

solution was evaporated to dryness. The residue was dissolved in 50 ml. of hot abs. alcohol, cooled and diluted with 3 volumes of anhyd. ether. The hydrochloride precipitated as a white powder which became slightly pink during filtration and drying; yield 915 mg., dec. at 220° after subliming at 210–215°.

*Anal.* Calcd. for  $C_6H_5ON_4 \cdot 2HCl$ : N, 25.12. Found: N, 25.53.

**6-Acetamido-4-hydroxybenzotriazole.**—A solution of 335 mg. (1.5 mM) of 6-amino-4-hydroxybenzotriazole dihydrochloride and 300 mg. of anhydrous sodium acetate in 15 ml. of water was treated with 0.5 ml. of acetic anhydride. A precipitate began to form in the yellow solution almost immediately. After refrigerating overnight, the crude product (230 mg.) was collected and washed with water. It was recrystallized from 75% acetic acid; m.p. 284–289° dec.

*Anal.* Calcd. for  $C_8H_8O_2N_4$ : C, 50.00; H, 4.17; N, 29.17. Found: C, 50.19; H, 4.41; N, 28.82.

**6-Amino-4-methoxybenzotriazole (VIIIa).**—This compound was prepared by catalytic reduction of Va as described for VIIa but without the addition of hydrochloric acid. From 390 mg. (0.02 mole) of 4-methoxy-6-nitrobenzotriazole there was obtained, after recrystallization from water (Darco), 207 mg. (63%) of 6-amino-4-methoxybenzotriazole, pink crystals; m.p. 196–198°.

*Anal.* Calcd. for  $C_8H_8ON_4$ : C, 51.22; H, 4.88; N, 34.15. Found: C, 51.10; H, 4.86; N, 33.93.

**4-Methoxy-6-nitrobenzimidazole (Vb).**—2,3-Diamino-5-nitroanisole hydrochloride, 7.7 g. (0.033 mole) and 2.4 g. (0.035 mole) of sodium formate were dissolved in 150 ml. of hot 3 *N* hydrochloric acid solution. After refluxing for two hours, the dark brown solution was clarified with Darco and made basic with 28% ammonium hydroxide solution while still hot. After cooling, a light yellow amorphous powder was collected by filtration, washed with water and dried in air. The crude product (5.8 g.) was recrystallized from 400 ml. of 50% ethanol (Nuchar) yielding 4.9 g. (78%) of colorless 4-methoxy-6-nitrobenzimidazole. This was recrystallized to constant m.p. 263–265°.

*Anal.* Calcd. for  $C_8H_8O_2N_3$ : C, 49.74; H, 3.63; N, 21.76. Found: C, 49.98; H, 3.72; N, 21.59.

**4-Hydroxy-6-nitrobenzimidazole (VIb).**—A solution of 3.9 g. (0.02 mole) of 4-methoxy-6-nitrobenzimidazole in

35 ml. of hot 48% hydrobromic acid was refluxed for 6 hours. After diluting the solution with 150 ml. of hot water, it was treated with Darco and filtered. The hot filtrate was brought to pH 5.0 by addition of 28% ammonium hydroxide solution. 4-Hydroxy-6-nitrobenzimidazole precipitated as a yellow powder. It was collected, after cooling, and recrystallized from 50% ethanol (250 ml.). The yield was 3.0 g. (83%) having m.p. 286–289°. A sample for analysis was sublimed at 210–215° under reduced pressure.

*Anal.* Calcd. for  $C_7H_5O_3N_3$ : C, 46.93; H, 2.79; N, 23.46. Found: C, 46.57; H, 2.91; N, 23.26.

