The Conversion of 4,1-Benzoxazepine-2,5(1*H*,3*H*)-diones into 2-(α-Hydroxyalkyl)-4-quinazolinones

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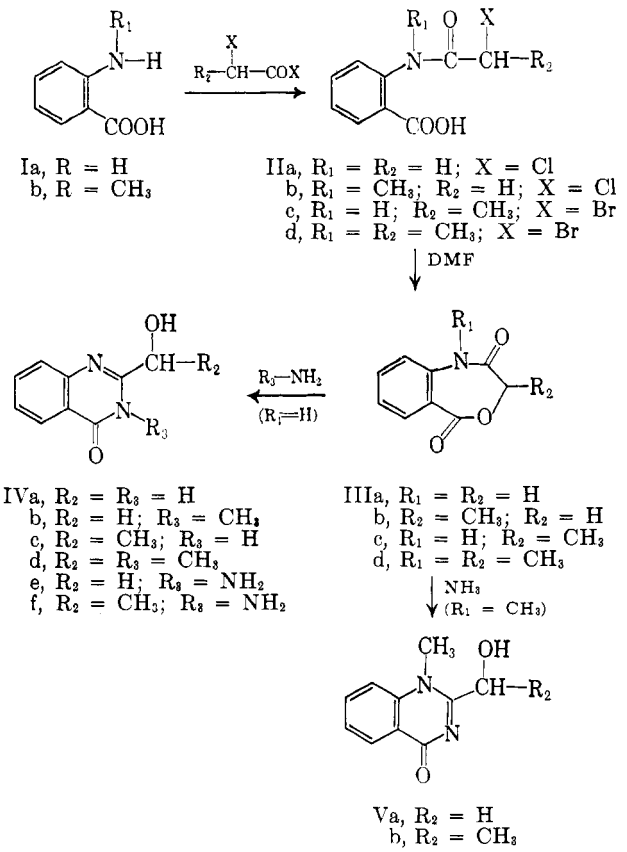
Received October 3, 1963

N-(α-Haloacyl)anthranilic acids (II) are cyclized with dimethylformamide to 4,1-benzoxazepine-2,5(1*H*,3*H*)-diones (III), which in turn undergo ring contraction to 2-(α-hydroxyalkyl)-4-quinazolinones (IV and V) when treated with ammonia, primary amines, or hydrazine.

The alkaloids vasicinone, isolated from *Adhatoda vasica*, arborine, isolated from *Glycosmis pentaphylla* Correa, glucosmicine, glucosminine, and glycorine, from *Glycosmis arborea*, show that 4-quinazolinone is an important structural element in the molecules of natural products.[1] We wish to report the synthesis of 2-(α-hydroxyalkyl)-4-quinazolinones, in which the hydroxyl group has the same relative position as in the molecule of vasicinone.[2]

The synthesis involves a novel cyclization of N-(α-haloacyl)anthranilic acids (II) to 4,1-benzoxazepine-2,5(1*H*,3*H*)-diones (III), characterized by the use of dimethylformamide as solvent. The compounds of formula III are useful intermediates for syntheses in



which the structural elements of anthranilic acid are built into larger molecules. Simple treatment with ammonia, methylamine, or hydrazine converts the N-unsubstituted benzoxazepinediones into 2-(α-hydroxyalkyl)-4(3*H*)-quinazolinones (IV). The N-methylbenzoxazepinediones give with ammonia the isomeric 2-(α-hydroxyalkyl)-4(1*H*)-quinazolinones (V).

The acylation of anthranilic acid (Ia) and N-methylanthranilic acid (Ib) with chloroacetyl chloride gave, respectively, N-(chloroacetyl)anthranilic acid (IIa),[3] and N-(chloroacetyl)-N-methylanthranilic acid (IIb), which was not obtained in crystalline form. With α-bromopropionyl bromide as acylating agent, Ia gave N-(α-bromopropionyl)anthranilic acid (IIc) and Ib gave N-(α-bromopropionyl)-N-methylanthranilic acid (IId), which could not be crystallized.

