Metalation of 14H-Dibenzo[a,h]-, 7H-Dibenzo[c,h]-, and 14H-Dibenzo[a,c]phenothiazine with *n*-Butyllithium

DAVID A. SHIRLEY AND JOHN C. GILMER[1]

Department of Chemistry, The University of Tennessee, Knoxville, Tennessee

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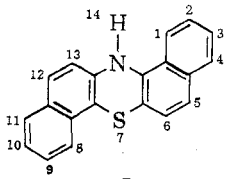
It has been demonstrated that use of *n*-butyllithium allows introduction of lithium into single positions adjacent to nitrogen in 14H-dibenzo[a,h]-, 7H-dibenzo[c,h]-, and 14H-dibenzo[a,c]phenothiazine. The metalation yields as shown by isolation of carboxylic acids subsequent to carbonation are in the range of 77–84%.

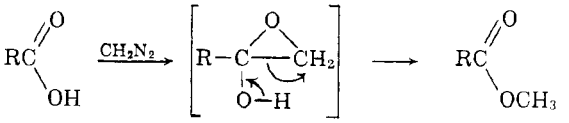
It is well established that the metalation reaction with alkyllithium reagents allows introduction of a lithium atom in a highly selective fashion into a wide variety of aromatic and heterocyclic ring systems.[2] In earlier work from this laboratory, the metalation reaction was carried out with the polynuclear heterocyclic systems benzo[a]phenothiazine[3] and benzo[c]phenothiazine.[4]

In connection with our current study of the chemistry of polynuclear derivatives of benzo- and dibenzophenothiazines and phenoxazines,[5] we have examined the metalation of three of the dibenzophenothiazines. The metalation of 14H-dibenzo[a,h]phenothiazine I provided an opportunity to compare the relative reactivities of the positions shown to be metalated preferentially in 12H-benzo[a]- and 7H-benzo[c]phenothiazine. Thus the 1-position of 14H-dibenzo[a,h]phenothiazine corresponds to the position of metalation of 12H-benzo[a]phenothiazine while the 13-position corresponds to the point of metalation of 7H-benzo[c]phenothiazine. The 1-position was found to be the site of monometalation (80% yield) of I. The carboxylic acid II formed by carbonation of the metalation product underwent a ready loss of water upon heating at about 200° to form the corresponding lactam III. The lactam III shows a carbonyl stretching band at 5.86 μ, while the carboxylic acid II shows a band at 6.01 μ. This shift to shorter wave length is expected for a carboxylic acid to lactam conversion, and also was observed in the carboxylic acid from the benzo[a]phenothiazine.[3] This observation, together with elemental analyses and other properties of the carboxylic acid and the lactam, provide adequate proof of structure for the carboxylic acid, and therefore, for the position of metalation of I.

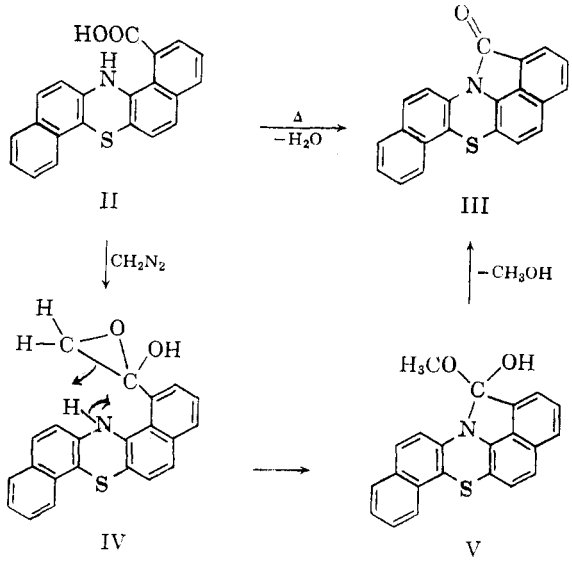


I

An unusual reaction was found to take place in an attempted conversion of II to the methyl ester with diazomethane. The lactam of the acid III rather than the ester was isolated from the reaction mixture. The same transformation was not effected in the ether–tetrahydrofuran reaction solvent in the absence of diazomethane. The mechanism of the reaction of diazomethane with carboxylic acids apparently has not been elucidated, but has been postulated to proceed as follows.[6]



If the cyclic intermediate shown above is applied to the dibenzophenothiazinecarboxylic acid case, it is possible to write an intermediate as shown in formula IV. It is seen in formula IV that the OH group and the NH group may compete for reaction with the three-membered ring. It is entirely probable that the NH bond lies in a more advantageous position, and therefore reacts preferentially as indi-



II III IV V

(1) Present address: Research Laboratories, Tennessee Eastman Company, Kingsport, Tenn.

