the solvent derived radical to I (reaction 7). In the presence of a large excess of solvent, abstraction of a hydrogen atom by the eliminated radical (reaction 6) apparently competes favorably with the addition of the ethyl radical to I (reaction 4).

TABLE I

REACTIONS OF DIETHYLKETENE ACETAL (I) WITH *t*-BUTYL PEROXIDE[a]

| mmoles of I | mmole of peroxide | mmole of ethyl *n*-butanoate | Kinetic chain length |
|---|---|---|---|
| 2.98 | 0.59 | 0.63 | 0.53 |
| 2.98 | 0.29 | 0.74 | 1.27 |
| 3.01 | 0.19 | 0.70 | 1.85 |
| 3.09 | 0.097 | 0.76 | 3.92 |
| 3.03 | 0.063 | 0.78 | 6.20 |

[a] At 125° for 21 hr.

$$\mathrm{RCH_2\dot{C}(OC_2H_5)_2 \longrightarrow RCH_2CO_2C_2H_5 + C_2H_5\cdot} \tag{5}$$

$$\mathrm{C_2H_5\cdot + RH \longrightarrow C_2H_6 + R\cdot} \tag{6}$$

$$\mathrm{R\cdot + I \longrightarrow RCH_2\dot{C}(OC_2H_5)_2} \tag{7}$$

$$\mathrm{R = \overline{CH_2CH_2CH_2OCH} \text{ or } \overline{CH_2OCH_2CH_2OCH}}$$

The very rapid reactions of I with protic solvents[5] to yield Markovnikov addition products precluded their reactions with I in free-radical reactions involving the chain sequence 5–7. Thus, heating I with a large excess of 2-propanol in the presence of *t*-butyl peroxide failed to yield the expected β-hydroxy ester but rather a mixed orthoacetate.

### Experimental Section[6]

**Materials.**—Diethylketene acetal (b.p. 85° at 200 mm.) was prepared from the diethyl acetal of α-bromoacetaldehyde (Aldrich Chemical Co.) in the manner described previously.[7] *t*-Butyl peroxide (Lucidol Corp.) and 1,4-dioxane (Matheson Coleman and Bell, reagent grade) were used without further purification. Tetrahydrofuran and 2-propanol were Fisher reagent grade chemicals and were distilled before use.

**Isomerization of Diethylketene Acetal to Ethyl *n*-Butanoate.**—A mixture consisting of diethylketene acetal (11.60 g., 0.10 mole) and *t*-butyl peroxide (1.46 g., 0.01 mole) was heated at 130° for 20 hr. During the course of the heating, 110 cc. (STP) of gas, presumed to be a mixture of ethane and methane (resulting from peroxide),[8] were evolved. After removal of the peroxide decomposition products by distillation, 2.30 g. (0.019 mole) of ethyl *n*-butanoate (b.p. 67–70° at 140 mm.) was obtained. The infrared spectrum and gas chromatographic retention time were identical with those of authentic samples. Reaction of a portion of this material with 3,5-dinitrobenzoic acid and a trace of sulfuric acid yielded ethyl 3,5-dinitrobenzoate, m.p. 89–90°, lit.[9] m.p. 93°. Hydrolysis of a portion of the ester yielded *n*-butanoic acid which was isolated as *p*-bromophenacyl *n*-butanoate, m.p. 62–62.8°, lit.[10] m.p. 63°. The material remaining after removal of the ethyl *n*-butanoate consisted mainly of unreacted diethylketene acetal and a small amount of a higher boiling residue. No attempt was made to identify this residue.

**Determination of Kinetic Chain Length.**—Mixtures of diethylketene acetal and *t*-butyl peroxide in the amounts shown in Table I were sealed in glass tubes and heated for 21 hr. at 125°. Gas chromatographic analysis showed that all of the peroxide was consumed at the end of the heating period. The amounts of ethyl *n*-butanoate produced were determined by the gas chromatographic analysis of the mixtures in the manner described previously[3d] employing cumene as an internal standard.