The cyclizations were performed in boiling dimethylformamide. All of the benzoxazepinediones so obtained can be purified conveniently by crystallization from methyl alcohol. Compound IIa yielded 4,1-benzoxazepine-2,5(1*H*,3*H*)-dione (IIIa). Compound IIc gave 3-methyl-4,1-benzoxazepine-2,5(1*H*,3*H*)-dione (IIIc); IIb yielded 1-methyl-4,1-benzoxazepine-2,5-(1*H*,3*H*)-dione (IIIb). From IId, 1,3-dimethyl-4,1-benzoxazepine-2,5(1*H*,3*H*)-dione (IIId) was obtained.

The assignment of the 4,1-benzoxazepine-2,5(1*H*,3*H*)-dione structure was supported by their infrared absorption spectra. The lactam group was shown by a carbonyl band and by the absence of the amide II band in the N-unsubstituted analogs, which is characteristic for secondary cyclic amides. The lactone group was evident by the absorptions in carbonyl and ether regions. In the ultraviolet spectra, the 4,1-benzoxazepine-2,5-(1*H*,3*H*)-diones show three maxima: at 215–217, 242–247, and 296–302 mμ.

The conversion of benzoxazepinediones into quinazolinones was carried out by treatment in methanolic or ethanolic solution at room temperature with ammonia or methylamine, or by boiling with anhydrous hydrazine. Compound IIIa gave, with ammonia, 2-hydroxymethyl-4(3*H*)-quinazolinone (IVa); with methylamine, 2-hydroxymethyl-3-methyl-4(3*H*)-quinazolinone (IVb); and, with hydrazine, 3-amino-2-hydroxymethyl-4(3*H*)-quinazolinone (IVe). In the same fashion, IIIc was transformed into 2-(1-hydroxyethyl)-4(3*H*)-quinazolinone (IVc), 2-(1-hydroxyethyl)-3-methyl-4(3*H*)-quinazolinone (IVd), and 3-amino-2-(1-hydroxyethyl)-4-(3*H*)-quinazolinone (IVf).

Under the same conditions, the N-methylbenzoxazepinediones, IIIb and IIId, were converted with ammonia into the isomeric 2-hydroxymethyl-1-methyl-4(1*H*)-quinazolinone (Va) and 2-(1-hydroxyethyl)-1-methyl-4(1*H*)-quinazolinone (Vb), respectively.

The assignment of the quinazoline structures to

(1) W. L. F. Armarego, "Advances in Heterocyclic Chemistry," by A. R. Katritzky, Academic Press, New York, N. Y., 1963, pp. 253–309.

(2) D. R. Mehta, J. S. Naravane, and D. M. Desai, *J. Org. Chem.*, **28**, 445 (1963).

(3) T. D. Riedel, *Riedel's Berichte*, 13 (1912).

these new compounds, based on the assumed reaction mechanism, was supported by spectroscopic evidence.[4]

Experimental[5]

N-Chloroacetylanthranilic Acid (IIa).—To the solution of 14 g. of anthranilic acid (Ia) and 9 ml. of pyridine in 2 l. of anhydrous ether, 12 g. of chloroacetyl chloride, dissolved in 200 ml. of ether, was added dropwise at 0°. After the addition was complete, the reaction mixture was stirred for 1 hr. at room temperature. A saturated solution of hydrogen chloride in ether was added to complete the precipitation of pyridine hydrochloride, which was filtered and washed with ether. The ether solution was evaporated, and the crystalline residue was recrystallized from 50% acetic acid, yielding 18 g. of IIa, m.p. 183–187°.[3]

4,1-Benzoxazepine-2,5(1H,3H)-dione (IIIa).—The solution of 5 g. of IIa in 150 ml. of dimethylformamide was refluxed for 7 hr. on an oil bath. After cooling, a large excess of water was added and a small precipitate was filtered off. The filtrate was evaporated to dryness; by crystallization from acetone, dimethylamine hydrochloride was removed, and the mother liquor evaporated to dryness. The residue was recrystallized from methylene chloride, giving 1 g. of IIIa, m.p 200–201°. Infrared (in $CHCl_3$): 1710 cm.$^{-1}$ (lactam); 1728 cm.$^{-1}$ (lactone); 1216, 1242, and 1278 cm.$^{-1}$ (C–O–C). Ultraviolet: λ_{max} 216 mμ (ε 25,500); 242–243 (8900); 301–302 (3100).