**6-Amino-4-hydroxybenzimidazole Sulfate (VIIb).**—A solution of 1.07 g. (6 mM) of 4-hydroxy-6-nitrobenzimidazole in 90 ml. of 95% ethanol was shaken in an hydrogen atmosphere (45 lb. pressure) with palladium catalyst for 3 hours. The catalyst was removed by centrifugation. Evaporation of the alcoholic solution left a dark red residue which was taken up in 30 ml. of hot 2 *N* sulfuric acid and the solution was filtered. On adding 75 ml. of ethanol to the filtrate and cooling 1.24 g. of crude 6-amino-4-hydroxybenzimidazole sulfate precipitated. This was collected on a filter and washed with ethanol and ether. The crude sulfate was redissolved in hot 2 *N* sulfuric acid, the solution clarified with Darco, and the sulfate reprecipitated by addition of ethanol. The yield was 622 mg. having m.p. 248–252°.

*Anal.* Calcd. for  $C_7H_7ON_3 \cdot H_2SO_4 \cdot H_2O$ : C, 31.70; H, 4.15; N, 15.85. Found: C, 32.01; H, 4.21; N, 15.64.

**6-Amino-4-methoxybenzimidazole (VIIIb).**—Reduction of 580 mg. (0.003 mole) of 4-methoxy-6-nitrobenzimidazole in 90 ml. of 95% ethanol by the procedure described for VIIb yielded 301 mg. (61%) of 6-amino-4-methoxybenzimidazole after recrystallization (Darco) from 25 ml. of water. A second recrystallization gave 258 mg. of the compound having m.p. 216–218°.

*Anal.* Calcd. for  $C_8H_9ON_3$ : C, 58.90; H, 5.52; N, 25.77. Found: C, 58.89; H, 5.47; N, 25.47.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

## Quinazoline. XIV. Preparations and Structure of Diquinazolyl Ethers<sup>1</sup>

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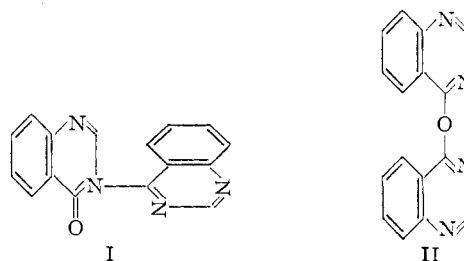
In an attempt to prove the N or O ether structure, the ether was warmed with dilute hydrochloric acid; this yielded a product ( $C_{15}H_{13}N_3O$ ) which appeared to be a compound containing a quinazoline unit bound to a degraded quinazoline nucleus. The failure to obtain 4-quinazolone, which should have resulted if it were an O-ether, supported the concept of an N-ether linkage. The proof of structure by the above method is only indicative and not certain since the hydrolysis product was not identified. For this reason it was decided to extend the study to include the synthesis of other diquinazolyl ethers and to study the infrared spectra of these compounds with a view of possibly establishing their structures. A series of three reactions were run using mixtures of 2-chloroquinazoline and potassium 2-quinazolate, 2-chloroquinazoline and potassium 4-quinazolate, and 4-chloroquinazoline and potassium 2-quinazolate using essentially the technique of Tomisek and Christensen.<sup>2</sup> If O-ethers resulted from the reactions, two new diquinazolyl ethers would be formed; on the other hand, if N-ethers resulted, there would be three new isomeric ethers produced.

The synthesis of a diquinazolyl ether whose structure was reported as either I or II has recently been described by Tomisek and Christensen<sup>2</sup>; this ether was obtained by refluxing potassium 4-quinazolate with 4-chloroquinazoline in dioxane.

2-Chloroquinazoline and potassium 4-quinazolate gave a white fibrous compound (m.p. 240°);

(1) The work described in this paper was made possible by a grant from the Research Corporation. Published with the approval of the Monograph Publications Committee, Oregon State College, as Research Paper No. 244, School of Science, Department of Chemistry.

(2) A. J. Tomisek and B. E. Christensen, *THIS JOURNAL*, **70**, 874 (1948).

