Chemistry of Aliphatic Disulfides. X. Studies on the Mechanism of the Alkoxide Cleavage of 1,6-Diphenyl-3,4-dithia-1,6-hexanedione[1,2]

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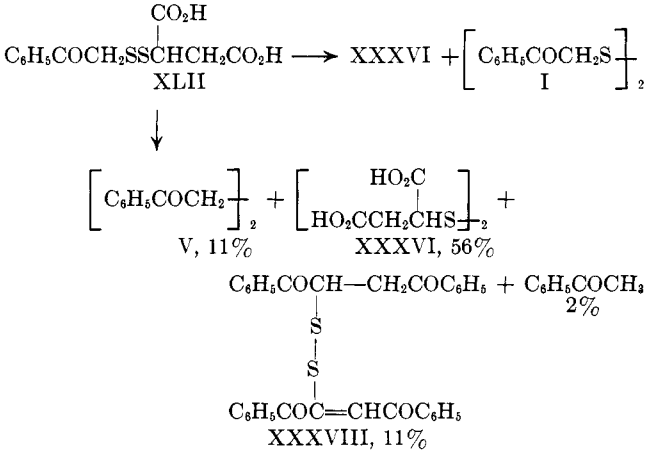
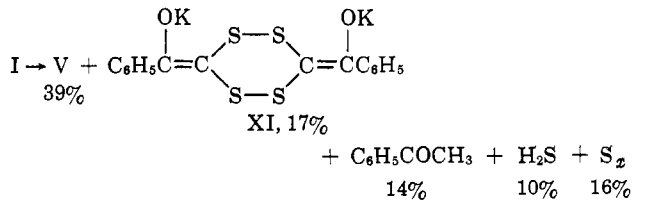
A mechanism for the formation of 1,4-diphenyl-1,4-butanedione (V) from 1,6-diphenyl-3,4-dithia-1,6-hexanedione (I) is proposed to involve dipotassio 1,4-diphenyl-1,4-butanedione-2,3-dimercaptide (XXVIII) as the intermediate. 2-Mercaptoacetophenone was converted to XXVIII with alkoxide alone or to V with alkoxide and elemental sulfur.

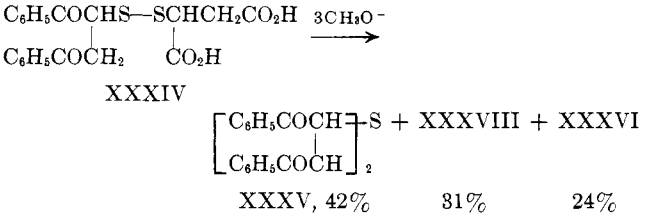
In the previous paper[2] the results of the alkoxide cleavage of two unsymmetrical β-keto disulfides were reported. One of these substrates, 5,6-dicarboxy-1-phenyl-3,4-dithiahexanone (XLII), was found to provide 1,4-diphenyl-1,4-butanedione (V), α,α′-dithiadisuccinic acid (XXXVI), the unsymmetrical disulfide XXXVIII, and acetophenone when cleaved with methoxide ion. Subsequently[2] it was established that XLII, in fact, was initially converted to the two symmetrical disulfides, 1,6-diphenyl-3,4-dithia-1,6-hexanedione (I) and XXXVI. Therefore V, XXXVIII, and acetophenone were produced from further decomposition of I.



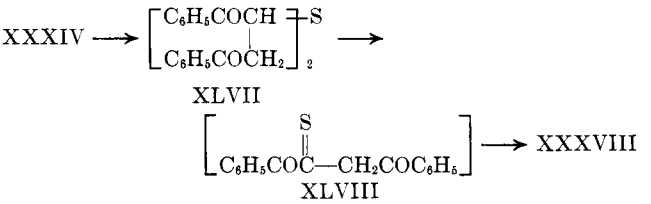
In separate experiments[6] I was found to provide a variety of products when allowed to react to completion with potassium ethoxide. No attempt was made to isolate the unsymmetrical disulfide XXXVIII from this reaction mixture. Another important interrelation of



reactions was established[2] when XXXVIII was isolated from the methoxide cleavage of 6,7-dibenzoyl-3-carboxy-4,5-dithiaheptanoic acid (XXXIV). The unsymmetrical disulfide XXXVIII was believed[2] to result from dimerization of the thio ketone XLVIII (formed from



XLVII, the disulfide interchange product of XXXIV, by α-elimination). Thus I and XLVII both provided sizable amounts of XXXVIII while only I yielded V on treatment with alkoxide. Therefore, the present investigation was initiated to determine the precursor of V and XLVIII in the alkoxide decomposition of I.