Anal. Calcd. for $C_9H_7NO_3$: C, 61.01; H, 3.98; N, 7.91. Found: C, 61.10; H, 3.95; N, 7.98.

1-Methyl-4,1-benzoxazepine-2,5(1H,3H)-dione (IIIb).—To the solution of 15.1 g. of Ib in 100 ml. of dimethylformamide at 0° was added 13.4 g. of chloroacetyl chloride, and the reaction mixture stirred for 2 hr. A large excess of water was added and the resulting suspension extracted with methylene chloride. The extract was washed with water, dried over sodium sulfate, and evaporated *in vacuo*. The residue was dissolved in 600 ml. of dimethylformamide and this solution was refluxed for 4.5 hr. The solution was evaporated *in vacuo* to dryness, and the residue dissolved in 500 ml. of methylene chloride. This solution was washed successively with water, 10% sodium bicarbonate, and water, dried, and evaporated. The solid residue was crystallized from methanol, giving 10.2 g. of IIIb, m.p. 157.5–159.5°. Infrared (in $CHCl_3$): 1732 cm.$^{-1}$ (lactone carbonyl); 1680 cm.$^{-1}$ (lactam carbonyl); 1265 cm.$^{-1}$ (C–O–C). Ultraviolet: λ_{max} 215–216 mμ (ε 24,100); 296–297 (2300); λ_{infl} 245–247 mμ (ε 9500).

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.33. Found: C, 63.00; H, 4.84; N, 7.25.

N-(α-Bromopropionyl)anthranilic Acid (IIc).—To the solution of 6.9 g. of Ia in 100 ml. of dimethylformamide at 0° was added 12.9 g. of α-bromopropionyl bromide, and the reaction mixture stirred for 3 hr. A large excess of water was added and the resulting precipitate collected, dried, and recrystallized from acetone–petroleum ether. It gave 7.8 g. of IIc, m.p. 169.5–171.5°. Infrared (in $CHCl_3$): 3380 cm.$^{-1}$ (>N–H); 2720, 2630, 2500, and 1700 cm.$^{-1}$ (–COOH); 1670 cm.$^{-1}$ (amide carbonyl); 1528 cm.$^{-1}$ (amide II). Ultraviolet: λ_{max} 211–212 mμ (ε 19,000); 225 (infl. 17,000); 257–258 (10,800); 302–303 (5600).

Anal. Calcd. for $C_{10}H_{10}BrNO_3$: C, 44.14; H, 3.71; N, 5.15. Found: C, 44.61; H, 3.49; N, 5.14.

3-Methyl-4,1-benzoxazepine-2,5(1H,3H)-dione (IIIc).—A solution of 8 g. of IIc in 500 ml. of dimethylformamide was refluxed for 3 hr. and then evaporated *in vacuo*. The residue was dissolved in 500 ml. of methylene chloride, and this solution washed with water, 10% sodium bicarbonate solution, and again with water, dried, and evaporated. The crude product was recrystallized from acetone–hexane to give 4 g. of IIIc, m.p. 194–196.5°. Infrared (KBr): 3280 cm.$^{-1}$ (>N–H); 1728 cm.$^{-1}$ (lactone carbonyl); 1700 cm.$^{-1}$ (amide carbonyl); 1222, 1260, and 1300 cm.$^{-1}$ (C–O–C). Ultraviolet: λ_{max} 242–243 mμ (ε 6390); 300–301 (1900).

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.32. Found: C, 62.41; H, 4.81; N, 7.36.