(2) Henry Gilman and John W. Morton, Jr., "Organic Reactions," Vol. 8, Jonn Wiley & Sons, Inc., New York, N. Y., 1954, p. 258.

(3) D. A. Shirley and J. C. Liu, *J. Org. Chem.*, **25**, 1189 (1960).

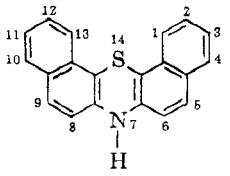
(4) D. A. Shirley and W. E. Tatum, *ibid.*, **25**, 2238 (1960).

(5) (a) K. Sen and D. A. Shirley, *ibid.*, **26**, 3861 (1961). (b) D. A. Shirley and W. E. Tatum, *J. Am. Chem. Soc.*, **81**, 496 (1959). (c) P. B. Talukdar and D. A. Shirley, *ibid.*, **80**, 3463 (1958).

(6) L. I. Smith, *Chem. Rev.*, **23**, 193 (1938).

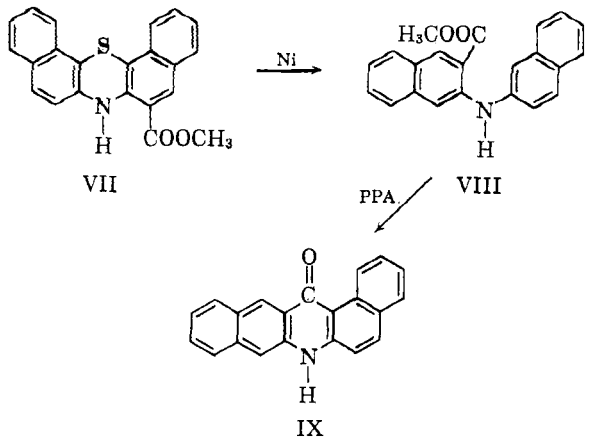
cated in IV. This would lead to the unstable intermediate V and by loss of methyl alcohol to the lactam product. We have been unable to find recorded in the literature any case of the conversion of an amino acid to the lactam through the use of diazomethane.

The metalation of 7H-dibenzo[c,h]phenothiazine (VI) occurred in the 6-position in 77% yield as indicated by the isolation of the corresponding monocarboxylic acid. The structure of the carboxylic



VI

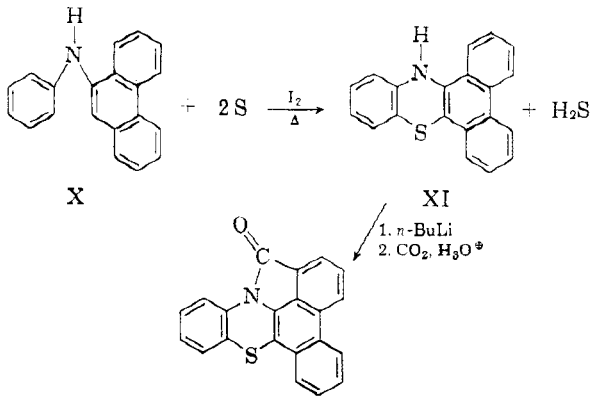
acid was proved by desulfurization of the corresponding methyl ester VII with Raney nickel in ethanol to form 3-carbomethoxy-2,2′-dinaphthylamine VIII. The desulfurization product was cyclized to dibenz[a,i]acridone IX with polyphosphoric acid.



VII VIII IX

The acridone IX is well characterized.[7,8]

14H-Dibenzo[a,c]phenothiazine XI is mentioned in the literature,[9] but there is no record of its synthesis or physical constants. We produced this compound in rather low yield (16%) by the thionation of N-phenyl-9-phenanthrylamine X. The metalation of XI with *n*-butyllithium followed by carbonation produced in 84% yield not the corresponding carboxylic acid but the lactam XII. The carboxylic acid apparently was present as the lithium salt in the aqueous extract of the reaction mixture; however, acidification of the solution precipitated the lactam. The structure of this product was indicated by characteristic infrared bands, elemental analyses, and the lack of solubility in dilute aqueous base.