Dipotassio-1,4-diphenyl-1,4-butanedione-2,3-dimercaptide (XXVIII) as the Precursor of V and XLVIII.—Of the various products isolated from the alkoxide cleavage of I, the dipotassio dimercaptide XXVIII appeared as the most likely source of V. The loss of two sulfur atoms from XXVIII could occur by several routes; however, a reductive process involving elemental sulfur (known to be present in the reaction mixture) was considered to be the most reasonable. Therefore, a suspension of XXVIII in ethanol was stirred for 72 hr. with 1 equiv. of elemental sulfur. Contrary to expectation only starting material was obtained from this experiment.

The low solubility of XXVIII in ethanol suggested that some other form of XXVIII was probably the reactive species. This was supported by the observation[6] that XXVIII was only obtained when 2 equiv. of ethoxide/equiv. of I was employed; at lower base concentrations V was always isolated. Thus XXVIII was dissolved in ethanol by conversion of the dipotassium salt to the monobasic form, LIII. This was accomplished by addition of 0.5 equiv. of acetic acid to the ethanolic suspension of XXVIII. Treatment of LIII with 1 equiv. of elemental sulfur provided a 38% yield of V after 72 hr. at room temperature.

Additional evidence supporting an intermediate such as LIII and the elemental sulfur requirement in

(1) Supported by Research Grant RG-7966 from the National Institute of General Medical Sciences of the National Institutes of Health, U. S. Public Health Service.

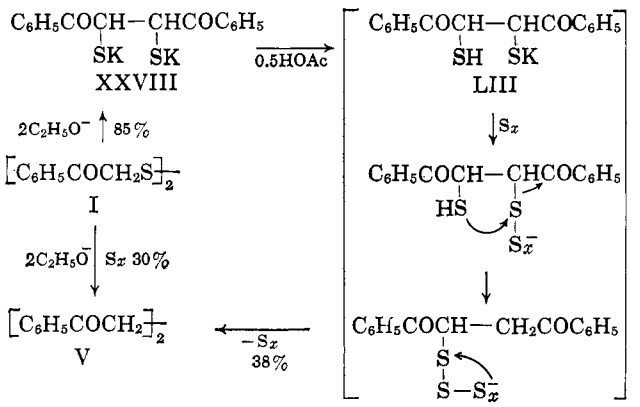
(2) For part IX of this series, see R. G. Hiskey and J. A. Kepler, *J. Org. Chem.*, **29**, 3678 (1964).

(3) Shell Chemical Corp. Fellow, 1962–1963.

(4) Abstracted in part from dissertations submitted to the University of North Carolina in partial fulfillment of the requirements for the Ph.D. degree by J. A. Kepler, Aug., 1963, and B. D. Thomas, June, 1962.

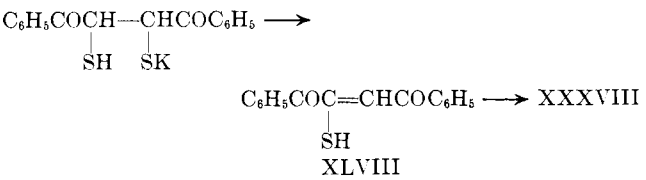
(5) Union Carbide Chemical Corp. Fellow, 1960–1961.

(6) R. G. Hiskey, B. D. Thomas, and J. A. Kepler, *J. Org. Chem.*, **29**, 3671 (1964).