1,3-Dimethyl-4,1-benzoxazepine-2,5(1H,3H)-dione (IIId).—A stirred solution of 15.1 g. of Ib and 9.6 g. of pyridine in 1000 ml. of anhydrous ether was cooled to 0°, and a solution of 25.9 g. of α-bromopropionyl bromide in ether was then added dropwise. The reaction mixture was stirred for an additional 2 hr., and then a saturated solution of hydrogen chloride in ether was added, until precipitation no longer occurred. The pyridine hydrochloride was filtered off, and the filtrate evaporated to dryness. The noncrystalline residue (XIVa) was dissolved in 1000 ml. of dimethylformamide, refluxed for 4 hr., and then evaporated. The residue was dissolved in methylene chloride; this solution was successively washed with water, 10% sodium bicarbonate, and water, dried, and evaporated. The crystalline residue was twice recrystallized from methanol to give 12.5 g. of IIId, m.p. 143–144°. Infrared (in $CHCl_3$): 1725 cm.$^{-1}$ (lactone carbonyl); 1680 cm.$^{-1}$ (lactam carbonyl); 1255 cm.$^{-1}$ (C–O–C). Ultraviolet: λ_{max} 216–217 mμ (ε 38,200); 295–296 (3650); infl. 245–247 (14,700).

Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.33; H, 5.43; N, 6.80.

2-Hydroxymethyl-4(3H)-quinazolinone (IVa).—The solution of 5.5 g. of IIIa in 1000 ml. of methanol was saturated with gaseous ammonia at room temperature. The reaction mixture was allowed to stand for 1 week and was then concentrated *in vacuo*. The resulting precipitate was collected and recrystallized several times from methanol to give 0.8 g. of IVa, which decomposes gradually above 214°. Infrared (KBr): 3280, 2830, and 1093 cm.$^{-1}$ (bonded –OH); 3150 cm.$^{-1}$ (bonded N–H); 1658 cm.$^{-1}$ (carbonyl); 1634 and 1608 cm.$^{-1}$ (>C=N—). Ultraviolet: λ_{max} 225 mμ (ε 26,000); 230 (sh, 23,000); 264–265 (7900); 271 (7300); 303–304 (4500); 314–315 (3500).

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.19; H, 4.54; N, 15.74.

2-Hydroxymethyl-3-methyl-4(3H)-quinazolinone (IVb).—The solution of 8.3 g. of IIIa in 500 ml. of methanol was saturated with methylamine and allowed to stand for 1 week. The reaction mixture was then evaporated to dryness, and the residue recrystallized from acetone. It gave 6.4 g. of IVb, m.p. 153–154°. Infrared (in $CHCl_3$): 3390 and 1078 cm.$^{-1}$ (–OH); 1680 cm.$^{-1}$ (carbonyl group); 1618 cm.$^{-1}$ (>C=N—). Ultraviolet: λ_{max} 225 mμ (ε 23,200); 267–268 (7500); 275 (8000); 303–304 (3900); 315 (3050).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.51; H, 5.29; N, 14.24.

2-(1-Hydroxyethyl)-4(3H)-quinazolinone (IVc).—The suspension of 9 g. of IIIc in methanol was saturated with ammonia at room temperature and allowed to stand for 1 week, and then evaporated. The residue was recrystallized twice from acetone to give 3.1 g. of IVc, m.p. 190–191°. Infrared (KBr): 3370, 2875, and 1050 cm.$^{-1}$ (–OH); 3120 cm.$^{-1}$ (>N–H); 1675 cm.$^{-1}$ (carbonyl); 1625 and 1605 cm.$^{-1}$ (>C=N—). Ultraviolet: λ_{max} 225–226 mμ (ε 27,500); 230 (sh, 25,500); 265 (8250); 271 (7500); 305 (4200); 315–316 (3450).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.63; H, 5.07; N, 15.02.

2-(1-Hydroxyethyl)-3-methyl-4(3H)-quinazolinone (IVd).—The suspension of 8.5 g. of IIIc in 500 ml. of methanol was saturated with methylamine, and the resulting solution was allowed to stand overnight. It was then evaporated, and the residue recrystallized from acetone, giving 4.5 g. of 2-(2-hydroxypropioamido)-N-methylbenzamide, m.p. 166–168°.