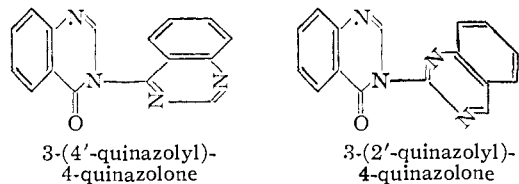


in both reactions involving potassium 2-quinazolate; however, the starting materials were re-

covered unchanged after refluxing for periods up to seven days. The failure of potassium 2-quinazolate to react indicated that 2-quinazalone is unreactive to alkylating agents. Since alkylations of 2-quinazalone have not been previously reported, the attempt was made using the procedure of Knappe.<sup>3</sup> 2-Quinazalone was refluxed in a methanolic solution of sodium hydroxide to which methyl iodide was added; however, only unchanged starting material was recovered. A second attempt was made using the procedure of Leonard and Curtin<sup>4</sup> in which a suspension of 2-quinazalone in ether is stirred several hours with an ethereal solution of diazomethane. No reaction was observed and the starting material was once again recovered.

The failure to produce an N-ether of 2-quinazalone by direct alkylation and the failure of potassium 2-quinazolate to react with either 2- or 4-chloroquinazoline appear to be related but offer no direct evidence as to the structure of the two diquinazolyl ethers which were prepared.

The infrared spectra of the two ethers (Table I), however, offer quite conclusive evidence that it is the N-ether which is formed in each case. The structural feature of the N-ethers which makes this interpretation possible is the N-acyl carbonyl. In the spectrum of the N-ether first prepared by Tomisek and Christensen,<sup>2</sup> there is a strong absorption band at 1668 cm.<sup>-1</sup>. A similar band is found at 1700 cm.<sup>-1</sup> in the case of the isomeric N-ether prepared during the current investigation. These absorption bands are definitely associated with the presence of a carbonyl and agree very well with the frequencies found (1637 to 1704 cm.<sup>-1</sup>) for the carbonyl of various 4-quinazolones.<sup>5</sup> The point of attachment to the quinazalone is almost certainly in the 3-position as no band arising from an N-H is observed in either spectrum. The structures of the two ethers are



The investigation of 3-(2'-quinazolyl)-4-quinazolone was continued by subjecting it to hydrolysis with warm dilute hydrochloric acid. The reaction proceeded in the same fashion as described with 3-(4'-quinazolyl)-4-quinazolone yielding almost quantitatively an amorphous white solid (C<sub>15</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>).

Inasmuch as only three atoms of nitrogen remain after this treatment, this indicates that either the quinazalone or the quinazoline unit must have been degraded. The fact that the hydrolysis products are not isomeric indicates that it is the quinazoline ring which is split since the point of attachment to the quinazalone ring is the same in both cases. Further confirmation of this supposition is provided by Gabriel,<sup>6</sup> who observed that quinazoline

itself was hydrolyzed by warm hydrochloric acid to yield *o*-aminobenzaldehyde. Since chemical tests were unable to establish the presence of acid, amino or alcohol groups, it is very likely that the ruptured molecule may have cyclized to a more complex condensed ring system. Support for this concept is provided by infrared spectrum (Table I) which shows a weak band at 3200 cm.<sup>-1</sup> and three strong bands at 1680, 1637 and 1594 cm.<sup>-1</sup> as well as a band of moderate intensity at 1481 cm.<sup>-1</sup>. The band at 3200 cm.<sup>-1</sup>, judging from quinazolones and quinazolinediones studied, indicates the presence of an N-H while the band at 1680 cm.<sup>-1</sup> almost certainly arises from a carbonyl. The band at 1637 cm.<sup>-1</sup> is indeterminate and could arise from either an N-acyl carbonyl or C=N. Since the empirical formula shows the presence of two oxygen atoms and there is apparently no hydroxyl or acid group present, the N-acyl carbonyl is favored. The band at 1594 cm.<sup>-1</sup> is strong enough to arise from a C=N group and is in the usual region found for such groups but the possibility of its being a phenyl vibration should not be discounted. However, it is difficult to propose a definite structure until more information is available.

The best explanation for the structure of the hydrolysis product of 3-(4'-quinazolyl)-4-quinazolone is the hypothesis that the ruptured molecule cyclized to a more complex ring system. At least infrared data support this supposition (Table I). In the spectrum of the hydrolysis product there is a strong absorption band at 1668 cm.<sup>-1</sup> which can be attributed to N-acyl carbonyl of the

TABLE I  
INFRARED ABSORPTION SPECTRA OF DIQUINAZOYL ETHERS  
AND HYDROLYSIS PRODUCTS

w = weak, s = strong, vw = very weak, m = medium.