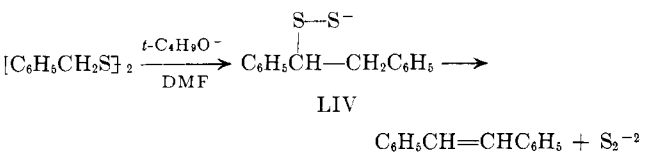


the conversion of XXVIII to V was obtained by treatment of I with 2 equiv. of ethoxide and 1 equiv. of sulfur. Under these conditions I was converted to V in 30% yield. No trace of XXVIII, obtained from I in 85% yield in the absence of sulfur, could be detected.

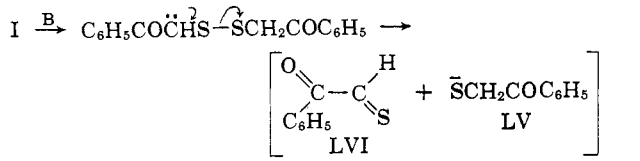
The choice of XXVIII (in the form of LIII) as the source of V is also consistent with the observation that the unsymmetrical disulfide XXXVIII is produced from both I and XXXIV. Loss of hydrosulfide ion from LIII, by β-elimination, would yield the same intermediate thio ketone, XLVIII, that was generated by α-elimination from XLVII. Dimerization of XLVIII would afford the observed unsymmetrical disulfide, XXXVIII.



The formation of V from I *via* LIII precludes a mechanism of the type suggested[7] for the base-catalyzed conversion of dibenzyl disulfide to stilbene in which LIV was the proposed intermediate.

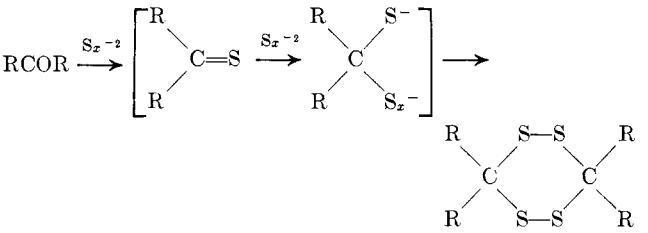


Formation of LIII from I.—Since the available data indicated that LIII was probably the immediate precursor of V, the pathway by which LIII was formed from I was considered. As previously[2] stated the unsymmetrical disulfide XLII was believed to decompose by a "direct displacement" mechanism, whereas I was probably initially attacked at an acidic α-hydrogen atom to provide an intermediate carbanion. Decomposition of the resulting carbanion by "α-elimination" would yield phenacyl mercaptide (LV) and phenylglyoxthial (LVI).



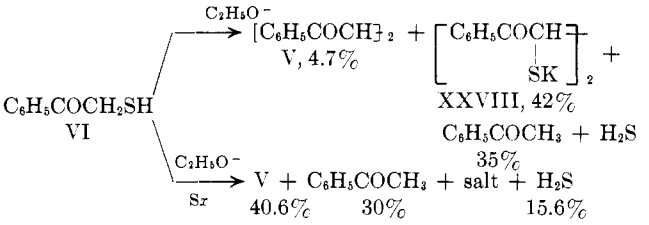
(7) T. J. Wallace, H. Pobiner, J. E. Hofmann, and A. Schriesheim, *Proc. Chem. Soc.*, 137 (1963).

Although compounds similar to LVI have been suggested[8] as intermediates in various transformations, substances of this type have not been isolated and characterized. In the present investigation the only positive evidence indicating an intermediate in the oxidation state of LVI was the formation[6] of the 1,2,4,5-tetrathiane XI. Fredga and Magnusson[9] have demonstrated that the action of ammonia polysulfide on ketones provides 1,2,4,5-tetrathianes, presumably by the condensation shown.



Several literature precedents[10] suggested that α-mercapto ketones yielded ketones and elemental sulfur when treated with alkali. Thus it was anticipated that the mercaptide resulting from initial α-elimination (LV) was probably the source of the acetophenone (17%) and the elemental sulfur (16%) detected[6] in the decomposition of I.