**Diethylketene Acetal and Tetrahydrofuran.**—A mixture consisting of tetrahydrofuran (108 g., 1.50 moles), diethylketene acetal (16.5 g., 0.14 mole), and *t*-butyl peroxide (2.0 g., 0.014 mole) was heated in a stainless steel autoclave at 120–130° for 18 hr. Removal of the peroxide decomposition products, unreacted tetrahydrofuran, and diethylketene acetal by distillation left a higher boiling residue. Further distillation yielded 7.6 g. (0.048 mole, 34% of theory) of ethyl 2-tetrahydrofurylacetate (b.p. 59–69° at 2 mm., $n^{29}\mathrm{D}$ 1.4350; lit.[11] $n^{20}\mathrm{D}$ 1.4369). The infrared spectrum showed, in addition to other characteristic features, a strong carbonyl absorption at 5.75–5.81 μ. The n.m.r. spectrum was consistent with that expected for this ester. The mass spectrum had a parent peak at *m/e* 158 (calcd. mol. wt., 158). Prominent peaks were found at *m/e* 71, 73, 129, and 130 corresponding to $(\overline{\mathrm{CH_2CH_2CH_2OCH}})^+$, $(\mathrm{CO_2C_2H_5})^+$, $(\overline{\mathrm{CH_2CH_2CH_2OCH}}\mathrm{CH_2CO_2})^+$, and $(\overline{\mathrm{CH_2CH_2CH_2OCH}}\mathrm{CH_2CO_2H})^+$ fragments, respectively. Basic hydrolysis yielded ethanol (3,5-dinitrobenzoate, m.p. 88–89°, lit.[9] m.p. 93°) and 2-tetrahydrofurylacetic acid which was isolated by distillation (b.p. 100° at 2-mm., $n^{28}\mathrm{D}$ 1.4561; lit.[11] $n^{20}\mathrm{D}$ 1.4589). The n.m.r. spectrum of the acid showed a complex adsorption centered at 2.0 p.p.m. owing to the protons on the 3- and 4-carbons, a multiplet centered at 2.6 p.p.m. owing to the α-methylene hydrogens, complex adsorptions centered at 3.9 and 4.3 p.p.m. owing to the protons

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[4] Kinetic chain length is defined here as the number of moles of I converted to II per mole of initiator fragment, assuming 2 moles of initiator fragments per mole of initiator.

[5] F. Beyerstedt and S. M. McElvain, *J. Am. Chem. Soc.*, **58**, 529 (1936).

[6] All melting points and boiling points are uncorrected. Elemental analyses performed by Huffman Laboratories, Inc., Wheatridge, Colo. The infrared spectra were obtained on a Beckman IR-8, the n.m.r. spectra on a Varian A-60 n.m.r. spectrometer, and the mass spectra on a Nuclide 12-90G mass spectrometer.

[7] S. M. McElvain and D. Kundiger, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 506.

[8] C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 470.

[9] R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 280.

[10] Reference 9, p. 276.

[11] P. M. Frearson, D. G. Hardy, and E. S. Stern, *J. Chem. Soc.*, 2103 (1960).

on the 5- and 2-carbons, respectively, and a sharp singlet at 10.01 p.p.m. owing to the acid proton. The integrations of these resonance absorptions were consistent with these assignments.

**Diethylketene Acetal and 1,4-Dioxane.**—A mixture consisting of 1,4-dioxane (132 g., 1.5 moles), diethylketene acetal (15.0 g., 0.13 mole), and *t*-butyl peroxide (1.5 g., 0.01 mole) was heated for 18 hr. at 120–130° in a stainless steel autoclave. Distillation of the resulting reaction mixture yielded 9.4 g. of ethyl 1,4-dioxylacetate which was collected at a boiling range of 85–108° at 2 mm., $n^{25}\text{D}$ 1.4400.

*Anal.* Calcd. for $C_8H_{14}O_4$: C, 55.15; H, 8.12. Found: C, 55.13; H, 8.04.

The infrared spectrum of this material had a strong carbonyl absorption at 5.75–5.80 μ. The n.m.r. spectrum showed a triplet centered at 1.25 p.p.m. owing to the methyl group and a complex absorption ranging from 3.0 to 4.3 p.p.m. owing to the ring protons and the methylene protons of the ethyl group. The peaks of a doublet centered at 2.3 p.p.m. owing to the α-methylene protons were split, presumably the result of coupling with the ring protons. The mass spectrum showed a parent peak at *m/e* 174 (calcd. mol. wt., 174). Prominent peaks in the mass spectrum were found at *m/e* 73, 87, 101, and 129 owing to $(CO_2C_2H_5)^+$, $(CH_2CO_2C_2H_5)^+$ and/or $(CH_2OCH_2CH_2OCH)^+$, $(CH_2OCH_2CH_2OCHCH_2)^+$, and $(CH_2OCH_2CH_2OCHCH_2CO)^+$ fragments, respectively.

**Attempted Free-Radical Addition of 2-Propanol to Diethylketene Acetal.**—A mixture of 2-propanol (60 g., 1.0 mole), diethylketene acetal (11.6 g., 0.10 mole), and *t*-butyl peroxide (1.46 g., 0.01 mole) was heated in sealed glass tubes at 125° for 18 hr. Distillation yielded a product (10.0 g., b.p. 45° at 10 mm.). The infrared spectrum of this material showed a very weak carbonyl absorption. Although not conclusively identified as such, the n.m.r. spectrum was consistent for that of diisopropyl ethyl orthoacetate.

**Acknowledgment.**—We wish to acknowledge the National Science Foundation for partial support of this work in form of a grant (GP-739).

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# The Chemistry of Pyrazine and Its Derivatives. XI. The Pyrazylethylation of Certain Active Hydrogen Compounds

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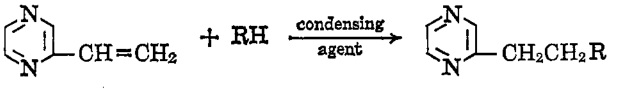
*Received July 16, 1965*

In an earlier publication[2] we indicated that a series of amines undergo conjugate addition (Michael condensation) with vinylpyrazine to give pyrazylethylated amines. We now report that four other types of active hydrogen compounds, RH, will undergo the Michael condensation with vinylpyrazine. The over-all reactions are indicated in the following equation.



