able. This view will not be discussed at length, as the explanation advanced in the next paragraph seems to dispose of it effectually.

The experimental evidence submitted in this paper, not only proves the absence of a transition point, but leads to the true explanation of the heat absorption. In a preceding section, (V), the actual changes of concentration which take place when liquid sulphur is heated rapidly, were given. Attention was directed to the very rapid formation of S_μ which is coincident with and accounts for the sudden thickening, and for the fall in temperature. The more rapidly the liquid is heated, the higher must it be heated before a concentration is reached sufficient to produce the increased viscosity. When the liquid is heated slowly, it never differs much from a condition of equilibrium, so that the rapid formation of S_μ is impossible, and consequently no fall of temperature takes place.

I owe my thanks to Professor Alexander Smith, for the privilege of working on this problem, for much advice while the work was in progress and for the use of some of his unpublished results.

[CONTRIBUTIONS FROM THE HAVEMEYER LABORATORIES OF COLUMBIA UNIVERSITY, NO. 131.]

RESEARCHES ON QUINAZOLINES (EIGHTEENTH PAPER), ON 2, 3-DIALKYL-4-QUINAZOLONES AND THE PRODUCTS OBTAINED BY ALKYLATING 2-ALKYL-4-QUINAZOLONES (2-ALKYL-4-HYDROXY QUINAZOLONES)[1]

BY MARSTON TAYLOR BOGERT AND HARVEY AMBROSE SEIL.

Received January 18, 1907.

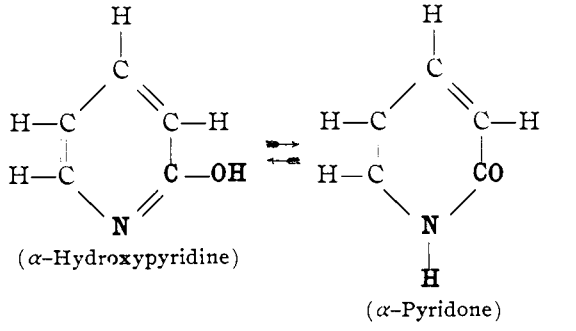
The tautomerism of the amide group, $-CO.NH- \rightleftarrows -C(OH) : N-$, has interested organic chemists for many years and has led to many valuable investigations. These investigations have had to do not only with straight-chain fatty amides, but also with those of cyclic structure, as in the α-hydroxy derivatives of pyrrole, pyridine, pyrimidine, and similar heterocycles. The tautomerism of the α-hydroxypyridines and α-pyridones, or of lactame and lactime condensation in general, is only the old question of amide tautomerism in a slightly different form. Whether in such cases we are dealing with a mixture of two or more tautomeric forms in a condition of equilibrium, or whether one form only is present, is a question not yet satisfactorily answered. One fact, however, seems clearly established, and that is that replacement of the labile hydrogen in such compounds by hydrocarbon radicals materially retards the tendency of one form to pass into the other, and stable derivatives of both types then appear. There thus arise two parallel series of derivatives, in one of which the radical is in union with oxygen, in the other with nitrogen,

[1] Read at the meeting of the New York Section, May 11, 1906.

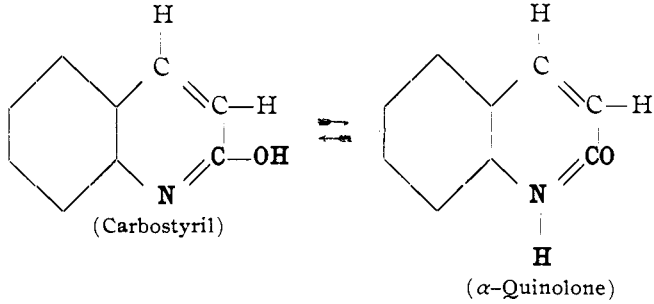
—CO.NR— and —C(OR) : N—, and which, on account of this dissimilarity of structure, behave quite differently towards the same chemical reagents, as a comparison of their properties in any given case will show. The existence of two such series in the quinazoline group has been known for a long time, and is a question which has interested us ever since we have been engaged in studying the synthesis and properties of the 4-quinazolones (4-hydroxyquinazolines). The results of certain of these recent investigations have led us to focus our attention more closely on the matter.

The specific question presented to us in the study of the 4-quinazolones (4-hydroxyquinazolines) is this: In alkylating such compounds by the action of alkali and alkyl iodide, or of alkyl iodide upon the silver salt, are oxygen or nitrogen derivatives produced, and what are the factors determining the character of the final product?