1 <sup>a</sup> cm. <sup>-1</sup>	2 <sup>a</sup> cm. <sup>-1</sup>	3 <sup>a</sup> cm. <sup>-1</sup>	4 <sup>a</sup> cm. <sup>-1</sup>
2915 <sup>b</sup>	2915vs <sup>b</sup>	3280w	3200w
1688vs	1700vs	3102s	3040w
1608m	1608m	1668s	2915vs <sup>b</sup>
1557m	1572m	1615w	1680vs
1492w	1471m	1566w	1637s
1459s <sup>b</sup>	1401w	1506vw	1594s
1381m <sup>b</sup>	1385w <sup>b</sup>	1469m	1481s
1357w	1349w	1445s	1343vw
1302m	1317m	1342vw	1306w
1276m	1304m	1271w	1270w
1244w	1268s	1158vw	1210w
1189w	1218w	1142vw	1155w
1138vw	1193w	1032vw	1026m
1085w	984w	945w	930vw
875w	922w	872vw	868w
825vw	885w	824w	804w
814vw	833w	806w	753s
796vw	800w	792w	719w
767s	788w	772m	
750w	776s	762w	
702m	766vs	739w	
	718m	690w	
		665w	

<sup>a</sup> 1,3-(4'-Quinazolyl)-4-quinazolone; 2,3-(2'-quinazolyl)-4-quinazolone; 3, hydrolysis product of 3-(4'-quinazole-4-quinazolone); 4, hydrolysis product of 3-(2'-quinazolyl)-4-quinazolone. <sup>b</sup> Nujol absorbent band.

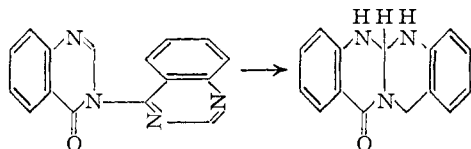
(3) E. Knappe, *J. prakt. Chem.*, **43**, 209 (1890).

(4) N. J. Leonard and D. Y. Curtin, *J. Org. Chem.*, **11**, 341 (1946).

(5) H. Culbertson, J. C. Decius and B. E. Christensen, *This Journal*, **74**, 4823 (1952).

(6) Gabriel, *Ber.*, **36**, 809 (1903).

quinazoline ring. There are three other absorption bands in the region 1500 to 1700  $\text{cm}^{-1}$ ; one at 1615  $\text{cm}^{-1}$ , another at 1566  $\text{cm}^{-1}$  and a third at 1506  $\text{cm}^{-1}$ . All three of these bands are weak, in contrast to the substituted 4-quinazolones which have a strong absorption in the region 1593 to 1625  $\text{cm}^{-1}$  associated with the presence of a  $\text{C}=\text{N}$  group. The weakness of these absorption bands would indicate the absence of a  $\text{C}=\text{N}$  group. It appears that the quinazoline nucleus ruptured in the 2- and 3-positions as in the instance of quinazoline itself may have cyclized with the remaining quinazolone unit to yield a more complex ring system such as 5-oxo-12,12a-dihydro-7,13(H)-quinazo[2,3-b]quinazoline.



The absorption bands 3280  $\text{cm}^{-1}$  indicate the presence of a weak NH band, a fact which lends support to such a hypothesis. However, confirmation of this complex ring structure awaits further chemical evidence.

### Experimental

**Preparation of Samples for Infrared Absorption.**—Three compounds of this series (3-(4'-quinazolyl)-4-quinazolone, 3-(2'-quinazolyl)-4-quinazolone and the hydrolysis product of 3-(2'-quinazolyl)-4-quinazolone) were prepared in the form of emulsions in a paraffin oil (sold under the trade name of "Nujol") as described by Randall, *et al.*<sup>7</sup> The strong bands due to this material which appear at about 2915, 1460 and 1375  $\text{cm}^{-1}$  are designated with a footnote in Table I.

