

3,4-Dimethyl-2-cycloheptenone (5), $C_9H_{14}O$, had mol wt 138; λ_{max} 238 $m\mu$ (ϵ 11,300); ν_{max} 1660 and 1650 cm^{-1} ; and τ 4.28 (1 H, vinyl, coupling with vinyl methyl unresolved), 7.5 (3 H, br, allylic and methylene adjacent to carbonyl), 8.09 (3 H, doublet, $J = 1.5$ cps, vinyl methyl coupled with vinyl), 8.15 (4 H, multiplet, methylene), and 8.82 (3 H, doublet, $J = 6.8$ cps, *sec*-methyl).

3,4-Dimethyl-3-cycloheptenone (7), $C_9H_{14}O$, had mol wt 138; λ_{max} 295 $m\mu$ (ϵ 450); ν_{max} 1705 and 1661 cm^{-1} ; and τ 6.98 (2 H, singlet, methylenes at C_2), 7.6 (4 H, multiplet, methylenes at C_5 and C_7), and 8.00 (2 H, multiplet, C_6), 8.20 (6 H, singlet, vinyl methyls).

Pyrolysis of 4 for 18 min gave a mixture of 13 compounds. Ketones 6 and 8 (ratio 4:1, respectively) amounted to 38% of the volatile pyrolysate. Collection gave 75 mg of 6 and 24 mg of 8 from the contents of 29 tubes.

2,3-Dimethyl-2-cycloheptenone (6), $C_9H_{14}O$, had mol wt 138; λ_{max} 248 $m\mu$ (ϵ 8700); ν_{max} 1665 and 1630 cm^{-1} ; and τ 7.60 (4 H, multiplet, methylenes at C_4 and C_7), 8.16 (3 H, singlet, α -vinyl methyl), and 8.28 (3 H, broad singlet, β -vinyl methyl). Methylenes at C_5 and C_6 are obscured by methyl signal at 8.28. Ketone 6 formed a red dinitrophenylhydrazone, mp 146–147°. Attempts to form crystalline derivatives of the other cycloheptenones failed.

2,3-Dimethyl-3-cycloheptenone (8), $C_9H_{14}O$, had mol wt 138; λ_{max} 290 $m\mu$ (ϵ 236); ν_{max} 1710 and 1680 cm^{-1} ; and τ 4.41 (multiplet, vinyl), 8.23 (singlet, vinyl methyl), and 8.82 (doublet, $J = 7.0$ cps, *sec*-methyl at C_2). The remainder of the spectrum was too ill defined to be of diagnostic value.

Isomerization of Ketones 5 and 7.—To a solution of 26.1 mg of 7 in 25 ml of ethanol was added 150 mg of solid sodium hydroxide and the ultraviolet spectrum was measured periodically over a period of several weeks. The extinction coefficient at 238 $m\mu$ increased from an initial value of 3040 to 6050. In like manner the extinction coefficient at 238 $m\mu$ of a solution of 3.4 mg of 5 in 25 ml of ethanol fell from 11,300 to 5300. The equilibrium concentration of 5 is, therefore, $28 \pm 4\%$.

Isomerization of ketone 6 was carried out as above. The equilibrium extinction coefficient at 248 $m\mu$ was 7250, indicating 80% 6 at equilibrium (ketone 8 had ϵ_{248} 1700).