Anal. Calcd. for $C_{11}H_{14}N_2O_3$ (222.25): C, 59.46; H, 6.35; N, 12.60. Found: C, 59.70; H, 6.24; N, 12.39.

This compound was heated at 180° for 1 hr., and the resulting melt was recrystallized twice from water to give 3 g. of IVd, m.p. 63.5–65.5°. Infrared (in $CHCl_3$): 3660, 3390, and 1088 cm.$^{-1}$ (–OH); 1676 cm.$^{-1}$ (carbonyl); 1605 cm.$^{-1}$ (>C=N—). Ultraviolet: λ_{max} 225 mμ (ε 23,600); 268 (7100); 275 (6700); 304 (3500); 317 (2650).

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 65.00; H, 5.97; N, 13.43.

3-Amino-2-hydroxymethyl-4(3H)-quinazolinone (IVa).—The solution of 6.0 g. of IIIa and 3.2 g. of anhydrous hydrazine in 500 ml. of methanol was refluxed for 24 hr. It was then allowed to stand at room temperature for 1 week, after which the formed precipitate was collected and recrystallized from methanol to give 5.1 g. (78% yield) of IVe, m.p. 216–220°. Infrared (in KBr): 3300 and 3200 cm.$^{-1}$ (–NH_2): 1676 cm.$^{-1}$ (carbonyl group); 1600 cm.$^{-1}$ (—C=N—); 1045 cm.$^{-1}$ (–OH). Ultraviolet: λ_{max} 222–223 mμ (ε 25,400); 273–275 (5400); 305 (3000); and 315–316 (2500).

(4) J. M. Hearn, R. H. Morton, and J. C. E. Simpson, *J. Chem. Soc.*, 3318 (1951); H. Culbertson, J. C. Decius, and B. E. Christensen, *J. Am. Chem. Soc.*, **74**, 4834 (1952).

(5) All melting points are uncorrected. Ultraviolet spectra were taken on a Cary Model 14M spectrophotometer in 2-propanol solution. Infrared spectra were taken on a Perkin-Elmer Model 21 spectrophotometer.

Anal. Calcd. for $C_9H_9N_3O_2$: C, 56.53; H, 4.74. Found: C, 56.61; H, 4.76.

3-Amino-2-(1-hydroxyethyl)-4(3*H*)-quinazolinone (IVf).—The solution of 24 g. of IIIc and 8.4 g. of anhydrous hydrazine in 2 l. of methanol was refluxed for 24 hr. and then allowed to stand at room temperature for 2 days, after which the solvent was distilled *in vacuo*. The residue was recrystallized from methylene chloride–hexane to give a quantitative yield (25 g.) of IVf, m.p. 108–110°. Infrared (in $CHCl_3$): 3450 and 3330 cm.$^{-1}$ (-NH_2); 1678 cm.$^{-1}$ (carbonyl group); 1605 cm.$^{-1}$ (—C=N—); 1034 cm.$^{-1}$ (-OH). Ultraviolet: λ_{max} 222 mμ (ϵ 24,000); 274 (6000); 305–306 (3500); and 316–317 (3000).

Anal. Calcd. for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40. Found: C, 58.71; H, 4.98.

2-Hydroxymethyl-1-methyl-4(1*H*)-quinazolinone (Va).—The suspension of 16 g. of IIIb in 1000 ml. of methanol was saturated with ammonia at room temperature, which resulted in a solution that was left to stand for 1 week. It was then evaporated *in vacuo*, and the solid residue recrystallized from methanol to give 5 g. of Va, m.p. 178–180°. Infrared (in $CHCl_3$): 3360 and 1078 cm.$^{-1}$ (-OH); 1653 cm.$^{-1}$ (carbonyl); 1603 cm.$^{-1}$ (>C=N—); 1528 cm.$^{-1}$ (Ar—CO—N=C—). Ultraviolet: λ_{max} 230 mμ (ϵ 16,500); 269 (4300); 276–277 (4500); 306–307 (6200); 317 (7900).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.29; N, 14.73. Found: C, 63.46; H, 5.07; N, 14.96.