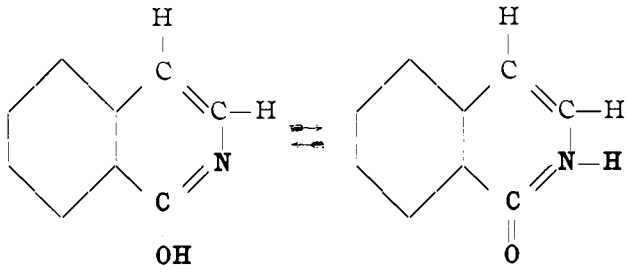
In the first place, a brief conspectus of the results obtained by other workers in this field is necessary for a clear understanding of the problem as it affects quinazolines. For purposes of comparison we have selected the α-hydroxypyridines (α-pyridones), carbostyrils (α-quinolones), isocarbostyrils (α-isoquinolones), 6-hydroxypyrimidines (6-pyrimidones), and 4-hydroxyquinazolines (4-quinazolones) :—



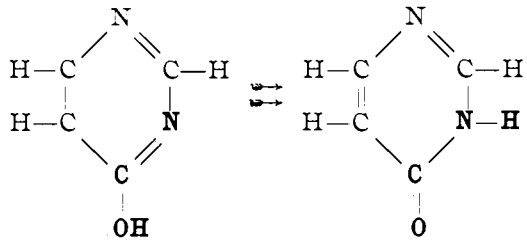
(α-Hydroxypyridine) (α-Pyridone)



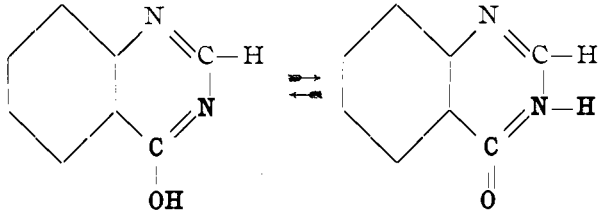
(Carbostyril) (α-Quinolone)



(Isocarbostyril) (α-Isoquinolone)

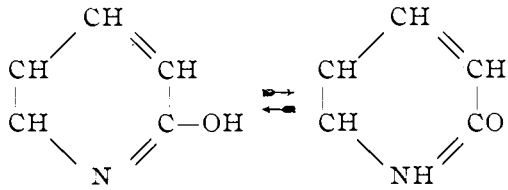


(6-Hydroxypyrimidine) (6-Pyrimidone)



(4-Hydroxyquinazoline) (4-Quinazolone)

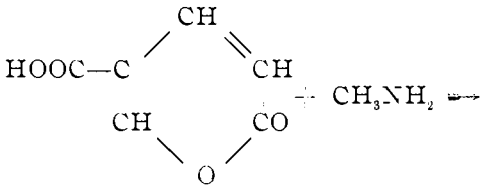
The object has been to bring together only those compounds and reactions which bear most closely upon the matter in hand.



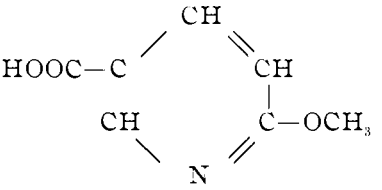
(α-Hydroxypyridines) (α-Pyridones)

Von Pechmann and Welsh[1] obtained the same product by the action of methylamine upon cumalinic acid as by the action of potassium hydroxide and methyl iodide upon hydroxynicotinic acid, and ascribed to it a methoxy formula :—

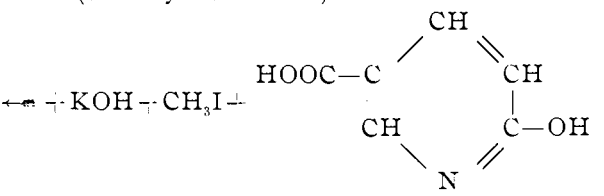
[1] Ber. 17, 2384 (1884).



(Cumalinic Acid)



(Methoxynicotinic Acid)



(Hydroxynicotinic Acid)

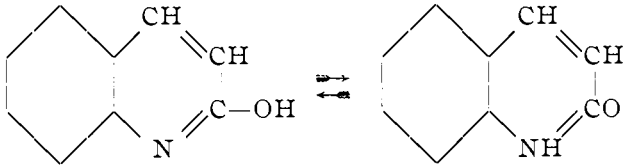
The phenyl derivative, prepared by the action of aniline upon cumalinic acid, was therefore given the —OR structure also. In both cases the authors were misled by assuming that the product obtained by methylating hydroxynicotinic acid must have the —OR structure, although they saw the difficulty this caused in explaining the formation of such a structure by the action of primary amines upon cumalinic acid. Being convinced that something was wrong, Von Pechmann examined the matter more closely[1] and found that both methyl and phenyl derivatives were — NR compounds, since when reduced in hot alkaline solution with sodium amalgam they gave methylamine and aniline, respectively, together with other products. From which it followed, that the methylation of hydroxynicotinic acid with alkali and methyl iodide, instead of giving an oxygen ether, in reality gave a nitrogen derivative.