X XI XII

These results point again to the high degree of position specificity shown by the metalation reaction. The yields of 77–84% in the metalation of single positions in the three dibenzophenothiazines is significant when the complexity of these polynuclear systems is considered. In each case, metalation occurred at a position adjacent to nitrogen.

Experimental[10]

Metalation of 14H-Dibenzo[a,h]phenothiazine.—Ten ml. of a hexane solution of *n*-butyllithium (0.015 mole) was added with stirring to a suspension of 1.50 g. of 14H-dibenzo[a,h]phenothiazine in 30 ml. of anhydrous ether under an atmosphere of dry nitrogen. Initially, a dark red solution was formed from which precipitated a red crystalline material. The mixture was refluxed for 5 hr., after which it was cooled in a solid carbon dioxide–acetone bath. An excess of crushed solid carbon dioxide was added, and the mixture was allowed to warm gradually to room temperature. The resulting yellow suspension was extracted several times with water. The combined aqueous extracts were washed with ether and then acidified. The maroon solid which precipitated was removed by filtration, washed with water, and dried. The yield of 1-carboxy-14H-dibenzo[a,h]phenothiazine was 1.38 g. (80%).

Anal. Calcd. for $C_{21}H_{13}NO_2S$: C, 73.50; H, 3.81; N, 4.07. Found: C, 73.23, 73.55; H, 4.06, 3.95; N, 4.26, 4.15.

The acid obtained above did not show a normal melting point, since it was converted to the corresponding lactam. A sample placed in the melting point block at temperatures above 170° melted after a short induction period and immediately resolidified to a bright red material. This material then melted with decomposition at about 265–267°, which is approximately the melting point of the lactam. The carboxylic acid was soluble in hot 10% aqueous sodium carbonate solution, but the lactam was insoluble.

Lactam of 1-Carboxy-14H-dibenzo[a,h]phenothiazine.—A procedure similar to the one used in the preparation of this compound was employed by Shirley and Liu[3] in the synthesis of the lactam of 1-carboxy-12H-benzo[a]phenothiazine. A sample of 0.37 g. (1.08 mmoles) of the acid obtained from the metalation of 14H-dibenzo-[a,h]phenothiazine was heated in a bath at a temperature of 190–210° for 8 min. Water vapor was evolved. The resulting solid

(7) E. Strohbach, *Ber.*, **34**, 4136 (1901).

(8) J. Cymerman-Craig and J. W. Loder, *J. Chem. Soc.*, 4309 (1955).

(9) A. Pacault, *Ann. chim.* [12] **1**, 527 (1946).

(10) Elementary microanalyses by Weiler and Strauss, Oxford, England. Melting points were determined on a "Mel-Temp" apparatus. Infrared spectra were determined on a Perkin–Elmer Infracord using the potassium bromide disk method.

was recrystallized from benzene to yield 0.25 g. (66%) of red-orange needles, m.p. 270–272°.

Anal. Calcd. for $C_{21}H_{12}NOS$: C, 77.55; H, 3.38; N, 4.30. Found: C, 77.32, 77.35; H, 3.46, 3.31; N, 4.22, 4.35.

Comparison of the infrared spectra of the acid and lactam revealed a shift in the carbonyl stretching band from 6.01 μ for the acid to 5.86 μ for the lactam. These band positions are expected for the structures assigned.[11]

Reaction of 1-Carboxy-14H-dibenzo[a,h]phenothiazine with Diazomethane.—In a mixture of 10 ml. of freshly distilled tetrahydrofuran and 10 ml. of anhydrous ether was dissolved (0.29 mmole) of 1-carboxy-14H-dibenzo[a,h]-phenothiazine. An ethereal solution of diazomethane prepared according to the procedures of DeBoer and Backer[12] was added and the mixture was allowed to evaporate. The red crystalline product, from which most of the solvent had evaporated, was slurried in a few ml. of ether, removed by filtration, and dried to yield 0.04 g. (42%) of the lactam, m.p. 269–271°. Recrystallization from benzene raised the melting point to 271–273°. A mixture of this compound and the lactam formed by heat treatment, as previously described, melted at 270–272°. The infrared spectra of the two samples were identical.