When 2-mercaptoacetophenone (VI) was treated with 1 equiv. of ethoxide under the cleavage conditions, a 35% yield of acetophenone was obtained. In addition a 42% yield of the dimercaptide XXVIII and a 4.7% yield of V resulted. When the same reaction was carried out in the presence of 1 equiv. of elemental sulfur *only* V, acetophenone, and a salt of unknown structure (shown not to be XXVIII) resulted. This data again suggests that XXVIII (in the form of LIII) and elemental sulfur provide V.

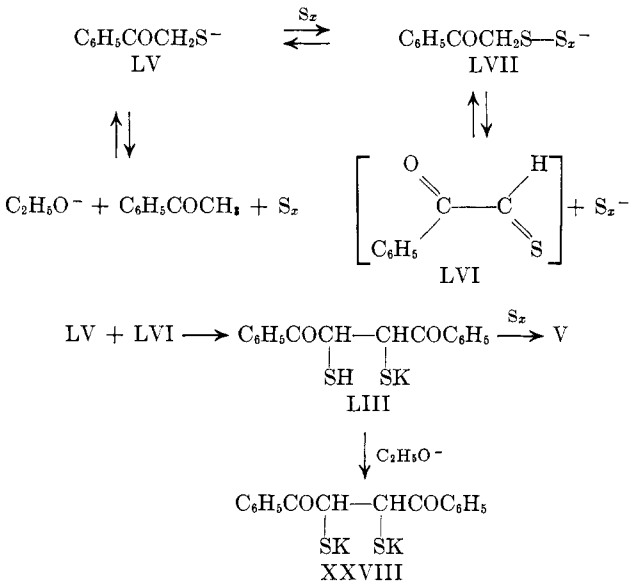


The formation of XXVIII, and hence V, from VI appears to represent a new reaction of α-mercapto ketones. The reaction of VI with ethoxide in the presence of sulfur may be rationalized in the following manner. Phenacyl mercaptide (LV) should react readily with elemental sulfur to afford phenacyl polysulfide (LVII). Loss of sulfide ion from LVII would be analogous to the decomposition of I and would provide equilibrium concentrations of phenylglyoxthial (LVI). Condensation of LV and LVI would provide XXVIII which in the presence of sulfur would be entirely converted to V. The formation of acetophenone can result from either initial decomposition of LV or a similar transformation involving LVII.

(8) See, for example, F. Asinger, W. Schäfer, K. Halcour, A. Saus, and H. Triem, *Angew. Chem.*, **75**, 1050 (1963).

(9) A. Fredga and B. Magnusson, *Acta Chem. Scand.*, **13**, 1031 (1959).

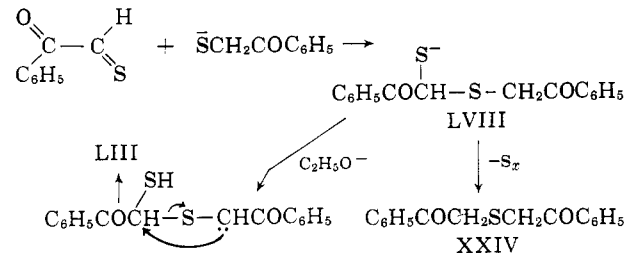
(10) B. Groth, *Arkiv Kemi Mineral Geol.*, **9**, 1 (1924); A. Schönberg and Y. Iskander, *J. Chem. Soc.*, 90 (1942).



The conversion of LV to XXVIII in the absence of added sulfur must be a somewhat different situation. In this reaction the decomposition of LV would initially provide acetophenone and sulfur. As the sulfur is formed it would react with LV and again provide LVII, LVI, and ultimately LIII. However, with no additional sulfur available for the reduction of LIII the predominant product is now XXVIII rather than V. Thus, while both reactions require sulfur, in the latter case it is generated by the decomposition of LV.

Several possible pathways can be written for the formation of LIII from LV and LVI. The route that incorporates the available data most conveniently is presented, although other mechanisms may be equally plausible.[11] A key consideration in the choice of mechanism was the fact that diphenacyl sulfide (XXIV) was formed from I at low ratios of base to disulfide[6] while decomposition[2] of XXXIV with 3 equiv. of alkoxide also provided a sulfide (XXXV).