The Synthesis of 2-Phenyl-1,3-di(4-pyridyl)-2-propanol

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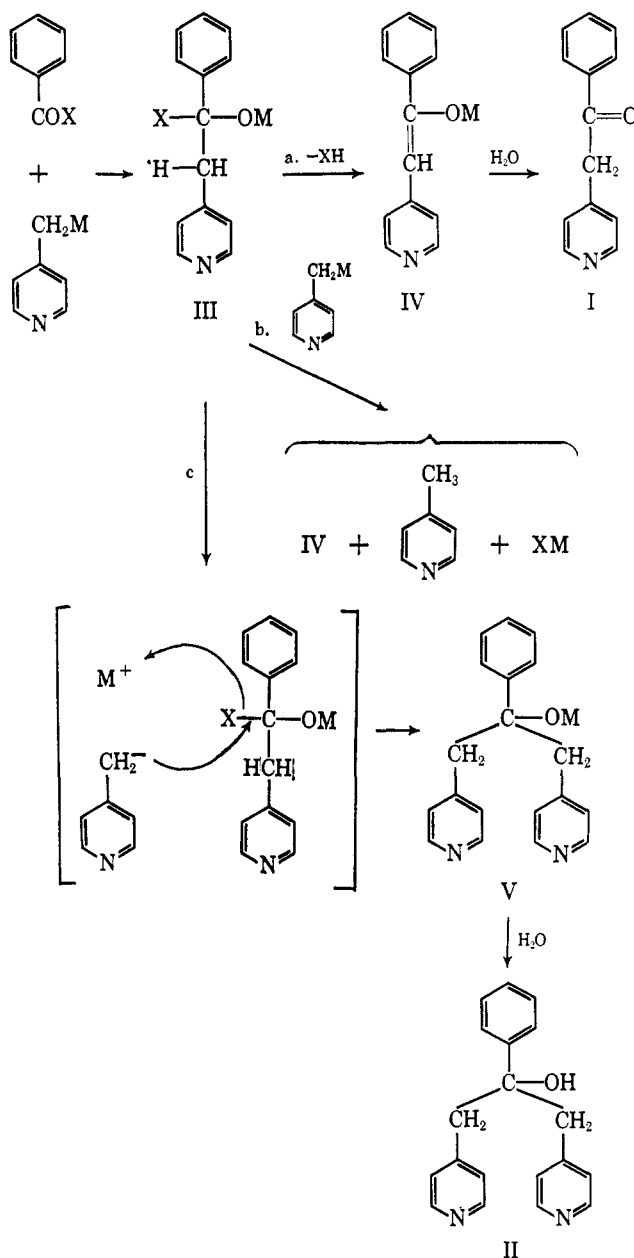
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In connection with other work¹ large quantities of 4-(phenacyl)pyridine (I) were required. Using a variation of the method of Raynolds and Levine^{1,2} we prepared compound I in several large batches, and isolated in some of these reactions small amounts (<2%) of the less soluble 2-phenyl-1,3-di(4-pyridyl)-2-propanol (II).

Since it had been reported that tertiary carbinols of this type were not formed under these conditions and could not be prepared from phenacylpyridines,² we studied this reaction and found that these substituted propanols can in fact be readily prepared by the reaction of picolylithium with esters or acid chlorides. However, when we reexamined the reaction of picolylsodium and picolylithium with phenacylpyridine under a wide variety of conditions (varying time, temperature, and solvents), we isolated only unchanged

starting materials and therefore concur with Raynold's and Levine's,² explanation that picolylsodium (or picolylithium) adds to phenacylpyridine by a process of anion formation to give the sodium (or lithium) enolate of I.³

It is apparent therefore, that in this instance, formation of the tertiary carbinol II cannot proceed *via* the ketone I. The yields of I and II, respectively, in such a reaction must depend on the relative ease with which an intermediate (III) can either be attacked further by picolylithium to give the salt of II, or can undergo elimination to form the stable enolate IV.



By varying both M and X, we have shown that the formation of the carbinol from such an intermediate is strongly influenced by the metal in the order $Mg < Na < Li$. We have also shown that the over-all yield

(1) R. I. Fryer, R. A. Schmidt, and L. H. Sternbach, *J. Pharm. Sci.*, **53**, 264 (1964).

(2) S. Raynolds, and R. Levine, *J. Am. Chem. Soc.*, **82**, 472 (1960).

(3) The yield of tertiary carbinol formed by the reaction of a ketone with a Grignard reagent has been reported to be substantially increased when carried out in the presence of an excess of metal halide: C. G. Swain and H. B. Boyles, *ibid.*, **73**, 870 (1951). We have also attempted to form compound II from I by the addition of a large excess of lithium chloride to the reaction mixture but were unable to detect any trace of the carbinol on work-up.

TABLE I
COMPARATIVE YIELDS OF 4-PHENACYLPYRIDINE (I) AND 2-PHENYL-1,3-DI(4-PYRIDYL)-2-PROPANOL (II)

M	Yield of products, %									
	X = OCH ₃		X = OC ₂ H ₅		X = OCH ₂ C ₆ H ₅		X = OC ₆ H ₅		X = Cl ^a	
	I	II	I	II	I	II	I	II	I	II
MgBr	24	1.4	NI ^b	1.2	NI	5	19.5	2.0
Na ^c	56 ± 11	11 ± 1	77 ± 4	11 ± 3	62 ± 2	15 ± 1	NI	8.3 ± 1
Li ^c	55 ± 6	37 ± 6	56 ± 2	41 ± 2	55 ± 3	35 ± 4	42 ± 5	48 ± 2	48 ± 4	48 ± 5

^a For the synthesis of II from esters there was no temperature dependence, while for the acid chloride the reaction was best carried out at -20° . ^b NI = not isolated. ^c Per cent yields are reported as averages of results from several experiments carried out under identical conditions.

of II obtained in these reactions was relatively independent of X (Table I). All of these reactions were carried out in the normal manner used for the preparation of carbinols; *i.e.*, the acid chloride or the ester was added to an excess of picolylithium.