Repetition of the above experiment, except with the omission of diazomethane, resulted in the isolation of unchanged carboxylic acid.

Metalation of 7H-Dibenzo[c,h]phenothiazine.—Thirty-two ml. of a hexane solution of *n*-butyllithium (0.048 mole) was added in a period of 10 min. to a slurry of 6.00 g. (0.020 mole) of 7H-dibenzo[c,h]phenothiazine in 200 ml. of anhydrous ether. The resulting red suspension was stirred under reflux for 4.5 hr. The mixture was cooled in a solid carbon dioxide–acetone bath, then carbonated with excess crushed solid carbon dioxide, and allowed to warm gradually to room temperature. The lithium salt of the carboxylic acid was removed by extraction with water. The combined aqueous extracts were washed with ether and then acidified. The maroon precipitate was collected, washed with water, and dried. A yield of 5.27 g. (77%) of acid, m.p. 311–312° *in vacuo* and 297–303° at atmospheric pressure, was obtained. The infrared spectrum of the material revealed a carbonyl stretching band at 5.95 μ. Attempts to purify the acid further by recrystallization and by chromatography were unsuccessful.

Anal. Calcd. for $C_{21}H_{13}NO_2S$: C, 73.50; H, 3.81; N, 4.07. Found: C, 73.40, 73.39; H, 4.26, 4.01; N, 4.11, 4.00.

6-Carbomethoxy-7H-dibenzo[c,h]phenothiazine.—To a solution of diazomethane (*ca.* 0.05 mole) in 160 ml. of ether was added 2.30 g. (6.70 mmoles) of 6-carboxy-7H-dibenzo-[c,h]phenothiazine which was dissolved in 90 ml. of freshly distilled tetrahydrofuran. The dark red solution was placed under a hood overnight to allow the solvent and the excess diazomethane to evaporate. Ligroin (b.p. 66–75°) was added and the remainder of the ether and tetrahydrofuran was removed on the steam bath. The product was crystallized from ligroin to yield 2.14 g. (89%) of the bright orange ester, m.p. 178–181°.

Anal. Calcd. for $C_{22}H_{15}NO_2S$: C, 73.92; H, 4.23; N, 3.92. Found: C, 73.70, 73.93; H, 4.29, 4.19; N, 3.66, 3.64.

Desulfurization of 6-Carbomethoxy-7H-dibenzo[c,h]-phenothiazine with Raney Nickel.—Although a number of attempts to desulfurize the acid with Raney nickel were unsuccessful, it was found that the methyl ester reacted smoothly.

To a suspension of 1.73 g. (4.84 mmoles) of 6-carbomethoxy-7H-dibenzo[c,h]phenothiazine in 200 ml. of absolute ethanol was added 14 g. of freshly prepared Raney nickel catalyst.[13] The mixture was stirred under reflux for 2 hr. When an additional 6 g. of the catalyst was added to the hot mixture, the color was immediately changed from orange to yellow. The mixture was refluxed for another 2 hr., and from the filtered solution was obtained 1.04 g. (66%) of yellow needles, m.p. 122–123°.

Anal. Calcd. for $C_{22}H_{17}NO_2$: C, 80.70; H, 5.24; N, 4.27. Found: C, 80.66, 80.32; H, 5.16, 5.16; N, 4.10, 4.44.

Dibenz[a,i]acridone.—One-fourth of a gram (0.764 mmole) of 3-carbomethoxy-2,2′-dinaphthylamine from the desulfurization of 6-carbomethoxy-7H-dibenzo[c,h]phenothiazine was dissolved in 40 ml. of polyphosphoric acid with heating and stirring. The deep red solution was held at a temperature of 120–125° for 1.5 hr. Addition of the solution to water precipitated a brown solid which was removed by filtration and washed with water. A solution of the material in acetone was filtered, benzene was added to the filtrate, and the acetone was removed by evaporation. Then the benzene solution was chromatographed on a 1.5 × 25-cm. column of Florisil. The majority of the product was eluted with benzene in the first fraction. A 1:9 mixture of acetone and benzene eluted an additional small amount of the acridone. A yield of 0.132 g. (58%) of bright yellow-gold dibenz[a,i]acridone, m.p. 372–374°, crystallized from a mixture of ligroin (b.p. 100–115°) and benzene. Strohbach[7] reports a melting point greater than 300° and Cymerman-Craig and Loder[8] obtained golden red plates, m.p. 372°. The infrared spectrum is in accord with the acridone structure.