In the case of I, recombination of LV and LVI could yield a hemidithioacetal (LVIII). In the presence of sizable base concentrations LVIII could then be converted to LIII by a "Stevens-type" rearrangement. However, any factor, such as α-alkylation (*e.g.*, XLVIII) or low base concentration, which would retard removal of the α-hydrogen atom should reduce the possibility of rearrangement and increase the amount of sulfide formed by loss of elemental sulfur from the hemidithioacetal.



(11) Two of the several alternative mechanisms which are of speculative interest are (a) dimerization of LVI to yield $C_6H_5COCH(S{-}S)CHCOC_6H_5$ which could be converted to LIII by S_x^{-2}; (b) formation of LIII by attack of the carbanion, $C_6H_5C\overset{-}{O}CHSH$ on LVI. This pathway bears some analogy to the suggested mechanism for the benzoin condensation.

Experimental[12]

Reaction of XXVIII with Sulfur in the Presence of Acetic Acid.—A stirred suspension of 1.9 g. (0.005 mole) of XXVIII and 0.16 g. (0.005 mole) of sulfur in 10 ml. of ethanol was treated with 10 ml. of a solution containing 1.5 g. (0.025 mole) of acetic acid in 100 ml. of ethanol. The reaction was allowed to proceed for 72 hr. and then filtered. The residue was washed with hot methanol and the alcohol solutions were combined. Concentration of the alcohol solution provided 0.45 g. (38%) of V, m.p. 143–146°.

Cleavage of I with Two Equivalents of Potassium Ethoxide in the Presence of Sulfur.—A 6.0-g. (0.02-mole) sample of I was dissolved in 20 ml. of ethanol containing 0.64 g. (0.02 g.-atom) of sulfur and 1.56 g. (0.04 g.-atom) of potassium. The reaction was stirred for 72 hr. at room temperature. Filtration of the residue provided 1.2 g. (29.7%) of V, m.p. 144–146°. The filtrate was cooled and deposited 1.4 g. of a salt which was dissolved in water and filtered to yield 0.17 g. of sulfur, m.p. 114–117°. Acidification of the aqueous layer provided hydrogen sulfide and 0.3 g. of sulfur.

The ethanol solution was treated as previously described[6] and afforded 0.26 g. of sulfur from the yellow polymeric solid obtained. The total yield of sulfur was 0.73 g. (38%).

Preparation of S-Phenacyl-O-carboxymethyldithiocarbonate.—The dithiocarbonate was prepared essentially according to the procedure of Groth.[10] Hydrolysis of 96 g. (1.02 mole) of chloroacetic acid was effected by mild heating with 400 ml. of 5.18 *N* potassium carbonate. The solution was cooled to 15° and treated with 115 ml. of 9.3 *N* potassium hydroxide and 80 g. (1.05 moles) of carbon disulfide. The solution was stirred for 16 hr., diluted to 900 ml. with water, and the hydrogen sulfide was expelled with carbon dioxide over a 1-hr. period. The solution was cooled to 5° and treated with 175 g. (0.88 mole) of 2-bromoacetophenone, added in small portions. After 8 hr. of stirring, the reaction was worked up in the manner described by Groth. The crude product was recrystallized from benzene to yield 125 g. (50%) of the desired acid, m.p. 105–107°, lit.[10] m.p. 105–106°.

Preparation of 2-Mercaptoacetophenone (VI).—To a solution of 230 ml. of 2.06 *N* potassium carbonate was added 120 g. (0.455 mole) of S-phenacyl-O-carboxymethyldithiocarbonate. A small amount of undissolved solid was filtered and the solution was placed in a reaction flask similar to that described by Groth.[10] Hydrogen sulfide was passed through the reaction mixture and the temperature was slowly raised to 50°; 2.67 g. (0.044 mole) of glacial acetic acid was then added to the solution. When the temperature of the mixture was increased to 70°, an oil separated. The oil was withdrawn from the basic solution into a separatory funnel containing hydrogen sulfide. Formation of the mercaptan was complete in about 2 hr. The layers were allowed to separate and the organic layer was quickly filtered through a thin layer of magnesium sulfate. The hydrogen sulfide in the dry oil was expelled with carbon dioxide and the resulting oil was distilled to give 35 g. (52%) of 2-mercaptoacetophenone (VI), b.p. 95–97° at 1 mm. The freshly distilled mercaptan was a deep violet but upon standing in a brown bottle under nitrogen for 3 to 4 hr. it turned yellow. The yellow mercaptan exhibited a maximum at 243 mμ (ϵ 10,900) in the ultraviolet and an intense carbonyl peak at 1670 cm.$^{-1}$ in the infrared.