At about the same time, Hantzsch[2] found that when "pseudolutidostyril" (α-hydroxylutidine) was dissolved in sodium methylate and treated with methyl iodide, an N-methyl derivative was obtained, and from this concluded not only that the structure of the original substance must be —NH.CO— and not —N : C(OH)—, but also that pyridines and quinolines differed in this respect that in the former the —NH.CO— arrangement was the more stable, in the latter the —N : C(OH)—.

[1] Ber. **18**, 318 (1885).

[2] Ber. **17**, 2907 (1884).

Seven years later, Von Pechmann and Baltzer[1] studied the alkylation of α-hydroxypyridine (α-pyridone) itself, and found that both oxygen and nitrogen derivatives were formed by the usual etherification reactions. When the hydroxypyridine was heated alone with alkyl iodide, the product was the nitrogen derivative, whereas the silver salt and alkyl iodide gave mainly the oxygen ether, except with methyl iodide, when the product was about equal parts oxygen ether and nitrogen derivative. With alkali and alkyl iodide the chief product was the nitrogen derivative, which the authors believed to be due to dissociation of the alkaline salt. No rearrangement of these isomers could be accomplished by the action of heat alone, although in the case of γ-methoxypyridine (from the γ-chlor compound and sodium methylate), Haitinger and Lieben[2] observed that at 220° the methyl wandered from oxygen to nitrogen. These latter investigators[3] obtained the same methyl derivative, of —NR structure, whether γ-hydroxypyridine was treated with potassium hydroxide and methyl iodide, or with methyl iodide followed by damp silver oxide.



(α-Hydroxyquinolines, Carbostyrils) (α-Quinolones, Pseudocarbostyrils)

Friedländer and Ostermaier[4] treated carbostyril with ethyl iodide, alcohol, and the calculated amount of potassium hydroxide, and obtained a compound which they assumed to be the oxygen ether, since it was volatile with steam, easily hydrolyzed by mineral acids, and very stable to alkalies. At the same time there was formed a basic high-boiling oil not volatile with steam. That the volatile compound was really the oxygen ether they proved by preparing the same substance from α-chlorquinoline and alcoholic potassium hydroxide[5]. In a similar manner, they prepared the methoxy compound, obtaining it as an oil with the odor of oranges.

Friedländer and Weinberg[6] obtained a quantitative yield of ethyl carbostyril (OC_2H_5) by the action of ethyl iodide upon silver carbostyril at 70°-80°, and later[7] prepared the same substance from ethyl *o*-aminocinnamate and alcoholic zinc chloride. They found it very stable to acid reducing agents, but easily reduced by sodium amalgam in alcoholic solu-

[1] Ber. **24**, 3146 (1891).
[2] Monatsh. **6**. 321 (1885).
[3] Ber. **17**, 1507 (1884).
[4] Ber. **14**, 1917 (1881).
[5] Ber. **15**, 335, (1882).
[6] Ber. **15**, 1421 (1882).
[7] Ber. **15**, 2103 (1882).

tion. Examining further the basic oil not volatile with steam, observed by Friedländer and Ostermaier[1] as one of the products of the action of ethyl iodide and alcoholic alkali upon carbostyril, they discovered that it had the same percentage composition as ethyl carbostyril and inclined to the opinion that it was a polymeric form until, as the result of subsequent work[2], it appeared evident that it was the N-ethyl compound. On treating hydrocarbostyril[3] with alcoholic potassium hydroxide and ethyl iodide at 100°, however, the product was the N-ethyl derivative and not the oxygen ether, as they demonstrated by preparing the same substance from *o*-ethylamino hydrocinnamic acid by spontaneous loss of water. The N-ethyl compound was stable to hydrochloric acid at 150°. The same authors[4] found that when carbostyril was treated with methyl iodide and alcoholic alkali, the product was almost wholly the N-methyl derivative. They make the suggestive remark that probably those α-hydroxy pyridines and quinolines which have hitherto been assigned a —CONH— structure on the basis of their behavior with methyl iodide would be found to give true oxygen ethers with ethyl iodide, and that the —OR reaction is really the normal one, the —NR abnormal. This difference in the behavior of tautomeric compounds with methyl and ethyl iodide is in accord with our own results as reported in the experimental part of this paper.

