Preparation of Condensing Agents. (a) **Phenylsodium.**—The procedure which was used for preparing phenylsodium was modeled after that described by Nobis and Moormeier.[19] Approximately 75 ml. of thiophene-free benzene and 0.23 mole of sodium dispersion, for each 0.1 mole of phenylsodium to be prepared, are introduced into the reactor. Then 2–3 ml. of a solution of bromobenzene (0.1 mole, 15.7 g.) in an equal volume of thiophene-free benzene was added followed by the addition of 1 ml. of a 10% solution of *t*-amyl alcohol in benzene maintaining the reaction temperature at 30°. More of the *t*-amyl alcohol–benzene solution was added every minute or two until the reaction between the bromobenzene and sodium was well started as indicated by a rise in temperature and a change in color of the reaction mixture from gray to black. The rest of the bromobenzene solution was added slowly and the reaction temperature was maintained at 30° using a cooling bath when necessary. The suspension of phenylsodium is stirred for 30 minutes after the addition of the bromobenzene is complete. The contents of the reactor are blanketed in a nitrogen atmosphere throughout the preparation of the sodium dispersion and its conversion to phenylsodium. The yield of phenylsodium, based on carbonation to benzoic acid, is greater than 95% of theory.

(b) **Sodium Diisopropylamide.**—Diisopropylamine (one equivalent), diluted with an equal volume of benzene, is added to the suspension of phenylsodium (one equivalent) at 5°. The mixture is stirred for an additional period of one hour and is then ready to be used. The conversion of diisopropylamine to sodium diisopropylamide is assumed to be quantitative.

(c) **Lithium Diisopropylamide.**—This condensing agent was prepared as described previously.[20] The procedure which was used in the one acylation (Table II) which was effected employing this base was the same as that involving the acylation of 2-picoline with esters using phenyllithium[6] as the condensing agent except that the phenyllithium was replaced by lithium diisopropylamide.

General Procedure for the Acylation of 3-Picoline, 4-Picoline and Their Derivatives Using Sodium Diisopropylamide as the Condensing Agent.—Two equivalents of the pyridine derivative, diluted with an equal volume of benzene, were added to two equivalents of a suspension of sodium diisopropylamide in benzene at 5° and the mixture was stirred for 30 minutes at 5°. One equivalent of the acylating ester, diluted with an equal volume of benzene, was then added and the mixture was stirred at 5° for an additional one-hour period. The mixture was then poured onto ice and filtered if any solid was present. It was then made strongly acidic with concentrated hydrochloric acid and was extracted with several portions of benzene to remove any unreacted ester. The aqueous phase was made basic with aqueous 20% sodium hydroxide solution and was extracted with several portions of ether or chloroform. The combined basic extracts were dried over anhydrous sodium sulfate, the solvents were removed by distillation at atmospheric pressure and the residue was fractionated in vacuum.

In those reactions which were effected using phenylsodium as the condensing agent, the procedure employed was the same as that described above except that phenylsodium was used in place of sodium diisopropylamide.

Alkylation of 4-Picoline and 4-Benzylpyridine with β-Dimethylaminoethyl Chloride Using Sodium Diisopropylamide as the Condensing Agent.—The procedure employed for these alkylations was the same as that described above for the acylations except that the esters were replaced by β-dimethylaminoethyl chloride and a 1:1:1 molar ratio of 4-picoline: or 4-benzylpyridine:sodium diisopropylamide:β-dimethylaminoethyl chloride was used. Thus, from the interaction of 0.5 mole each of 4-picoline, sodium diisopropylamide and β-dimethylaminoethyl chloride there was obtained 65.4 g. (80%) of 1-(4-pyridyl)-3-dimethylaminopropane, b.p. 80.0–80.5° at 1.59 mm. *Anal.* Calcd. for $C_{10}H_{16}N_2$: C, 73.12; H, 9.82. Found: C, 73.56; H, 10.40. This compound forms a dipicrate, m.p. 188.2–188.8° (from 95% ethanol). *Anal.* Calcd. for $C_{22}H_{22}N_8O_{14}$: C, 42.45; H, 3.56. Found: C, 42.45; H, 3.93.

From a similar experiment in which 0.2 mole each of 4-benzylpyridine, β-dimethylaminoethyl chloride and sodium diisopropylamide were used, there was isolated 42.2 g. (88%) of 1-phenyl-1-(4-pyridyl)-3-dimethylaminopropane, b.p. 144–146° at 1.0 mm.[15]

PITTSBURGH 13, PENNA.

(19) J. F. Nobis and L. F. Moormeier, *Ind. Eng. Chem.*, **46**, 539 (1954).

(20) M. Hamell and R. Levine, *J. Org. Chem.*, **15**, 162 (1950).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF HOFFMANN–LA ROCHE INC.]

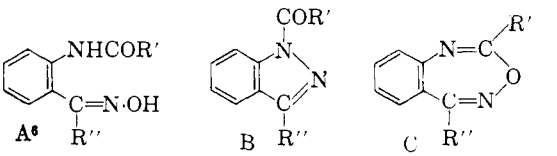
Quinazoline 3-Oxide Structure of Compounds Previously Described in the Literature as 3.1.4-Benzoxadiazepines[1]

BY L. H. STERNBACH, S. KAISER AND E. REEDER

RECEIVED MAY 18, 1959

It has been shown that the compounds formed by the dehydration of *o*-acylaminobenzophenone oximes (I and XII) with a Beckmann mixture are quinazoline 3-oxides (II and XIII) and not, as formerly postulated, 3.1.4-benzoxadiazepines (C).[1]

A study has been made on the structure of compounds described in the literature as 3.1.4-benzoxadiazepines.[1] These heterocycles are obtained by dehydration of *o*-acylaminoaldoximes or ketoximes (A) with a Beckmann mixture. Auwers and F. v. Meyenburg[2] who had discovered and studied this reaction, initially considered these compounds to be acylindazoles (B). Later Bischler[3] postulated the structure C, which was accepted by other investigators[4] as well as by Auwers.[5] Ried and Stahlhofen[7] made the interesting observation that compounds of this type, on hydrogenation with a Raney nickel catalyst, absorb two moles of hydrogen and yield dihydroquinazolines. They postulated that the reaction proceeded *via* the intermediate D which lost the elements of water to form the dihydroquinazoline, and considered this result an additional proof for the seven-membered ring present in their starting material.