The benzoate derivative of 2-mercaptoacetophenone (XXVII) was prepared from the yellow mercaptan. Recrystallization from ethanol provided 3.0 g. (89%) of phenacyl thiobenzoate, m.p. 84–85°, lit.[10] m.p. 84–85°. The ultraviolet spectrum of XXVII in ethanol exhibited a maximum at 243 mμ (ϵ 23,400). The infrared spectrum exhibited a single carbonyl peak at 1675 and another intense absorption peak at 909 cm.$^{-1}$.

The N,N-diphenylthiocarbamate derivative of VI, prepared[13] from the violet mercaptan, melted at 133.5–134.5°.

Reaction of 2-Mercaptoacetophenone (VI) with Potassium Ethoxide.—A 4.5-g. (0.029-mole) sample of VI was dissolved in a solution containing 1.08 g. (0.028 g.-atom) of potassium in 20 ml. of ethanol. The mercaptan dissolved giving a clear orange solution which became cloudy in about 0.5 hr. The reaction mixture was allowed to stand at room temperature for 72 hr. Analysis of a 1-ml. aliquot in the vapor fractometer[6] indicated 35.3% of acetophenone was present in the reaction.

The suspension was filtered and the salt XXVIII, 2.6 g. (42%), was converted to the diacetate derivative XXVIb, m.p. 202–204°.

(12) Melting points are uncorrected.

(13) R. G. Hiskey, F. I. Carroll, R. L. Smith, and R. T. Corbett, *J. Org. Chem.*, **26**, 4756 (1961).

A mixture melting point with an authentic sample[6] of the diacetate was not depressed.

The solvent was removed from the filtrate and the resulting oil was dissolved in water and extracted with ether. The combined extracts were concentrated and gave 0.12 g. (4.7%) of V, m.p. 144–146°. A mixture melting point with an authentic sample was not depressed.

Reaction of 2-Mercaptoacetophenone (VI) with Potassium Ethoxide in the Presence of Sulfur.—To a suspension of 0.9 g. (0.03 g.-atom) of sulfur in 20 ml. of ethanol containing 1.08 g. (0.028 g.-atom) of potassium, was added 0.5 g. (0.0229 mole) of VI. On addition of the mercaptan, the solution turned red and the suspended sulfur dissolved. After 2 hr. a solid began to precipitate from the reaction mixture. The suspension was allowed to stand at room temperature for 72 hr. Analysis of a 1-ml. aliquot in the vapor fractometer indicated the presence of 30.2% acetophenone in the reaction mixture.

Filtration of the suspension gave 1.46 g. (40.6%) of V, m.p. 144–146°, m.m.p. 145–146°. The filtrate, worked up in the usual manner,[6] provided 0.3 g. (15.6%) of hydrogen sulfide (as lead sulfide) and 1.02 g. of a salt which was not identical with XXVIII and not further characterized.