Friedländer and Müller[5] made a careful study of the behavior of carbostyril on alkylation with alkyl iodides. They found that the sodium salt was very easily dissociated, and that with methyl iodide the methyl group went mainly to the nitrogen, the yield of N-methyl derivative increasing as the dilution of the alkaline solution (*i. e.*, the amount of liberated carbostyril) increased, while by the action of either methyl or ethyl iodide upon the undissociated silver salt practically only the oxygen ether was obtained. It seems rather strange, in view of the remark quoted above concerning the different behavior of methyl and ethyl iodides, that the authors say nothing whatever about the action of ethyl iodide upon the dissociated sodium salt, nor do they give any experimental data for the reaction between the silver salt and methyl iodide. The only experiment recorded is that between carbostyril, alcoholic alkali and methyl iodide, which gave the N-methyl derivative.

By the action of methyl iodide upon the silver salt of 6-nitro carbostyril, Feer and Königs[6] obtained the oxygen ether. Claus and Setzer[7] heated 5-

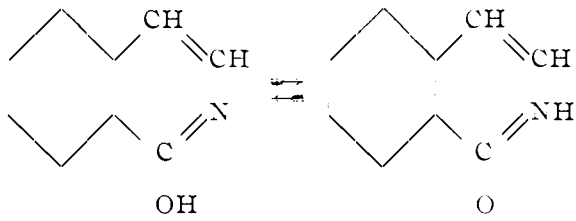
[1] Loc. cit.
[2] Ber. **18**, 1529 (1885).
[3] Ber. **15**, 2103 (1882).
[4] Ber. **18**, 1529 (1885).
[5] Ber. **20**, 2010 (1887).
[6] Ber. **18**, 2396 (1885).
[7] J. pr. Chem (2) **53**, 392 (1896).

nitro carbostyril with methyl iodide, sodium hydroxide and benzene, for a long time at 200-250°, and obtained the N-methyl derivative. Decker and his co-workers[1], by treating the sodium salts of 6- and 8-nitro carbostyrils with methyl or ethyl iodide also obtained —NR derivatives, and the result was similar when dimethyl sulphate was used (on 8-nitro carbostyril) instead of methyl iodide.

Knorr[2] subjected oxylepidine (α-hydroxy-γ-methylquinoline) to the action of methyl iodide and sodium methylate and found that both —OR and —NR compounds resulted and, further, that when the oxygen ether was heated above its boiling-point it changed to the nitrogen isomer. From his study of the behavior of carbostyril and oxylepidine with methyl iodide he came to the following conclusions[3]:—1. Nitrogen ethers of α-quinolones do not form iodomethylates even when heated, on account of their true amide structure (differing in this respect from the γ-quinolones)[4]. 2. Oxygen ethers of α-hydroxyquinolines are rearranged by methyl iodide to the —NR isomers, slowly in the cold, rapidly and completely when heated. That this rearrangement is due to an addition and splitting-off process is supported by the fact that when Knorr heated the ethoxy compound with methyl iodide at 100° he obtained the N-methyl derivative and ethyl iodide.

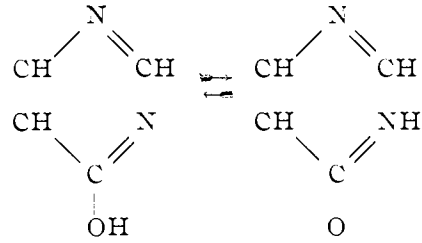
Knorr and Antrick[5] had many years before investigated γ-hydroxyquinaldine, and reported that in most of its reactions (for example, the fact that it was unattacked by methyl iodide at 180°) it behaved like a true hydroxy quinoline, but when treated with alcoholic alkali and methyl iodide it gave the N-methyl compound, with a very small amount of what may have been the oxygen ether. According to Wenzel's results[6], the oxygen ethers of γ-hydroxyquinoline (kynurine) are apparently incapable of existence under ordinary conditions, for he invariably obtained the —NR body whether he treated the kynurine with alcoholic alkali and alkyl iodide, the silver salt with alkyl iodide, or the γ-chlor compound with alcoholate. Comparing this with the experience of Haitinger and Lieben in the case of γ-methoxy pyridine reported above, it would seem that the γ-methoxy quinolines show a still stronger tendency to pass into the isomeric —NR compounds than do the corresponding methoxy pyridines.