A[6] B C

(1) In the German literature these compounds are known as 4,5-benzo-[hept-1,2,6-oxdiazines].

(2) K. Auwers and F. von Meyenburg, *Ber.*, **24**, 2370 (1891).

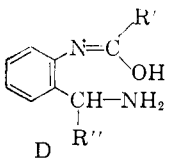
(3) Aug. Bischler, *ibid.*, **26**, 1891, 1901 (1893).

(4) J. Meisenheimer and A. Diedrich, *ibid.*, **57**, 1715 (1924).

(5) K. von Auwers, *ibid.*, **57**, 1723 (1924).

(6) The structures discussed or described in the literature are marked with capital letters; compounds prepared in the course of this study with Roman numerals.

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



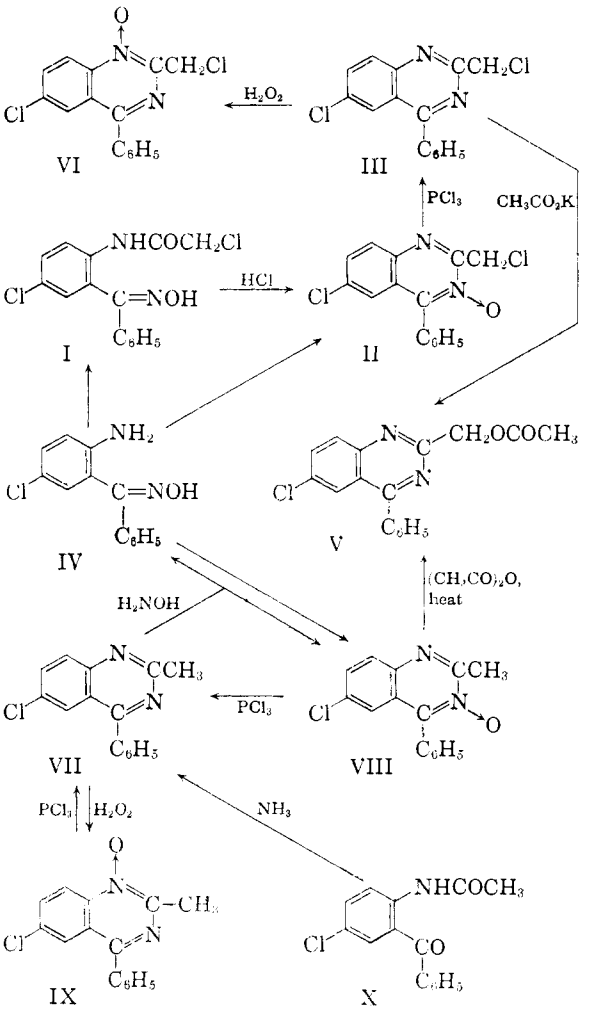
D

Our study of compounds belonging to this group led us to question this structure. We came to the conclusion that the compounds described in the literature as 3.1.4-benzoxadiazepines were in fact quinazoline 3-oxides, and proved this as shown below.

We treated 2-amino-4-chlorobenzophenone[8] in the customary way with hydroxylamine hydrochloride and obtained a mixture of the α- and β-oximes (IV).[9] Both yielded on treatment with an excess of acetyl chloride the expected dehydration product for which we postulated the quinazoline 3-oxide (VIII) structure.

The formation of quinazoline 3-oxides under the reaction conditions seemed quite reasonable since similar cyclizations of oximes to N-oxides are described in the literature.[10] The infrared spectrum was also consistent with such a structure since this compound and analogs discussed in this paper showed a strong band in the 1318–1290 cm.$^{-1}$ [11]) region which could be attributed to N–O stretching.

For the final structural proof, we used two reactions which are characteristic for N-oxides. One reaction is the reduction of N-oxides to the corresponding tertiary bases by treatment with phosphorus trichloride.[12] Another reaction typical for N-oxides is the conversion of compounds such as α-picoline N-oxide into α-acetoxymethylpyridine on treatment with acetic anhydride.[13]



Compound VIII was treated with phosphorus trichloride and gave an almost quantitative yield of the quinazoline VII[14] which was identical with the compound synthesized in the classical way (X → VII).[15] Secondly, when the quinazoline N-oxide was treated with acetic anhydride, it yielded as expected[13] the acetoxy derivative V (50% yield) whose structure was proved by the reaction sequence I → II → III → V.

Attempts to reoxidize the quinazolines III and VII to the 3-oxides did not give the desired results as the 1-oxides VI and IX were formed instead.[16] The N-oxide structure of these compounds was proved by the reconversion of one of them (IX) into the corresponding tertiary base VII by treatment with phosphorus trichloride.

(8) F. D. Chattaway, *J. Chem. Soc.*, **85**, 344 (1904); K. Dziewoński and L. H. Sternbach, *Bull. intern. acad. Polonaise, Classe Sc. math. nat. Ser. A*, 333–348 (1935); *C. A.*, **30**, 2972[1] (1936).

(9) In order to determine the configuration, we prepared the two known *o*-aminobenzophenone oximes and compared their infrared spectra in chloroform solution (1–5%) with those of our oximes. K. Auwers and F. v. Meyenburg (*Ber.*, **24**, 2370, 2383, 2385 (1891)) have described the two aminobenzophenone oximes, and Meyenburg (*ibid.*, **26**, 1657 (1893)) established, for the higher melting isomer, the *syn*-structure (oxime hydroxyl in *syn* position to the substituted benzene nucleus). According to the more recent nomenclature (see K. Freudenberg, "Stereochemie," Franz Deuticke, Leipzig, Wien, 1933, p. 1023) the higher melting oxime is called α, the lower melting, β. The 3550–3200 cm.$^{-1}$ region of the infrared spectrum gave the most valuable information. Both the α- and β-*o*-aminobenzophenone oximes had sharp free OH stretching bands at 3550 and 3530 cm.$^{-1}$, respectively; the α-isomer showed in addition a broad absorption band between 3400 and 3200 cm.$^{-1}$ due to hydrogen bonding, the β-isomer, two distinct bands at 3450 and 3300 cm.$^{-1}$. This difference between the two forms was also observed in the oximes described in this paper. The spectra of the higher melting α-forms showed hydrogen bonding in the 3400–3150 cm.$^{-1}$ region; the β-forms, two distinct maxima at 3450–3400 cm.$^{-1}$ and at 3300–3210 cm.$^{-1}$. H. Palm and H. Werbin (*Can. J. Chem.*, **31**, 1004 (1953)) have studied the infrared spectra of α- and β-aldoximes and also found some characteristic differences in the same region.