In order to obtain some insight into the mechanism of attack of the second molecule of picolylithium on the intermediate, two comparative experiments were carried out. Two solutions of benzoyl chloride were first treated with an equimolar amount of picolylithium. In one experiment the intermediate thus formed was treated immediately with 1 additional mole of picolylithium. In the other experiment the intermediate was stirred for 5 hr at -20° in an atmosphere of dry nitrogen before the second mole of picolylithium was added. Comparison of the yields of compounds I and II obtained in each case (58:40% and 84:12%, respectively) suggests that the intermediate formed (III) is probably unstable and can undergo intramolecular elimination to the enolate IV as shown by path a.

Intermolecular attack of III by additional picolylithium (in an acid-base type of reaction) could again lead to IV as illustrated by path b. An indication that the major reaction can proceed by this second route was demonstrated in Raynold's and Levine's work,² where a low yield of I was obtained when the molar ratio of reactants was 1:1,⁴ whereas an extremely high yield of I was isolated when the molar ratio of reactants was 2:1. In our own work, where picolylithium and benzoyl chloride were used, it would appear that I is formed by the intramolecular route since optimal yields of I were obtained when an equimolar ratio of reactants was employed. Furthermore, an excess of picolylithium had an adverse effect on the yield of I while the yield of II was increased. For the preparation of II a molar ratio of 5:2 was optimal.

Thus for an optimal yield of I in the case where conditions are unfavorable for the synthesis of II (path b), a 2:1 molar ratio of reactants would be required. For an optimal yield of I under conditions favorable for the synthesis of II (path c) a 1:1 molar ratio would be required (making path a the operative mechanism). We have in fact prepared I under conditions favorable for the synthesis of II using an equimolar ratio, and obtained a 54% yield of I and an 11% yield of II.⁵ These yields are comparable to those obtained where we allowed the intermediate to stand for 5 hr.

It is reasonable to assume from the above discussion, that the course of the reaction by either path b or c

would depend on the relative electrophilic character of the two carbon atoms involved. Only the OM and X groups are variable and both would be expected to have an effect on the carbon atom to which they are attached. This was verified by the sequence for OM, which we found for path b to be Na > Li and for path c to be Li > Na.

We were unable to detect any substantial increase in the carbonium ion character of the carbon atom attached to the phenyl ring by making R a better leaving group. We observed differences in the yields of products only for X = OC₆H₅ and X = Cl where M = Li (Table I). Thus it would appear qualitatively, that for increasing the carbonium ion character of the adjacent carbon atom OCH₃ \simeq OCH₂C₆H₅ < OC₆H₅ \simeq Cl.

Experimental Section

This section describes the synthesis of 2-phenyl-1,3-di(4-pyridyl)-2-propanol II from benzoyl chloride and 4-picolylithium.⁶ This reaction gave optimal yields of the carbinol. The only difference in reaction conditions when esters were employed was the addition of the ester to the picolylithium at room temperature. Melting points were determined microscopically on a hot stage and were corrected.

2-Phenyl-1,3-di(4-pyridyl)-2-propanol (II).—A commercial (Foote Mineral Co.) ether-benzene solution of phenyllithium (0.25 mole, total volume 135 ml) was added over 1 hr to a stirred solution of 4-picoline (23.4 g, 0.25 mole) in tetrahydrofuran⁷ (100 ml) in an atmosphere of dry nitrogen. The reaction mixture changed from blood red to dark brown during the addition. There was no appreciable heat of reaction (the temperature was kept at approximately 30°). When the addition of phenyllithium had been completed, the solution of picolylithium was stirred for 15 min longer, and then cooled to -20° in a Dry Ice-acetone bath. A mixture of benzoyl chloride (14.1 g, 0.1 mole) and tetrahydrofuran⁸ (50 ml) was added over 50 min, while the temperature was kept at $-20 \pm 1^{\circ}$. The pale green reaction mixture was stirred at -20° for 1 hr and at room temperature for 1 hr and then 15 ml of water was added dropwise. Ice (50 g) was added followed by 100 ml of ether with vigorous stirring. The mixture was next transferred to a large separatory funnel and acidified with 3 N hydrochloric acid (200 ml). The acid layer was separated and the organic phase was extracted with 3 N hydrochloric acid (three 50-ml portions). The combined acid extracts were washed with ether (three 100-ml portions). Ice (200 g) was added to the acid solution which was then made basic with ammonium hydroxide while the temperature was kept about 10° . The two products (I and II) precipitated as solids which were filtered and washed with water (three 75-ml portions). The precipitate was partitioned between methylene chloride (60 ml) and water (80 ml) and the mixture was shaken thoroughly to remove inorganic salts and the methylene chloride soluble 4-(phenacyl)pyridine I. The insoluble residue (II) was removed by filtration, washed with water (two 300-ml portions), methylene chloride (two 25-ml portions), and ether (30 ml), and was dried in a vacuum oven at 50° for