[1] J. pr. Chem. (2) 64, 89 (1901).
[2] Ann. 236, 87 (1887).
[3] Ber. 30, 929 (1897).
[4] In opposition to this, see Knape, and Knorr and Antrick beyond.
[5] Ber. 17, 2872 (1884).
[6] Monatsh. 15, 461 (1894).



(Isocarbostyrils) (α-Isoquinolones)

The literature in this group is very scanty. Fernau[1] treated isocarbostyril with methyl alcohol, methyl iodide and potassium hydroxide, and obtained the N-methyl derivative. By heating the silver salt 12-15 hours at 100° with the calculated amount of methyl iodide an oil was produced which was apparently the methoxy compound. Gabriel[2] subjected 1,3-dichlorisoquinoline to the action of sodium methylate and ethylate, and obtained the 1-alkoxy-3-chlorisoquinolines, from which the alkyl group could be removed by the action of dry hydrogen chloride with formation of the corresponding hydroxychlor compound. When the latter was dissolved in methyl alcoholic potassium hydroxide, and heated for an hour at 100° with methyl iodide, the N-methyl compound was produced, from which he concluded that the original hydroxychlorisoquinoline must have the —CONH— structure.



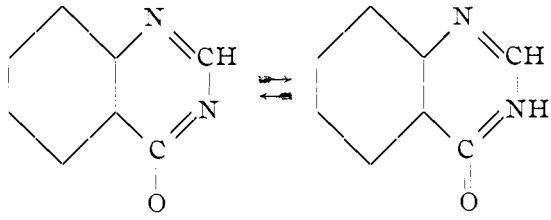
(6-Hydroxypyrimidines) (6-Pyrimidones)

Selecting among the pyrimidines the 6-hydroxy derivatives as most closely related to the 4-hydroxy quinazolines, we cull the following statements from the literature:—

Pinner[3] treated 2,4-dialkyl-6-hydroxypyrimidines with alcoholic potassium hydroxide and ethyl bromide at 100°, and obtained the N-ethyl compound. Meyer's experience with oxycyanconiine (5-methyl-2,4-diethyl-6-hydroxypyrimidine)[4] was similar, for he found on heating it at 150° with methyl iodide that he obtained the hydriodide of the N-methyl compound, and, further, that the same —NR derivative resulted whether the oxycyanconiine was heated with methyl iodide at 150°, with alcoholic potassium

[1] Monatsh. **14**, 65 (1893).
[2] Ber. **19**, 2359 (1886).
[3] Die Imidoäther, p. 222.
[4] J. pr. Chem. (2) **26**, 348 (1882); **39**, 271 (1889).

hydroxide and methyl iodide, or the isomeric oxygen ether heated alone at 260-270°. As the oxycyanconiine has a weak alkaline reaction and does not unite with silver oxide, he could only secure the oxygen ether from the chlorine compound and sodium methylate.



(4-Hydroxyquinazolines) (4-Quinazolones)

Knape[1] treated 4-hydroxyquinazoline with alcoholic alkali and methyl iodide and obtained the N-methyl compound. He also observed the formation of a methyl iodide addition-product of the latter, an observation which would support the theory that the formation of these nitrogen derivatives is due to an addition and splitting-off process.

Weddige[2], who was the first to investigate this question in the quinazoline group, treated 2-methyl-4-hydroxyquinazoline with alcoholic potassium hydroxide and methyl iodide and also obtained the N-methyl derivative, as he proved by the synthesis of the same substance from anthranilic methylamide and by the fact that it was unchanged when heated with concentrated hydrochloric acid at 170°-180°. Körner[3] carried out the same reactions with 2-phenyl-4-hydroxyquinazoline with similar results.

Dehoff[4] and Thieme[5] investigated 6-nitro-2-methyl-4-hydroxyquinazoline. The latter found that on methylation with alcoholic alkali and methyl iodide it yielded the N-methyl derivative, and that the result was practically the same when the silver salt was used. Zacharias[6] likewise obtained only the N-methyl derivative when he subjected 8-nitro-2-methyl-4-hydroxyquinazoline to the action of alcoholic alkali and methyl iodide.