3-Carboxy-2,2′-dinaphthylamine.—A small sample of the methyl ester from the desulfurization of 6-carbomethoxy-7H-dibenzo[c,h]phenothiazine was dissolved in approximately 30 ml. of methanol. Three grams of sodium hydroxide was dissolved in the yellow solution and the resulting mixture was refluxed on the steam bath for 1.5 hr. Conventional work-up, involving one recrystallization from ligroin (b.p. 66–75°) and two recrystallizations from ether, gave bright yellow needles, m.p. 229–230°.

Anal. Calcd. for $C_{21}H_{15}NO_2$: C, 80.47; H, 4.82; N, 4.47. Found: C, 80.28, 80.07; H, 4.79, 4.79; N, 4.46.

Metalation of 14H-Dibenzo[a,c]phenothiazine.—To a suspension of 1.03 g. (3.44 mmoles) of 14H-dibenzo[a,c]-phenothiazine, m.p. 163–165°, in 70 ml. of anhydrous ether was added 7.40 ml. of a 1.60 molar hexane solution of *n*-butyllithium in a period of 5 min. A dark red suspension formed initially which, after the addition of the first 4.5 ml. (7.2 mmoles) of the solution of *n*-butyllithium, became bright orange-red. It was noted that after the mixture had been stirred for 21.5 hr. at room temperature the color again became dark red. The addition of 3.0 ml. of *n*-butyllithium (4.8 mmoles) solution produced the orange-red color once more. The solution then was stirred for 0.5 hr. after which it was cooled in a solid carbon dioxide–acetone bath and carbonated with excess crushed solid carbon dioxide. The yellow suspension was extracted several times with water. The aqueous extracts were combined, washed with ether and benzene, and acidified with 50% hydrochloric acid. The reddish brown precipitate was collected and washed with water. The crude yellow-brown product, m.p. 286–289°, amounted to 0.95 g. (85%). Two recrystallizations from benzene yielded gold needles, m.p. 289–290°.

Anal. Calcd. for $C_{21}H_{11}NOS$: C, 77.55; H, 3.38; N, 4.30. Found: C, 77.66, 77.73; H, 3.32, 3.60; N, 4.06, 4.24.

Comparison of the infrared spectra of the acids and lactams of 12H-benzo[a]- and 14H-dibenzo[a,h]phenothiazine with the spectrum of the product from the metalation of 14H-dibenzo[a,c]phenothiazine indicated that the lactam rather than the carboxylic acid was isolated. The elemental analysis confirmed the infrared evidence.

(11) L. F. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley & Sons, Inc. New York, N. Y., 1958.

(12) T. J. DeBoer and H. J. Backer, *Rec. trav. chim.*, **73**, 229 (1954).

(13) L. W. Covert and H. Adkins, *J. Am. Chem. Soc.*, **54**, 1641 1932).

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The Formation and Subsequent Rearrangement of 7-Chloro-5-phenyl-3,1,4-benzoxadiazepin-2(1H)-one

THEODORE S. SULKOWSKI AND SCOTT J. CHILDRESS

Research and Development Division, Wyeth Laboratories, Inc., Radnor, Pennsylvania

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2-Amino-5-chlorobenzophenone α-oxime has been converted into 7-chloro-5-phenyl-3,1,4-benzoxadiazepin-2(1H)-one (II) by the action of phosgene. 2-Amino-5-chlorobenzophenone β-oxime afforded 6-chloro-4-phenyl-2(1H)-quinazolinone 3-oxide (VII). Compound II underwent a Beckmann rearrangement at its melting point to give 6-chloro-3-phenyl-2,4-(1H,3H)-quinazolinedione (V).

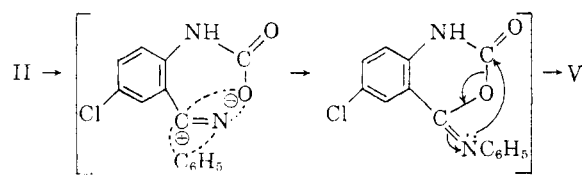
Compounds described in the literature as 3,1,4-benzoxadiazepines have been shown by Sternbach, Kaiser, and Reeder[1] to be quinazoline 3-oxides. Because 3,1,4-benzoxadiazepines have a structural similarity to 1,4-benzodiazepines in which we have been interested[2] we have prepared a 3,1,4-benzoxadiazepin-2-one and established its structure.