(4) The ratios throughout are given for picolylmetal-acid derivatives, respectively.

(5) Also isolated from this reaction was 16% of the known enolate ester of IV, α -4-pyridylmethylenebenzyl alcohol benzoate: W. von E. Doering and W. E. McEwen, *J. Am. Chem. Soc.*, **73**, 2104 (1951).

(6) During the course of this investigation a number of analogous di(4-pyridyl)-2-propanols were prepared. Physical data for these compounds are given by B. Brust, R. I. Fryer, and L. H. Sternbach, in Belgium Patent 645,241 (Sept 16, 1964); *Chem. Abstr.*, **63**, 13223e (1965).

(7) Purified by filtration through grade I neutral alumina.

15 hr to give 16.5 g of product, mp 92–99°⁸ (resolidifies and remelts at 166–168°). Recrystallization from an acetone–water mixture gave 15.5 g (53.4%) of the pure carbinol II, as white prisms, mp 167.5–169°.

Anal. Calcd for C₁₉H₁₈N₂O: C, 78.59; H, 6.25; N, 9.65. Found: 78.90; H, 6.04; N, 9.59.

The methylene chloride solution obtained from the separation of the mixture of products was washed with water, dried, and evaporated. Recrystallization of the residue from a mixture of dichloromethane and hexane gave 8.6 g (43.7%) of pure 4-(phenacyl)pyridine (I) as white prisms, mp 113–115°.²

Acknowledgment.—We are indebted to Dr. A. Steyermark and his staff for the microanalyses and to Mr. S. Traiman for the determination of infrared spectra.

(8) The compound is polymorphic and melting points of 117–118° and 126–127° have also been observed. Recrystallization from acetone however raises the melting point to 167.5–169°.

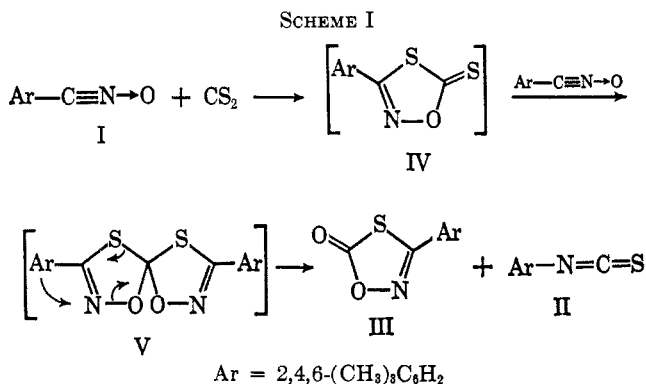
1,3-Dipolar Cycloaddition of Carbon Disulfide to a Nitrile Oxide¹

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Reports on the reactions of nitrile oxides with thiocarbonyl functions² have not heretofore included carbon disulfide. We have found that 2,4,6-trimethylbenzonitrile oxide³ (I) reacts with carbon disulfide at 80–90° to form mesityl isothiocyanate (II) and 3-mesityl-1,4,2-oxathiazoline-5-one (III). The latter compound is analogous to the 5,5-disubstituted (alkyl, alkoxy, or alkylthio) 1,4,2-oxathiazolines which have been obtained using other thiocarbonyl compounds.² See Scheme I.



These products could arise by prior formation of the thione (IV) by a conventional 1,3-dipolar cycloaddition, followed by rapid reaction of the thione with a second mole of nitrile oxide to give the spiro intermediate (V),⁴ and thermal decomposition of V to form the

observed products. A "thionecarbonate" such as IV would be expected² to react with a nitrile oxide under much milder conditions than were required to cause reaction of I with carbon disulfide. The isothiocyanate is a well-known compound and has been observed^{2,5} as a product in reactions of nitrile oxides with various sulfur compounds. The oxathiazoline-5-one has infrared absorption at 1796 cm⁻¹, which is characteristic of a "carbonate" carbonyl group in a five-membered ring,⁶ and shows no absorption above 3100 cm⁻¹. This compound decomposes above 150° with evolution of an odorless gas and forms mesityl isothiocyanate.