(10) See, for example, A. F. Katritzky, *Quart. Revs.*, **10**, 395, 397 (1956); W. v. E. Doering and J. A. Berson, THIS JOURNAL, **72**, 1118 (1950); E. Schmitz, *Angew. Chem.*, **69**, 728 (1957).

(11) R. H. Wiley and S. C. Slaymaker (THIS JOURNAL, **79**, 2233 (1957)) who studied the infrared spectra of some pyridine and pyrimidine N-oxides assign a strong band in the 1300–1255 cm.$^{-1}$ region to the N–O stretching frequency.

(12) E. Ochiai, *J. Org. Chem.*, **18**, 354 (1953).

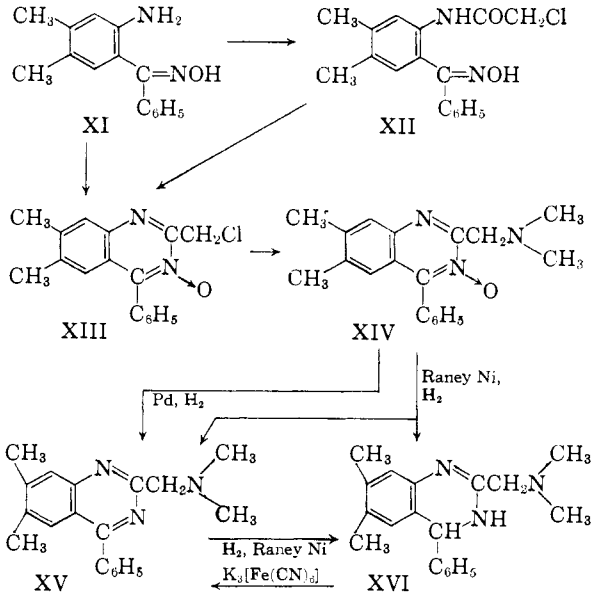
(13) V. Boekelheide and W. J. Linn, THIS JOURNAL, **76**, 1286 (1954); O. H. Bullitt, Jr., and J. T. Maynard, *ibid.*, **76**, 1370 (1954); V. J. Traynelis and R. F. Martello, *ibid.*, **80**, 6590 (1958).

(14) The oxygen could also be removed by hydrogenation in the presence of a palladium catalyst. This reaction, however, gave a lower yield since dehalogenation occurred as a side reaction.

(15) All the 4-phenylquinazolines studied by us showed very strong infrared absorption bands in the 1543–1539 and in the 1482–1472 cm.$^{-1}$ region. H. Culbertson, J. C. Decius and B. E. Christenson (THIS JOURNAL, **74**, 4834 (1952)) have studied the infrared spectra of some quinazoline derivatives. They found three characteristic bands and called them quinazoline bands I (1517–1478 cm.$^{-1}$), II (1588–1566 cm.$^{-1}$) and III (1628–1612 cm.$^{-1}$). The quinazolines studied by us did not show these bands.

(16) This is, as far as we know, the first time that a quinazoline has been oxidized to a quinazoline N-oxide. The infrared spectra of these two 1-N-oxides are similar. The oxide IX has the strongest band at 1300 cm.$^{-1}$, VI, a very strong doublet at 1319, 1306 cm.$^{-1}$.[11]

Another series of experiments was carried out with 2-amino-4,5-dimethylbenzophenone[17] as starting material. It was treated with hydroxylamine and yielded a mixture of the α- and β-oximes (XI).[9] The former was treated with one mole of chloroacetyl chloride to yield the chloroacetamide XII, which on treatment with hydrogen chloride[18] lost the elements of water and formed the 6,7-dimethyl-2-chloromethyl-4-phenylquinazoline 3-oxide (XIII). In the hope of obtaining biologically active products, we converted the compound into the corresponding dimethylamino derivative XIV[19] and studied its hydrogenation. The chart below which is self-explanatory shows the results.



The hydrogenation of XIV to XV confirms the quinazoline 3-oxide structure of XIV. The structure of XV was proved by the similarity of its infrared spectrum with the one of the quinazoline VII. The hydrogenation of XV to XVI and the reoxidation of XVI to XV establishes the relationship of these two compounds.

While our studies were in progress, three Japanese papers were published[20] on the reaction of quinazoline and 4-methylquinazoline with hydroxylamine.[21] The author obtained compounds to which he ascribes the structure of quinazoline-3-oxides.[22] He proved the structure by reduction to the corresponding quinazolines with iron and ferrous sulfate or phosphorus trichloride. It seemed very probable that the compounds described by Adachi were identical in their structure with the ones formerly called [3.1.4.]benzoxadiazepines, and with our quinazoline 3-oxides. Since a direct comparison was not possible, we treated one of our quinazolines (VII) with hydroxylamine and obtained, as expected, the quinazoline-3-oxide VIII and the oxime IV. These experiments prove that Adachi's compounds belong to the group of compounds formerly described as 3.1.4-benzoxadiazepines and are quinazoline 3-oxides as he correctly postulated.

Acknowledgment.—We are indebted to Dr. A. Motchane, S. Traiman and Dr. V. Toome for the infrared and ultraviolet spectra and to Dr. Al Steyermark and his staff for the microanalyses.