Working with the 2,4-dihydroxyquinazoline (benzoylene urea), Abt[7] found that whether one or two methyls were introduced by the action of alcoholic alkali and methyl iodide, the methyl was invariably combined with nitrogen in the final product, whence it could not be dislodged by heating with concentrated hydrochloric acid at 160°-170°. By treating the

[1] J. pr. Chem. (2) **43**, 209 (1891).
[2] Ibid. (2) **36**, 141 (1887).
[3] Ibid., **36**, 155 (1887).
[4] Ibid., **42**, 346 (1890).
[5] Ibid., **43**, 451 (1891).
[6] Ibid., **43**, 432 (1891).
[7] Ibid., **39**, 140 (1889).

dihydroxyquinazoline with phosphorus halide, he obtained a dichlor derivative which yielded a dimethoxy derivative with sodium methylate or with a solution of sodium hydroxide in methyl alcohol. By the action of heat alone, this dimethoxyquinazoline suffered no rearrangement, but boiling with water or even with alcohol, hydrolyzed it to the dihydroxyquinazoline again. Dehoff[1] evaporated Bz-trichlor-2-methyl-4-chlorquinazoline with a solution of potassium hydroxide in absolute alcohol and obtained both Bz-trichlor-2-methyl-4-ethoxyquinazoline and Bz-trichlor-2-methyl-4-hydroxyquinazoline, the ethyl ether being easily saponified by alcoholic potassium hydroxide.

Summing up the above statements concerning the behavior of the α-hydroxy derivatives of the closely related series of pyridines, benzopyridines (quinolines), pyrimidines and benzopyrimidines (quinazolines), the following conclusions are reached:—

1. Alkylation by the action of alcohol, alkali and methyl iodide, as usually carried out, gives invariably the N-methyl derivative, and only occasionally small amounts of the oxygen ether are observed. This result is not changed when dimethyl sulphate is used instead of methyl iodide. But when ethyl halide is used, the chances of obtaining the oxygen ether appear far better. Much then depends upon the particular substance under investigation and upon the conditions prevailing, as to whether the chief product will be the —OR or —NR derivative.

2. When the silver salt is treated with methyl iodide, both oxygen and nitrogen derivatives are apt to be formed, but with ethyl iodide the pure ethoxy compound often results.

3. The best method of preparing the pure oxygen ethers is by the action of the alcoholate upon the chlorine compounds.

4. The oxygen ethers show lower melting- and boiling-points, are more apt to possess an odor, are much more readily hydrolyzed by mineral acids, and are more stable to oxidizing agents than the tautomeric nitrogen compounds. Just as these α-hydroxy nitrogen heterocycles show affiliations in structure and behavior with the amides, and as the corresponding α-halogen derivatives seem to stand between the true aryl halides and the acyl halides, so these oxygen ethers, in the ease with which many of them are hydrolyzed by mineral acids, recall the behavior of the esters.

5. While many oxygen ethers have been rearranged to the nitrogen tautomers by the action of heat alone, or in other ways, so far as we are aware, no case is recorded in the literature where the alkyl has been driven back from the nitrogen to the oxygen.

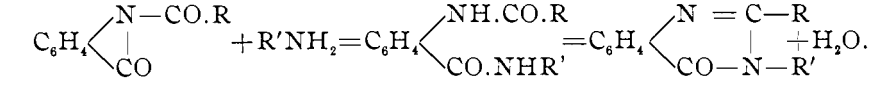
As the character of the derivatives obtained on alkylating these —CONH— $\rightleftarrows$ —C(OH)N— heterocyclic compounds was for many

[1] J. pr. Chem., 42, 354 (1890).

years regarded as conclusive proof of the structure of the mother-substance, some of the controversies which arose 20 to 25 years ago over this question are directly traceable to the method of alkylation. Thus, Friedländer[1] ethylated carbostyril by bringing its silver salt in contact with ethyl iodide and, obtaining a quantitative yield of the ethoxy compound, naturally decided that carbostyril was a lactime. On the other hand, von Pechmann[2] and Hantzsch[3] methylated their compounds, the one hydroxynicotinic acid, the other pseudolutidostyril, and as they both obtained N-methyl derivatives concluded that, contrary to the behavior of the α-hydroxyquinolines, in the case of the α-hydroxypyridines themselves the lactame structure was the more stable one. Many similar cases might be cited.

In taking up the problem of tautomerism in the quinazoline group, two main lines of attack suggested themselves:—I. What might be termed purely synthetic methods, and II. Physical-chemical methods. Beginning under the first general heading, our idea has been to select two distinct reactions, one of which would give pure —NR derivatives, and the other pure oxygen ethers, of the 4-hydroxyquinazolines (4-quinazolones); then to alkylate the free 4-hydroxyquinazolines by various methods and compare the products with the pure —NR and —OR compounds.