2-Amino-5-chlorobenzophenone α-oxime[3] (I) was treated with phosgene in benzene to afford 7-chloro-5-phenyl-3,1,4-benzoxadiazepin-3(1H)-one (II). Upon heating in ethanol II was converted into 2-carbethoxyamino-5-chlorobenzophenone α-oxime (III). In an attempt to obtain III alternatively from I and ethyl chloroformate, only 2-amino-5-chlorobenzophenone α-oxime, ethyl carbonate ester (IV), was obtained. Compounds III and IV could be distinguished by their infrared absorption spectra, the carbonyl stretching band of III appearing at 1735 cm.$^{-1}$ whereas that of IV appeared at 1769 cm.$^{-1}$. In addition IV showed the characteristic NH stretching absorptions of a primary amine (3350, 3435 cm.$^{-1}$).

Treatment of III with sodium hydroxide did not afford II, but returned unchanged III. Ried and Stahlhofen[4] reported the conversion of 2-carbethoxyaminobenzaldoxime into 3,1,4-benzoxadiazepin-2(1H)-one upon treatment with sodium hydroxide. Under the conditions employed by these authors II was actually converted into I.

The possibility that II was 6-chloro-4-phenyl-2-(1H)-quinazolinone 3-oxide (VII) could not be overlooked. The infrared absorption spectrum of II was not helpful, the carbonyl stretching band appearing at 1722 cm.$^{-1}$, a lower frequency than that of III or IV. The ultraviolet absorption spectrum of II had a peak at 315 mμ (ε 2,300) that might be attributable to the $C_6H_5—C(=N)—$ chromophore and was consistent with the spectrum of 7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one[2] which has a peak at 314 mμ (ε 2,300). Although structure II could have resulted only from the α-oxime, structure VII could form from either the α- or β-oxime.[5] Therefore, 2-amino-5-chlorobenzophenone β-oxime (VI) was treated with phosgene and a product differing from II was obtained. The carbonyl stretching frequency (1771 cm.$^{-1}$) indicated an activated carbonyl function. The formulation of this product as 6-chloro-4-phenyl-2(1H)-quinazolinone 3-oxide (VII) was confirmed by its deoxygenation to 6-chloro-4-phenyl-2(1H)-quinazolinone (VIII) by means of phosphorus trichloride. Compound VIII was prepared for comparison by fusing 2-amino-5-chlorobenzophenone with urea. The ultraviolet absorption spectrum of VII did not show a peak at 315 mμ thus differing from that of II.

Compound II was observed to resolidify just above its melting point. It was found that a rearrangement had taken place at the original melting point to give 6-chloro-3-phenyl-2,4-(1H,-3H)-quinazolinedione (V). This product was also obtained on heating III or IV above their melting points. The structure of V was established by an alternative preparation from 5-chloroanthranilic acid and phenylisocyanate. Compound V appears to be formed from II in a Beckmann rearrangement[6] with subsequent O → N migration of the carbonyl group.



(1) L. H. Sternbach, S. Kaiser, and E. Reeder, *J. Am. Chem. Soc.*, **82**, 475 (1960).

(2) S. C. Bell, T. S. Sulkowski, C. Gochman, and S. J. Childress, *J. Org. Chem.*, **27**, 562 (1962).

(3) The α-oxime is *syn* to the substituted phenyl.

(4) W. Ried and P. Stahlhofen, *Chem. Ber.*, **87**, 1814 (1954).

(5) 6-Chloro-2-methyl-4-phenylquinazoline 3-oxide has been formed from the α- or β-oxime of 2-amino-5-chlorobenzophenone by treatment with acetyl chloride (ref. 1).

(6) An analogous reaction has been observed in the formation of N-phenylphthalimide from 4-phenyl-1H-2,3-benzoxaxin-1-one. F. H. Thorp, *Ber.*, **26**, 1261, 1795 (1893).

(7) K. Dziewonski and L. Sternbach, *Bull. intern. acad. polonaise, Classe sci. math. nat.*, **1935A**, 333; *Chem. Abstr.*, **30**, 2971 (1936).