Experimental

All melting points are corrected. The infrared and ultraviolet absorption spectra of starting materials and reaction products were compared whenever necessary in order to establish whether structural changes had occurred. The infrared spectra were determined in 1–5% chloroform solutions using a Perkin-Elmer model 21 spectrophotometer, the ultraviolet absorption spectra in isopropyl alcohol and in 0.1 *N* hydrochloric acid.

2-Amino-5-chlorobenzophenone α- and β-Oximes (IV).—A mixture of 200 g. of 2-amino-5-chlorobenzophenone,[8] 100 g. of hydroxylamine hydrochloride and 1 l. of alcohol was stirred and refluxed for 22 hours. The mixture was concentrated *in vacuo* to a small volume, diluted with water and neutralized with sodium carbonate. Benzene was then added, and the stirring was continued for several hours until a considerable amount of crystalline precipitate had formed. Some petroleum ether was added, and the mixture was filtered. The crude α-oxime (139 g., m.p. 150–160°) remaining on the funnel was washed with a mixture of benzene and petroleum ether. After recrystallization from a mixture of ether and petroleum ether, it forms colorless prisms melting at 164–167°. The infrared spectrum[9] ($CHCl_3$, 1.6%) shows a sharp peak (m) at 3500 cm.$^{-1}$ and a broad band (X) at 3330–3180 cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{11}ON_2Cl$: C, 63.29; H, 4.49. Found: C, 62.80; H, 4.81.

The aqueous layer of the filtrate was separated and discarded. The organic solution was dried, concentrated *in vacuo*, and the residue was taken up in ether. The ether solution was filtered, diluted with petroleum ether and kept at 0° for 20 hours. The precipitated crystals, a mixture of the α- and β-isomers (42 g., m.p. 119–122°), were filtered off. A third crop of crystals was obtained from the mother liquors after concentration to a sirup. It consisted of 8 g. of prisms melting at 127–130°. This product was recrystallized for analysis from a mixture of ether and petroleum ether. The pure β-oxime thus obtained forms prisms melting at 129–132°. The infrared spectrum ($CHCl_3$, 5%) has three peaks (m) at 3500, 3400 and 3210 cm.$^{-1}$. The total yield of 189 g. (α- and β-oximes) corresponds to 89%.

Anal. Calcd. for $C_{13}H_{11}ON_2Cl$: C, 63.29; H, 4.49. Found: C, 63.27; H, 4.71.

2-Methyl-4-phenyl-6-chloro-quinazoline 3-Oxide (VIII).—To a solution of 49.3 g. (0.2 mole) of 2-amino-5-chlorobenzophenone α-oxime in 350 cc. of glacial acetic acid was added 47.1 g. (0.6 mole) of acetyl chloride. The mixture was then heated for a short time to dissolve the formed precipitate and then left at room temperature for 15 hours. The precipitated crystals of the hydrochloride of the reaction product (37 g., m.p. 128–131°) were filtered off, and the mother liquors were concentrated *in vacuo*. The concentrate was dissolved in methylene chloride, combined with the crystalline hydrochloride, and the mixture was then shaken with an excess of an ice-cold sodium carbonate solution. The methylene chloride solution containing the free quinazoline oxide was separated from the alkaline aqueous layer, dried and concentrated *in vacuo*. The residue was crystallized from acetone and yielded 42 g. (78%) of yellowish needles melting at 157–158°.

Anal. Calcd. for $C_{15}H_{11}N_2OCl$: C, 66.55; H, 4.10; N, 10.35. Found: C, 66.85; H, 3.88; N, 10.77.

2-Methyl-4-phenyl-6-chloroquinazoline (VII). (A) From the Quinazoline 3-Oxide (VIII).—A solution of 10.8 g.

(17) G. Kränzlein and Th. Meissner, *Frdl.*, **23**, 234 (1936); German Patent 630.021 (1936).

(18) The same compound was obtained in one step by treating a mixture of the α- and β-oximes (XI) with two moles of chloroacetyl chloride in acetic acid, a method which we found very practical and used in subsequent cases.

(19) The reaction with dimethylamine occurred without change in molecular structure, as was established by the similarity of the infrared and the ultraviolet spectra of XIII and XIV.

(20) Kikuo Adachi, *Yakugaku Zasshi*, **77**, 507, 510, 514 (1957); *C. A.*, **51**, 14744i–14746c (1957).

(21) NOTE ADDED IN PROOF.—See also Kikuo Adachi, *Chem. and Pharm. Bull. (Tokyo)*, **7**, 479 (1959).

(22) Quinazoline yielded in addition also o-aminobenzaldehyde oxime.

(40 millimoles) of 2-methyl-4-phenyl-6-chloroquinazoline 3-oxide (VIII) and 20 cc. of phosphorus trichloride in 150 cc. of chloroform was refluxed for 1 hour, cooled, and decomposed with ice and an excess of sodium hydroxide solution. The organic layer was separated, dried and concentrated *in vacuo*. The residue was dissolved in hot petroleum ether, a small amount of suspended impurities was filtered off, and the solution was concentrated at atmospheric pressure to a small volume and cooled. The reaction product precipitated in fine needles melting at 104–105°. The yield was 9.3 g. or 92%. After recrystallization from petroleum ether, the product forms fine, white needles melting at 105–106°.

Anal. Calcd. for $C_{15}H_{11}N_2Cl$: C, 70.73; H, 4.35. Found: C, 70.79; H, 4.13.

The same product was formed on catalytic hydrogenation of the quinazoline 3-oxide in methanol with a Lindlar palladium catalyst[23] at atmospheric pressure. The yield was *ca.* 40%.

(B) **From 2-Acetamino-5-chlorobenzophenone[8] (X).**—A mixture of 3 g. of 2-acetamino-5-chlorobenzophenone and 13 cc. of 9% alcoholic ammonia was heated in a closed tube for 5 hours at 160°. The reaction product crystallized after cooling and was dissolved by the addition of ether. The solution was concentrated *in vacuo*, and the residue crystallized from petroleum ether. The yield was 2.2 g. of material melting at 105–106° which was identical with the product obtained according to procedure A.