For the prepartion of the pure 3-N-alkyl-4-quinazolones an excellent method is available in that of Anschütz, Schmidt and Greiffenberg[4] These investigators showed that 4-quinazolones are formed when acylanthranils are condensed with primary amines:



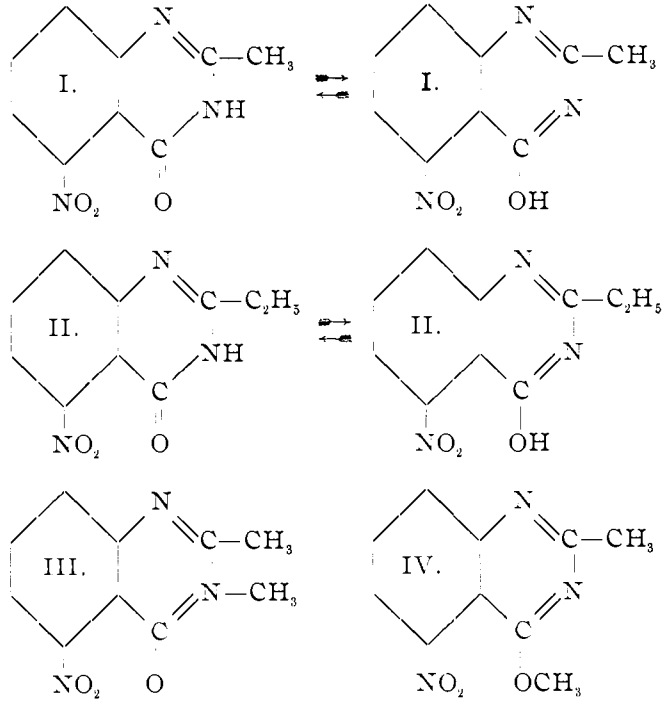
This reaction has been extended by us to other acylanthranils with similar results[5]: (Bogert and Seil[6], Bogert and Steiner[7], Bogert and Hand[8], Bogert and Cook[9]), and in several cases we isolated the intermediate amide. The reaction can generally be carried out with ease and rapidity, and the yield is usually large (often quantitative). From the method of preparation, when R and R′ are hydrocarbon radicals and not H, the products must be true 2,3-dialkyl-4-quinazolones, and this conclusion is in entire harmony with their properties so far observed (insolubility in alkalies, formation of hydrazones, etc.).

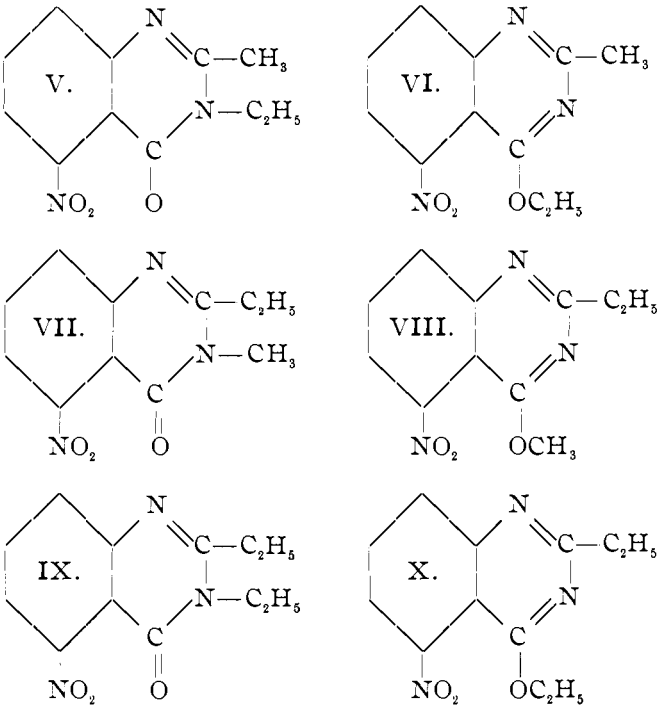
[1] Ber. **14**, 1917 (1881); **15**, 1421 (1882); **18**, 1528 (1885).
[2] Ibid., **17**, 2384 (1884).
[3] Ibid., **17**, 2907 (1884).
[4] Ibid., **35**, 3480 (1902).
[5] Bogert and Chambers, this Journal, **27**, 649 (1905); **28**, 207 (1906).
[6] Ibid., **27**, 1305; **28**, 884.
[7] Ibid., **27**, 1327.
[8] Ibid., **28**, 94.
[9] Ibid., **28**, 1449.

The best method for the preparation of pure 4-alkoxy quinazolines is probably that in which the sodium alcoholate acts upon the 4-halogen quinazoline.