The hydrolysis product of 3-(4'-quinazolyl)-4-quinazolone was prepared in the form of a sublimed solid film as described by Blout and Fields.<sup>8</sup> The spectrum of this sample was comparable to one in which the same material was prepared as a "Nujol" emulsion showing that the sample was sublimed without decomposition. The sublimed film technique reduces light scattering and permits the use of thicker films thus increasing the absorption of weak peaks.

(7) H. N. Randall, *et al.*, "Infrared Determination of Organic Structures," D. Van Nostrand Co., Inc., New York, N. Y., 1949.

(8) E. R. Blout and M. Fields, *THIS JOURNAL*, **72**, 479 (1950).

It also permits observation of absorption peaks at 3102, 1469 and 1445  $\text{cm}^{-1}$  which would be masked by the absorption bands of paraffin oil.

**Infrared Spectrometer.**—The instrument employed consisted of the source, monochromator and detector of the Perkin-Elmer Model 12C instrument together with a light chopper, amplifier and recording unit designed after the double beam modification described by Salvitsky and Halford.<sup>9</sup> The present data were, however, obtained by the single beam method, *i.e.*, by recording the absorption of a suitable blank followed by that of the sample; the transmission curves were plotted by determining  $I/I_0$  point by point.

A sodium chloride prism was employed between 3800 and 650  $\text{cm}^{-1}$ . Relatively large slits were used, namely, 0.045 mm. starting at 3800  $\text{cm}^{-1}$ , 0.090 mm. at 2000  $\text{cm}^{-1}$ , 0.225 mm. at 1200  $\text{cm}^{-1}$  and 0.500 mm. at 700  $\text{cm}^{-1}$ .

**3-(2'-Quinazolyl)-4-quinazolone.**—This diquinazolyl ether was synthesized by the procedure described by Tomisek and Christensen.<sup>3</sup> Two and eight-tenths grams of 4-quinazolone was added to a solution containing 1.1 g. of potassium hydroxide in 25 ml. of absolute alcohol. The solvent was then removed on a steam-bath and the quinazolinone thoroughly dried under high vacuum and then pulverized. To this residue was added 30 ml. of dry dioxane and 3.2 g. of 2-chloroquinazoline and the mixture was then refluxed for ten days. The mixture was evaporated to dryness and triturated with dilute sodium hydroxide solution. The crude product, purified by charcoal treatment of a hot alcohol solution, yielded 1.2 g. (23%) of pure 3-(2'-quinazolyl)-4-quinazolone. The product recrystallized from alcohol as thin, wool-like fibers, m.p. 242°, was insoluble in water and soluble to a very slight extent in dioxane.

*Anal.* Calcd. for  $\text{C}_{16}\text{H}_{10}\text{N}_4\text{O}$ : C, 70.06; H, 3.68. Found: C, 69.88; H, 3.72.

**Acid Hydrolysis Product of 3-(2'-Quinazolyl)-4-quinazolone.**—The 3-(2'-quinazolyl)-4-quinazolone (600 mg.) was dissolved in hot dilute hydrochloric acid. In a few minutes the hydrochloride of the cleavage product precipitated. The mixture was cooled and filtered and the solid material was treated with excess sodium bicarbonate solution. The free base was then filtered, washed with water and dried. After recrystallization from pyridine-water, 350 mg. (70%) of a fine, white, amorphous material melting with decomposition at 234–236° was obtained.

*Anal.* Calcd. for  $\text{C}_{15}\text{H}_{11}\text{N}_3\text{O}_2$ : C, 67.92; H, 4.15; N, 15.84. Found: C, 67.68; H, 4.13; N, 15.78.

**Acknowledgment.**—We wish to thank Dr. J. C. Decius without whose assistance this work would not have been possible.

CORVALLIS, OREGON

(9) A. Salvitsky and R. S. Halford, *Rev. Sci. Instruments*, **21**, 203 (1950).