2-Acetoxymethyl-4-phenyl-6-chloroquinazoline (V) from 2-Methyl-4-phenyl-6-chloroquinazoline 3-Oxide (VIII).—A solution of 2 g. of 2-methyl-4-phenyl-6-chloroquinazoline 3-oxide (VIII) in 50 cc. of acetic anhydride was heated on the steam-bath for 3 hours, then concentrated *in vacuo*. The residue was dissolved in methylene chloride and the organic solution washed with alkali, dried and concentrated *in vacuo*. The residual sirup (1.9 g.) was dissolved in absolute ether and adsorbed on a chromatographic column (3 cm. inner diameter) prepared with 150 g. of activated alumina and absolute ether. The elution was carried out with ether. Fractions of 50 cc. each were collected: fraction one: 0.15 g. of impure material; fraction two: 0.70 g. of reaction product; fraction three: no residue; fraction 4 + 5: 0.88 g. of starting material. Fractions 4 and 5 were identified with the starting material by melting and mixed melting points and analysis. Fraction 2 was recrystallized from petroleum ether. The product (V) formed colorless plates melting at 116–117°, and was found to be identical with the compound prepared from 2-chloromethyl-4-phenyl-6-chloroquinazoline (III) as described herein. The yield was over 50% taking into account the recovered starting material.

Anal. Calcd. for $C_{17}H_{13}N_2O_2Cl$: C, 65.28; H, 4.19. Found: C, 65.31; H, 4.30.

2-Chloroacetamido-5-chlorobenzophenone Oxime (I).—Into a stirred, cooled (10–15°) solution of 24.6 g. (0.1 mole) of 2-amino-5-chlorobenzophenone α-oxime in 150 cc. of dioxane, were introduced in small portions 12.4 g. (0.11 mole) of chloroacetyl chloride and the corresponding amount of 3 *N* sodium hydroxide. The introduction was carried out at such a rate as to keep the temperature below 15° and the mixture neutral or slightly alkaline. The reaction was finished after 30 minutes; the mixture was acidified to *p*H 5, diluted with water and extracted with ether. The ether extract was dried, concentrated *in vacuo* and the oily residue was crystallized by the addition of ether. The yield was 24.5 g. (76%). The product forms colorless plates melting at 171–172°.

Anal. Calcd. for $C_{15}H_{12}N_2O_2Cl_2$: C, 55.74; H, 3.74. Found: C, 55.48; H, 3.87.

2-Chloromethyl-4-phenyl-6-chloroquinazoline 3-Oxide (II). (A) From 2-Amino-5-chlorobenzophenone Oxime (IV).—To a warm (50°) solution of 172.5 g. (0.7 mole) of the α-oxime[24] of 2-amino-5-chlorobenzophenone in 1 l. of glacial acetic acid was added 110 cc. (1.47 moles) of chloroacetyl chloride. The mixture was heated for 10 minutes to 50° and then stirred at room temperature for 15 hours. The precipitated yellow prisms (130 g.) were then filtered off. The product is the hydrochloride of the reaction product and melts with decomposition at 128–150°.[25]

(23) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).

(24) The β-oxime gives the same result.

Anal. Calcd. for $C_{15}H_{11}N_2OCl_3$: C, 52.73; H, 3.25; Cl, 31.14. Found: C, 52.91; H, 2.84; Cl, 30.63.

The acetic acid mother liquors containing the rest of the reaction product were concentrated *in vacuo*. The residue was dissolved in methylene chloride and washed with ice-cold sodium carbonate solution. The organic solution was dried, concentrated *in vacuo* to a small volume and diluted with ether and petroleum ether to yield 79 g. of fine yellow needles of the reaction product. The total yield (hydrochloride + base) was 91%. The pure base crystallizes from a mixture of methylene chloride, ether and petroleum ether in fine yellow needles melting at 133–134°.

Anal. Calcd. for $C_{15}H_{10}N_2OCl_2$: C, 59.03; H, 3.30. Found: C, 58.75; H, 3.49.

In similar reactions 2-chloroacetamido-5-chlorobenzophenone oxime was sometimes isolated as by-product.

(B) **From 2-Chloroacetamido-5-chlorobenzophenone Oxime (I).**—A solution of 1 g. of I in 25 cc. of acetic acid was saturated with hydrogen chloride gas. The mixture warmed up to about 60°, was then left at room temperature for 16 hours and concentrated *in vacuo*. The residue consisted of the chemically pure compound, formed in almost quantitative yield.

2-Chloromethyl-4-phenyl-6-chloroquinazoline (III).—A solution of 40 g. of 2-chloromethyl-4-phenyl-6-chloroquinazoline 3-oxide (II) and 76 cc. of phosphorus trichloride in 600 cc. of chloroform was refluxed for 1 hour. The solution was cooled and decomposed with ice and an excess of sodium carbonate solution. The organic layer was separated, dried with sodium sulfate and concentrated *in vacuo*. The residue was dissolved in a large amount of ether; some impurities were filtered off, and the solution was partly concentrated *in vacuo*. The product crystallized in rosettes of colorless needles melting at 125–126°. The yield was 27.7 g. (73%). The pure product melts after recrystallization from petroleum ether at 126–127°.

Anal. Calcd. for $C_{15}H_{10}N_2Cl_2$: C, 62.30; H, 3.49. Found: C, 62.17; H, 3.50.

2-Acetoxymethyl-4-phenyl-6-chloroquinazoline (V) from 2-chloromethyl-4-phenyl-6-chloroquinazoline (III).—A solution of 2 g. of 2-chloromethyl-4-phenyl-6-chloroquinazoline and 8 g. of potassium acetate in 50 cc. of glacial acetic acid was refluxed for 16 hours and then concentrated *in vacuo*. The residue was dissolved in methylene chloride, the solution was washed with an excess of ice-cold sodium carbonate solution, dried and concentrated *in vacuo*. Extraction with boiling petroleum ether and concentration of the resulting solution to a small volume yielded the reaction product crystallizing in plates melting at 116–117°. It was identical with the product described (*vide infra*).

Anal. Calcd. for $C_{17}H_{13}N_2O_2Cl$: C, 65.28; H, 4.19. Found: C, 64.86; H, 4.04.