An attempt to obtain the same heterocycle using carbon oxysulfide in toluene under the same reaction conditions returned only the starting mesitronitrile oxide. Anthracene-9-nitrile oxide³ under the same reaction conditions with carbon disulfide gave only the isothiocyanate.

Production of mesityl isothiocyanate from the nitrile oxide and thiocyanate ion as recently reported⁵ has been verified. Use of buffered solutions at pH 5–7 in our case gave the same result.

Compounds I and III will be screened for radioprotective activity, since they possess reactive functions that should readily combine with cellular thiols.

Experimental Section

Melting points were determined in capillaries on a Mel-Temp aluminum block. Infrared spectra were obtained from a Perkin-Elmer Infracord 137B with sodium chloride optics. Evaporations were carried out with a rotary evaporator and water aspirator. Analyses were done by Carol K. Fitz, Needham Heights, Mass.

Reaction of 2,4,6-Trimethylbenzonitrile Oxide with Carbon Disulfide.—A 250-ml conical flask was charged with 8.05 g of 2,4,6-trimethylbenzonitrile oxide³ (0.05 mole) and 100 ml of dry carbon disulfide,⁷ capped with aluminum foil and sealed in a 1000-ml Parr bomb. The bomb was placed in a water bath preheated to 80°, maintained at 80–90° for 22 hr, then cooled to room temperature before opening. The light yellow solution was freed of carbon disulfide on a water bath, and the clear oil remaining was taken up in 50 ml of hexane and cooled overnight at –15° to complete crystallization. The large, white prisms were recrystallized from 50 ml of hexane to give 3-mesityl-1,4,2-oxathiazoline-5-one (III): 1.71 g (31%); mp 72–73.5°; $\nu_{\text{min}}^{\text{Nujol}}$ 1796, 1741, 1052, 900, 857, and 725 cm⁻¹. Five recrystallizations from hexane gave the analytical sample: mp 75–76°; dec pt 150°.

Anal. Calcd for C₁₁H₁₁NO₂S: C, 59.8; H, 5.0; N, 6.3. Found: C, 60.0; H, 5.2; N, 6.3.

Heating a sample in a 200° oil bath for a few seconds produced mesityl isothiocyanate: mp 59–61° (lit. 63°,⁸ 61–62°⁵).

The hexane liquors were combined and concentrated to about 20 ml, cooled, and seeded. This yielded 0.40 g of mesityl isothiocyanate, mp 57–59°; a second crop of less pure material comprised 4.78 g. The crude material (6 g) was recrystallized twice from hexane and once from methanol giving 1.75 g of large, white spars, mp 60–62°.

Anal. Calcd for C₁₀H₁₁NS: C, 67.8; H, 6.2; N, 7.9. Found: C, 67.3; H, 6.2; N, 8.1.

Reaction of Anthracene-9-nitrile Oxide with Carbon Disulfide.—The above reaction conditions were applied to 1.1 g of anthracene-9-nitrile oxide.³ There was obtained 1.3 g of yellow solid, mp 125–136°, $\nu_{\text{min}}^{\text{CHCl}_3}$ 2090 cm⁻¹, characteristic of isothiocyanates, and a sodium fusion test for sulfur was strongly

(1) Part of a project supported by grant RH 00297 from the Division of Radiological Health, Bureau of State Services, U. S. Public Health Service, Bethesda, Md.

(2) R. Huisgen, W. Mack, and E. Anneser, *Angew. Chem.*, **73**, 656 (1961).

(3) C. Grundmann and J. M. Dean, *J. Org. Chem.*, **30**, 2809 (1965).

(4) A stable spiro adduct has been obtained from the reaction of a nitrilimine with carbon disulfide: R. Huisgen, R. Grashey, M. Seidel, H. Knupfer, and R. Schmidt, *Ann.*, **658**, 169 (1962).

(5) C. Grundmann and H.-D. Frommelt, *J. Org. Chem.*, **31**, 157 (1966).

(6) N. B. Colthup, L. H. Daly, and S. E. Wiberley, "Introduction to Infrared and Raman Spectroscopy," Academic Press, Inc., New York, N. Y., 1964, p 255.

(7) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., 1955, pp 282–283.

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