I

From the interaction of vinylpyrazine (I) with cyclohexanone using sodium metal as the condensing agent, there was obtained 2-(2-pyrazylethyl)cyclohexanone in 67.5% yield. This is considerably lower than the 81% yield of the same product which was isolated from the interaction of the pyrrolidine enamine of cyclohexanone and vinylpyrazine followed by hydrolysis.[3] However, the latter method involves the prior formation of the enamine, and the reaction conditions are considerably more drastic than those used in the present study. When I was treated with cyclopentanone in the presence of metallic sodium, a mixture of products was obtained, *i.e.*, the desired product, 2-(2-pyrazylethyl)cyclopentanone (21.9%), and the self-condensed derivative of cyclopentanone, cyclopentylidenecyclopentanone (42.9%). Again, a very much higher yield (66%) was obtained by the pyrrolidine enamine of cyclopentanone–vinylpyrazine method.

The pyrazylethylation of acetophenone failed in the presence of sodium but was effected by sodamide in liquid ammonia to give low yields of two products: (a) phenyl 3-pyrazyl-1-propyl ketone (8.9%, monopyrazylethylated product), and (b) the bis Michael adduct, 1,5-dipyrazyl-3-benzoylpentane, 9.7%).

That the pyrazylethylation of ethyl phenylacetate gives ethyl 2-phenyl-4-pyrazylbutanoate and that phenylacetonitrile was pyrazylethylated to give 2-phenyl-4-pyrazylbutanenitrile was established by hydrolyzing a sample of each of these compounds to 2-phenyl-4-pyrazylbutanoic acid.

Finally, acetamide was pyrazylethylated on its nitrogen atom to give N-(2-pyrazylethyl)acetamide. The structure of the product was elucidated by subjecting a sample to basic hydrolysis to give 2-aminoethylpyrazine, which was identical in its properties with the compound that had been obtained earlier[2] by the direct pyrazylethylation of ammonia.

## Experimental Section

**Pyrazylethylation of Cyclohexanone.**—A mixture of cyclohexanone (19.6 g., 0.2 mole), vinylpyrazine (10.6 g., 0.1 mole), and small pieces of sodium (0.1 g.) was stirred and heated at 90°. The reaction became exothermic and the temperature rose spontaneously to 160°. The reaction was allowed to cool to 100° and then was heated at 100–115° for 30 min. The mixture was cooled to room temperature, absolute ethanol (2 ml.) was added, and the mixture was poured onto ice. It was extracted with several portions of ether and dried over sodium sulfate, and, after removing the solvent at atmospheric pressure, the residue was distilled to give 2-(2-pyrazylethyl)cyclohexanone (13.8 g., 67.5%, b.p. 129–130° at 0.5 mm.). The product gave a semicarbazone, m.p. 176–177° alone and when mixed with a sample obtained from the product produced by the interaction of N-(1-cyclohexenyl)pyrrolidine with vinylpyrazine.[3]

**Pyrazylethylation of Cyclopentanone.**—A mixture of cyclopentanone (16.8 g., 0.2 mole), vinylpyrazine (10.6 g., 0.1 mole), and sodium (0.1 g.) was stirred and heated at 90°. The reaction became exothermic and the temperature rose spontaneously to 140°. The mixture was allowed to cool to 100°, heated at 100–105° for 30 min., and processed as described in the last experiment to give a mixture of 2-(2-pyrazylethyl)cyclopentanone (4.2 g., 21.9%, b.p. 139–140° at 1.5 mm.; semicarbazone, m.p. 185–186° alone and when mixed with a sample obtained from the product prepared by the enamine method[3]) and cyclopentylidenecyclopentanone (3.6 g., 42.9%, b.p. 85–86° at 1.3 mm.; semicarbazone, m.p. 216–217°[4] from 95% ethanol).

**Pyrazylethylation of Acetophenone.**—A solution of acetophenone (12.0 g., 0.1 mole in 25 ml. of anhydrous ether) was added over a 15-min. period to sodamide which was prepared from sodium metal (2.3 g., 0.1 g.-atom) in 100 ml. of liquid ammonia using a ferric nitrate catalyst,[5] and the mixture was stirred for 1 hr.

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[1] This work is based on part of the thesis submitted by G. M. S. to the Graduate Faculty of the University of Pittsburgh in partial fulfillment of the requirements of the Ph.D. degree.

[2] G. M. Singerman and R. Levine, *J. Heterocyclic Chem.*, **1**, 151 (1964).

[3] G. M. Singerman and S. Danishefsky, *Tetrahedron Letters*, **No. 33**, 2249 (1964).

[4] M. Godchot and F. Taboury, *Bull. soc. chim. France*, [4] **13**, 14 (1913).

[5] J. T. Adams and C. R. Hauser, *J. Am. Chem. Soc.*, **66**, 1220 (1944).