Treatment of 2-Methyl-4-phenyl-6-chloroquinazoline (VII) with Hydroxylamine. Isolation of 2-Methyl-4-phenyl-6-chloroquinazoline 3-Oxide (VIII) and 2-Amino-5-chlorobenzophenone α-Oxime (IV).—A mixture of 3.6 g. of 2-methyl-4-phenyl-6-chloroquinazoline, 3.6 g. of hydroxylamine hydrochloride, 9 cc. of pyridine and 75 cc. of alcohol was refluxed for 16 hours, cooled, diluted with ice, acidified to *p*H 5 with hydrochloric acid and extracted with methylene chloride. The organic layer was dried and concentrated *in vacuo*. The residue (3.2 g.) was dissolved in 40 cc. of methylene chloride and adsorbed on a chromatographic column (3-cm. inner diameter) prepared with 80 g. of activated alumina and methylene chloride. The products were eluted with methylene chloride followed by methylene chloride containing 10% methanol, and gave the results

Fraction	Eluent	Vol., cc.	Wt., g.	
I	CH_2Cl_2	150	1.0	"Quinazoline 3-oxide" (VIII)
II	CH_2Cl_2	250	0.3	Mixture, but mostly VIII
III	CH_2Cl_2	900	0.4	Yellow prisms
IV	CH_2Bl_2 + 10% CH_3OH	250	0.6	Oxime IV

(25) The salt is unstable in the presence of water. It can be used as such for further reactions, or after conversion into the base, which is done by treatment in aqueous suspension with sodium carbonate and extraction into methylene chloride.

Fraction I: The material was identified with an original sample of 2-methyl-4-phenyl-6-chloroquinazoline 3-oxide by melting point, mixed melting point and infrared spectrum. Fraction III: The product crystallized from a mixture of methylene chloride, acetone and petroleum ether in yellow prisms and had a melting point of 211–212°. The structure of this compound has not yet been investigated.

Anal. Calcd. for $C_{15}H_{13}N_2OCl$: C, 66.06; H, 4.80; N, 10.27; Cl, 13.00. Found: C, 65.14, 66.13; H, 5.13, 5.49; N, 9.54; Cl, 12.85, 12.61.

Fraction V: The material was identified with an original sample of the α-oxime of 2-amino-4-chlorobenzophenone by melting point, mixed melting point, analysis and infrared spectrum.

2-Methyl-4-phenyl-6-chloroquinazoline 1-Oxide (IX) and its Reconversion into 2-Methyl-4-phenyl-6-chloroquinazoline (VII).—A solution of 2.5 g. (10 millimoles) of 2-methyl-4-phenyl-6-chloroquinazoline (VII) and 1.2 cc. (10 millimoles of H_2O_2) of 30% hydrogen peroxide in 15 cc. of acetic acid was heated on the steam-bath for 10 hours. After the third and seventh hour an additional 0.6 cc. (5 millimoles of H_2O_2) of 30% hydrogen peroxide were added. After 10 hours the mixture was concentrated *in vacuo* to a small volume, diluted with methylene chloride and washed with an excess of ice-cold sodium carbonate solution. The organic layer was dried, concentrated *in vacuo* and the residue recrystallized from acetone. The yield was 1.4 g. The product forms long orange prisms or yellow rhombic prisms, both forms melting at 156°. The strongest band in its infrared spectrum is at 1300 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{11}N_2OCl$: C, 66.55; H, 4.10. Found: C, 66.70; H, 4.06.

Removal of Oxygen.—A solution of 0.3 g. of 2-methyl-4-phenyl-6-chloroquinazoline 1-oxide (IX) and 0.6 cc. of phosphorus trichloride in 4.5 cc. of chloroform was refluxed for 1 hour, diluted with methylene chloride and then treated with ice and an excess of sodium carbonate solution. The alkaline aqueous part was discarded, the methylene chloride solution dried, concentrated *in vacuo*, and the residue crystallized from petroleum ether. The yield was 0.14 g. of fine needles melting at 105–106°. The product was identical with an original sample of 2-methyl-4-phenyl-6-chloroquinazoline as proven by mixed melting point and infrared spectrum.

2-Chloromethyl-4-phenyl-6-chloroquinazoline 1-Oxide (VI).—A solution of 2.9 g. (10 millimoles) of 2-chloromethyl-4-phenyl-6-chloroquinazoline and 0.6 cc. (5 millimoles of H_2O_2) of 30% hydrogen peroxide in 15 cc. of acetic acid was heated on the steam-bath. After the second, fourth and sixth hour, an additional 0.6 cc. of hydrogen peroxide was added. After 10 hours heating, the mixture was concentrated *in vacuo* to a small volume, diluted with methylene chloride, and washed with an excess of ice-cold sodium carbonate solution. The organic layer was dried, concentrated *in vacuo* to a small volume, and diluted with some ether and petroleum ether. The product crystallized in yellow prisms or needles (0.7 g.) and was recrystallized from acetone. It forms yellow prisms melting at 168–169°. The infrared spectrum shows a very strong doublet at 1319, 1306 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{10}N_2OCl_2$: C, 59.03; H, 3.30. Found: C, 59.31; H, 3.21.

α- and β-Oximes of 2-Amino-4,5-dimethylbenzophenone (XI).—A solution of 70 g. of 2-amino-4,5-dimethylbenzophenone[17] and 70 g. of hydroxylamine hydrochloride in 120 cc. of pyridine and 400 cc. of alcohol was refluxed for 3 hours. The mixture was then partly concentrated *in vacuo*, diluted with some water, cooled, and seeded. After crystallization has started, additional amounts of water were added. The mixture was cooled to +5° for 20 hours and the precipitated crystals were filtered off. The yield of the crude mixture of the α- and β-oximes was 95%. The material softened at 120° and melted at 173–177°. After recrystallization from a mixture of dioxane and petroleum ether, the α-oxime crystallized in pale yellow prisms melting at 183–184°. The infrared spectrum[9] ($CHCl_3$, 2.5%) shows a sharp peak (m) at 3500 cm.$^{-1}$ and a broad band at 3350–3150 cm.$^{-1}$. The dioxane–petroleum ether mother liquor was concentrated *in vacuo* and the residue crystallized from ether with the addition of petroleum ether. The mixture of prisms and needles which precipitated was filtered off and separated mechanically. The needles were recrystallized from a mixture of ether and petroleum ether. The product forms slightly yellow needles melting at 124–125° and is the β-oxime. The infrared spectrum[1] ($CHCl_3$, 5%) shows a sharp peak at 3500 cm.$^{-1}$ and two bands at 3400 and 3200 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{16}ON_2$: C, 74.97; H, 6.71. Found: (α-Oxime, m.p. 183–184°) C, 75.18; H, 6.74. (β-Oxime, m.p. 124–125°): C, 75.24; H, 6.64.