Notes

The Formation of N-(β-Anilinoethyl)-2-pyridone from the Action of N-Phenylethanolamine on 2-Bromopyridine

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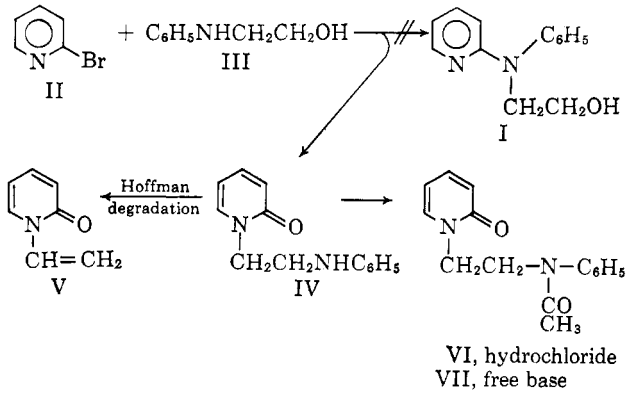
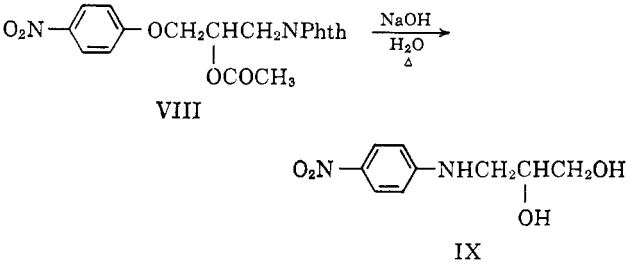
As part of another program a sample of 2-(N-β-hydroxyethylanilino)pyridine (I) was desired for investigation. A well-known route to compounds of this type[2a-c] involves displacement of a halogen by the appropriate amine. When 2-bromopyridine (II) was heated at 200–250° with 2 equiv. of N-phenylethanolamine (III), a crystalline solid (analysis showed $C_{13}H_{14}N_2O$) was obtained in 41.5% yield. The structure of this product was assigned as N-(β-anilinoethyl)-2-pyridone (IV) on the basis of the following transformations. The alkylation product, IV, reacted smoothly with dry hydrogen chloride and phenyl isothiocyanate to provide the corresponding amine derivatives. A Hofmann degradation converted IV to N-vinyl-2-pyridone (V) and N,N-dimethylaniline.



Acylation of IV with acetyl chloride in benzene provided the hydrochloride of N-(β-acetanilinoethyl)-2-pyridone (VI) which could be converted to N-(β-acetanilinoethyl)-2-pyridone (VII) with either silver oxide or triethylamine. The amide VII could also be prepared directly from IV by acylation with acetic anhydride in the presence of base. Hydrolysis of VII with either acid or base provided IV.

Several mechanistic possibilities can be proposed to explain the rather unusual course of the alkylation reaction. The 2-alkoxypyridines are known[3] to rearrange to N-alkyl-2-pyridones when heated. Caldwell and Schweiber[4] have reported that a similar rearrangement of VIII afforded IX and suggested that the transformation



was analogous to the Smiles rearrangement.[5,6] Thus O-alkylation of III followed by rearrangement may have occurred. However, the initial formation of a O-alkylation product is considered unlikely since N-phenylethanolamine normally provides N-alkyl derivatives. Alternatively I may have been produced and rearranged to IV *via* either intermediate X or XI. Compounds similar to X have previously been reported[2] in reactions of this type while decomposition of XI would provide the 2-alkoxypyridine. No decision between these possible pathways can be reached from the present data.

(1) Abstracted in part from a dissertation by J. Hollander submitted in partial fulfillment of the requirements for the Ph.D. degree to the University of North Carolina, June, 1959.

(2) (a) H. S. Mosher "Heterocyclic Compounds," Vol. I., R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1950, p. 397; (b) N. Weiner and I. A. Kaye, *J. Org. Chem.*, **14**, 868 (1949); (c) A. P. Gray, D. E. Heitmeier, and E. E. Spinner, *J. Am. Chem. Soc.*, **81**, 4351 (1959).

(3) K. B. Wiberg, T. M. Shryne, and R. R. Kintner [*ibid.*, **79**, 3160 (1957)] have shown that the reaction is probably intermolecular and may involve a radical chain mechanism.

(4) W. T. Caldwell and G. C. Schweiber, *ibid.*, **74**, 5187 (1952).

(5) W. Evans and S. Smiles, *J. Chem. Soc.*, 181 (1935).

(6) J. F. Bunnet and R. Zahler, *Quart. Rev.*, **69**, 273 (1951).