2-(1-Hydroxyethyl)-1-methyl-4(1*H*)-quinazolinone (Vb).—The suspension of 10.2 g. of IIId in 500 ml. of methanol was saturated with ammonia at room temperature, and the resulting solution left to stand for 1 week. It was then evaporated to dryness and the residue recrystallized from methanol to give 7.6 g. of Vb, m.p. 155–157°. Infrared (in $CHCl_3$): 3400 and 1088 cm.$^{-1}$ (-OH); 1648 cm.$^{-1}$ (carbonyl); 1605 cm.$^{-1}$ (>C=N—); 1535 cm.$^{-1}$ (Ar—CO—N=C—). Ultraviolet: λ_{max} 230 mμ (ϵ 16,600); 267 (4150); 276 (4350); 306 (8700); 314–315 (7750).

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.96; H, 5.80; N, 13.72.

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

The Aromatization of Dihydroquinolines by Loss of the Elements of a Hydrocarbon[1]

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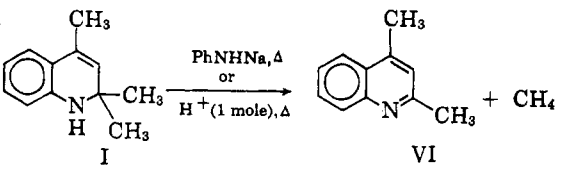
Received July 12, 1963

The aromatization of the hydrochloride of 2,2,4-trimethyl-1,2-dihydroquinoline has been carried out in solution and as the pure molten salt. In solution the reaction is initiated by *t*-butyl peroxide and catalyzed by β-naphthalenethiol. Eight quinoline products have been identified in the reaction without solvent. These products and the results in solution are consistent with the free-radical chain reaction mechanism proposed.

There exists a number of examples of reduced aromatic systems which are aromatized by loss of hydrogen and an alkyl group. One of the most familiar is the formation of Diels hydrocarbon involving the loss of two angular methyl groups from a steroid skeleton. Most of these aromatizations occur with reagents commonly associated with homolytic bond cleavage; however, there are examples of aromatizations of heteroaromatic systems which are subject to acid or base catalysis. Two reactions studied extensively by Elderfield are the loss of RH from a 2,2-disubstituted benzimidazoline or a 2,2-disubstituted benzothiazoline. Here no acid catalysis was observed, perhaps, as suggested by Elderfield, because these ring systems are unstable to acid. However, strong base catalysis has been observed in both reactions and a mechanism with a carbanion leaving group has been proposed.[2]

Another example is the Riehm quinoline synthesis.[3] Here a 1,2-dihydroquinoline intermediate must lose the elements R and H to give the quinoline product. This occurs under the acid conditions of the reaction mixture. If the 1,2-dihydroquinoline is isolated, the aromatization can be carried out in a separate step with acid or base catalysis. Thus, treatment of 2,2,4-trimethyl-1,2-dihydroquinoline (I) with sodium anilide yields 2,4-dimethylquinoline and methane.[4]

This paper reports the results of a study of the acid-catalyzed aromatization of I, one of several unusual reactions of I catalyzed by acid or base.[5,6]



Results

The aromatization of the hydrochloride of I was carried out by heating the pure salt above its melting point or by heating solutions of the hydrochloride of I in appropriate solvents. The hydrochloride of I was relatively soluble in aliphatic polyethers such as diethylene glycol diethyl ether, but the products of reaction in these solvents were complex and obviously involved solvent decomposition. Both diphenylmethane and diphenyl ether dissolved the hydrochloride of I near its melting point and were used as solvents for the aromatization.

Carefully purified hydrochloride of I heated in freshly distilled diphenylmethane or diphenyl ether to 250–260° gave less than 10% reaction after long heating. The gaseous products collected consisted of methane, hydrochloric acid, and, in the case of diphenyl ether, ethane. When 25 mole % of β-naphthalenethiol was added, the reaction at 250–260° proceeded to 83% completion in 1 hr. Reactions with the thiol at lower temperatures gave lower yields; at 160–170° less than

(1) This paper was presented at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963.

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