2-Chloroacetamino-4,5-dimethylbenzophenone Oxime (XII).—To a stirred solution of 7.2 g. of 2-amino-4,5-dimethylbenzophenone (30 mmoles) α-oxime in 300 cc. of ether was added 50 cc. of water and then in portions with external cooling 2.5 cc. (33 mmoles) of chloroacetyl chloride and 11 cc. of 3 *N* sodium hydroxide in such a manner as to keep the solution neutral. The precipitated pure reaction product was filtered off, the separated ether layer was concentrated *in vacuo*, and the residue was recrystallized from a mixture of dioxane and petroleum ether. The total yield was 7.9 g. (83%) of white rhombic prisms (m.p. 177–182°). After crystallization from a mixture of dioxane and petroleum ether, the pure product forms rhombic prisms melting at 182–183°.

Anal. Calcd. for $C_{17}H_{17}N_2O_2Cl$: C, 64.45; H, 5.41. Found: C, 64.40; H, 5.33.

6,7-Dimethyl-2-chloromethyl-4-phenylquinazoline 3-Oxide (XIII).—To a warm (50°) solution of a mixture of 30 g. (0.125 mole) of a mixture of the α- and β-oximes of 2-amino-4,5-dimethylbenzophenone in 300 cc. of glacial acetic acid was added 18.8 cc. (0.25 mole) of chloroacetyl chloride. The mixture was left at room temperature for 14 hours and concentrated *in vacuo*. The residue was crystallized from dilute dioxane and yielded 25.8 g. (69%) of yellowish needles melting at 159–165°. After recrystallization from benzene, the product forms yellow needles or prisms melting at 169–170°.

Anal. Calcd. for $C_{17}H_{15}ON_2Cl$: C, 68.34; H, 5.06. Found: C, 68.13; H, 5.21.

The same product is obtained on treating of an acetic anhydride solution of 2-chloroacetamino-4,5-dimethylbenzophenone oxime (XII) with hydrogen chloride.

6,7-Dimethyl-2-dimethylaminomethyl-4-phenylquinazoline 3-Oxide (XIV).—A solution of 3.2 g. of 6,7-dimethyl-2-chloromethyl-4-phenylquinazoline 3-oxide in 20 cc. of dioxane was combined with a solution of 4 g. of dimethylamine in 20 cc. of dioxane and left at room temperature for 20 hours. The mixture was concentrated *in vacuo*, then acidified with dilute hydrochloric acid. Neutral impurities were extracted with ether. The aqueous acidic layer was made alkaline and the reaction product extracted with ether. This ether layer was dried, concentrated and the residue was crystallized from ether. It gave 1.5 g. of slightly yellow needles melting at 125–128°. The mother liquors yielded further amounts of crystals. The total yield was 82%. The analysis sample was recrystallized by addition of ether and petroleum ether to a solution of the product in a very small amount of methanol. It forms fine pale yellow needles melting at 129–130°.

Anal. Calcd. for $C_{19}H_{21}ON_3$: C, 74.24; H, 6.89. Found: C, 74.32; H, 6.71.

Hydrochloride Monohydrate.—A solution of the base in the calculated amount of 1 *N* hydrochloric acid was concentrated *in vacuo*, and the residue was crystallized from a mixture of isopropyl alcohol, acetone and ether. The salt forms fine, pale yellow needles melting at 180–184°.

Anal. Calcd. for $C_{19}H_{21}ON_3 \cdot HCl \cdot H_2O$: C, 63.06; H, 6.69. Found: C, 63.11; H, 6.93.

6,7-Dimethyl-4-phenyl-2-dimethylaminomethylquinazoline (XV).—6,7-Dimethyl-2-dimethylaminomethyl-4-phenylquinazoline 3-oxide (XIV) (6.5 g.) dissolved in 100 cc. of methanol was hydrogenated at room temperature and atmospheric pressure using 6.5 g. of 10% palladium–charcoal as catalyst. The rate of hydrogen uptake decreased after one mole was absorbed; the reaction was then interrupted, the catalyst filtered off, the solution concentrated *in vacuo*, and the residue crystallized from ether. The yield was 4.1 g. (66.2%) of colorless needles melting at 105–109°. (In other similar experiments more material was isolated from the mother liquors as the hydrochloride.) The analysis sample was recrystallized from ether, forming colorless needles melting at 109–110°.

Anal. Calcd. for $C_{19}H_{21}N_3$: C, 78.31; H, 7.26. Found: C, 78.06; H, 7.19.

Hydrochloride.—A solution of the base in the calculated amount of 1 *N* hydrochloric acid was concentrated *in vacuo*. The residual salt was purified by crystallization from acetone. It forms colorless needles melting at 198–199°.

Anal. Calcd. for $C_{19}H_{21}N_3 \cdot HCl$: C, 69.60; H, 6.76; N, 12.82. Found: C, 69.36; H, 7.03; N, 12.47.

6,7-Dimethyl-4-phenyl-2-dimethylaminomethyl-3,4-dihydroquinazoline (XVI).—6,7-Dimethyl-4-phenyl-2-dimethylaminomethylquinazoline (XV) (0.8 g.) was hydrogenated in 50 cc. of methanol at room temperature and atmospheric pressure in the presence of 5 g. of wet Raney nickel, until about 1 mole of hydrogen was absorbed. The mixture was filtered, concentrated, the residue dissolved in ether and filtered again. The ether solution was concentrated *in vacuo*, and the residue crystallized from a mixture of ether and petroleum ether. The yield was 0.3 g. (37%). After recrystallization from a mixture of ether and petroleum ether, the product forms colorless prisms melting at 125–126°. It gives a melting point depression with the starting material.

Anal. Calcd. for $C_{19}H_{23}N_3$: C, 77.77; H, 7.90. Found: C, 77.71; H, 7.86.

Dihydrochloride.—An alcoholic solution of the base was neutralized with two moles of hydrochloric acid, and concentrated *in vacuo*. The salt was purified by crystallization from acetone or from a mixture of methanol, acetone and petroleum ether. It forms white prisms melting at 235–236° dec. The product turns pink on exposure to light.

Anal. Calcd. for $C_{19}H_{25}N_3Cl_2$: C, 62.30; H, 6.87; N, 11.47. Found: C, 62.31; H, 7.17; N, 11.38.

A Mixture of 6,7-Dimethyl-4-phenyl-2-dimethylaminomethylquinazoline and 6,7-Dimethyl-4-phenyl-2-dimethylaminomethyl-3,4-dihydroquinazoline by Hydrogenation of 6,7-Dimethyl-2-dimethylaminomethyl-4-phenylquinazoline 3-Oxide.—6,7-Dimethyl-2-dimethylaminomethyl-4-phenylquinazoline 3-oxide (XIV) (8.1 g.) dissolved in 200 cc. of methanol was hydrogenated in the presence of 10 g. of wet Raney nickel at atmospheric pressure and room temperature. After the absorption of 1.1 moles of hydrogen, the solution was filtered, concentrated *in vacuo* and the residue crystallized from ether. Thus 4.5 g. of crude 6,7-dimethyl-4-phenyl-2-dimethylaminoquinazoline (XV) was obtained melting at 100°. The product was purified by crystallization or by conversion into the hydrochloride. It was identical with the compound described above. The mother liquors obtained after the separation of the crude base contained the dihydroquinazoline XVI which was isolated as crude dihydrochloride melting at 221–228° (1.4 g.). In addition 1.2 g. more of crude quinazoline XV hydrochloride was obtained.

Oxidation of 6,7-Dimethyl-4-phenyl-4-dimethylaminomethyl-3,4-dihydroquinazoline (XVI) to 6,7-Dimethyl-4-phenyl-2-dimethylaminomethylquinazoline (XV).—A solution of 0.6 g. of 6,7-dimethyl-4-phenyl-4-dimethylaminomethyl-3,4-dihydroquinazoline (XVI) in 10 cc. of benzene was stirred vigorously at room temperature with a solution of 1.4 g. of potassium ferricyanide and 1.3 g. of potassium hydroxide in 30 cc. of water. After 2 hours the benzene solution was separated and the water layer extracted with some ether. The organic layers were combined, concentrated and the residue crystallized from a mixture of ether and petroleum ether. It yielded 0.16 g. of 6,7-dimethyl-4-phenyl-2-dimethylaminomethyl-quinazoline (XV) melting at 109–110°. The product gave no melting point depression with an original sample and a considerable depression with the starting material. In addition, 0.13 g. of the hydrochloride of 6,7-dimethyl-4-phenyl-2-dimethylaminomethylquinazoline (XV) was obtained in crystalline form.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CORNELL UNIVERSITY]

The Acid-catalyzed Rearrangement of Cinenic Acid. IV. Synthesis and Rearrangement of 6-Carboxy-6-ethyl-2,2-dimethyltetrahydropyran

BY JERROLD MEINWALD AND JOHN THOMAS OUDERKIRK

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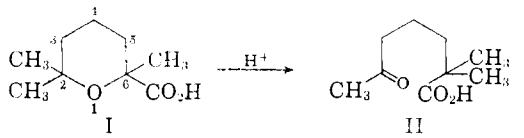
A synthesis of 6-carboxy-6-ethyl-2,2-dimethyltetrahydropyran (III) is described. This acid undergoes a reaction analogous to the cinenic acid rearrangement, giving rise to 2,2-dimethyl-6-oxoöctanoic acid (V), whose structure was proved by independent synthesis. This transformation can be rationalized only in terms of a carboxyl transfer process.

The rearrangement of cinenic acid (I) to geronic acid (II) was first observed by Rupe and Liechtenhan.[1] Early attempts to rationalize the transformation were based on the implicit assumption that an alkyl migration (2 → 6) was taking place.[1,2] More recently it was suggested that II could form

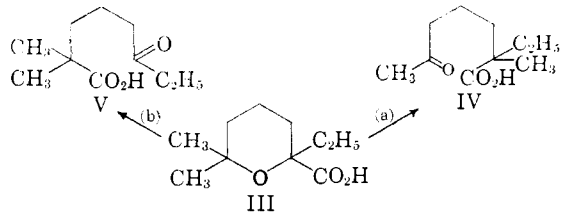


I II

from I by means of a carboxyl transfer (6 → 2).[3] In this Laboratory, two series of experiments were undertaken in parallel to decide between these alternatives. The first of these studies, involving the rearrangement of isotopically labeled cinenic acid, has already been described.[3] The second provides the subject of the present communication.

(1) H. Rupe and C. Liechtenhan, *Ber.*, **41**, 1278 (1908).
(2) H. Rupe and H. Hirschmann, *Helv. Chim. Acta*, **16**, 505 (1933).
(3) J. Meinwald, THIS JOURNAL, **77**, 1617 (1955).

The ambiguity in recognizing the migrating group in the cinenic acid to geronic acid transformation would vanish if the rearrangement of a homologous compound such as 6-carboxy-6-ethyl-2,2-dimethyltetrahydropyran (III) were studied. Thus, whereas alkyl migration (a) would yield IV, carboxyl transfer (b) would give rise to the easily distinguishable isomer V.



V IV III

The synthesis of 6-carboxy-6-ethyl-2,2-dimethyltetrahydropyran (III) was carried out as outlined in Chart 1. The key intermediate, 7-methyl-6-octen-3-one (VIII), was prepared by two independent routes. The first of these was convenient