As one of us (Dr. Seil) has been compelled to withdraw from the research, it seems best to publish the results to date, although only a portion of the work outlined above has been completed.

In the prosecution of the investigation some new anthranils and quinazolines have been prepared by old methods, and certain well-known anthranils and quinazolines have been produced by new methods. Acetanthranil, 4- and 6-nitro acetanthranils, and 6-nitro propionanthranil were prepared, and from them, by the action of ammonia, methyl-, ethyl- or amylamine, the corresponding quinazolines were obtained. 5-Nitro-2-methyl-4-hydroxyquinazoline, 5-nitro-2-ethyl-4-hydroxyquinazoline, and 7-nitro-2-methyl-4-hydroxyquinazoline were then subjected to the action of alcoholic alkali and alkyl iodide, and the products compared with the corresponding N-alkyl quinazolones prepared from the anthranils. To take the 5-nitro compounds as a concrete example, we wished to study the following compounds:—





From the anthranils, we prepared I, II, III, V, VII and IX. By ethylation of I and II, VI and X were formed. IV and VIII have not been obtained, as we have not yet carried out the reaction between the chlorquinazolines and alcoholates. By the action of alcoholic alkali and methyl iodide upon I and II, and upon the 7-nitro quinazoline corresponding to I, the N-methyl derivatives resulted in every case. On the other hand, when ethyl iodide was used, the main products were the oxygen ethers VI and X. Of the latter, VI is quite stable, while X is rearranged to IX by crystallization from alcohol.

The investigation is being continued.

Experimental.

I. PREPARATION OF ACYLANTHRANILS.

Acetanthranil, $C_6H_4\begin{cases}CO\\ \\ NCOCH_3\end{cases}$, has been prepared by several methods within recent years. Among others, by the action of acetic anhydride at 150° upon acetanthranilic acid[1]. We have found that it can be prepared in a few minutes, and in any desired amount, simply by boiling down a solution of anthranilic acid in excess of acetic anhy-

[1] Anschütz and Schmidt, Ber. 36, 3473 (1902).

dride. On cooling, the acetanthranil crystallizes out. It is sucked free from excess of acetic anhydride, and pressed dry on a porous plate. This crude product is pure enough for the amine condensations recorded beyond; but, if desired, it may be purified by dissolving in carbon tetrachloride and adding ligroin carefully. A single recrystallization of this kind raised the melting-point to 79°-80°. Anschütz and Schmidt[1] give the melting-point of the pure substance as 80°-81°. The formation of anhydroethenyldianthranilic acid was not observed by us in this method of preparing acetanthranil.

4-Nitro Acetanthranil, $(4)O_2NC_6H_3\langle^{CO\ (1)}_{NCOCH_3\ (2)}$, was prepared from 4-nitro acetanthranilic acid and acetic anhydride, as already reported by Bogert and Steiner[2]. In this former article the anthranil was stated to have a greenish tinge. We have since succeeded in removing this trace of color, and have obtained the substance in colorless crystals of the same melting-point (137°-138° cor.).

6-Nitro Acetanthranil, $(6)O_2NC_6H_3\langle^{CO\ (1)}_{NCOCH_3\ (2)}$, was prepared from 6-nitro acetanthranilic acid and acetic anhydride, as described by Bogert and Chambers[3]. It melts at 155°-156° (cor.).

6-Nitro Propionanthranil, $(6)\ O_2NC_6H_3\langle^{CO\ (1)}_{NCOC_2H_5\ (2)}$ Boiling down 6-nitro anthranilic acid with excess of propionic anhydride, no matter how great the excess of the latter, invariably resulted in a mixture of nitro propionanthranilic acid and nitro propionanthranil. The addition of such condensing agents as concentrated sulphuric acid, zinc chloride, phosphorus chlorides or aluminum chloride, only caused decomposition and charring, and failed to yield the desired anthranil. The method finally worked out was as follows:—The nitro anthranilic acid was boiled for a short time with excess of propionic anhydride. On cooling, nitro propionanthranilic acid separated in small crystals, which were purified by a single recrystallization from ethyl acetate (which removes the anthranil). The purified acid was then treated with considerable excess of acetic anhydride and boiled down directly, in an open flask, to very small bulk. From this highly concentrated solution, the anthranil crystallized out on cooling. It appears to be essential to remove almost all of the solvent acetic acid and anhydride, and then to cool quickly, in order to get a good yield of the anthranil. We did not succeed in getting our product perfectly pure

[1] loc. cit.

[2] This Journal 27. 1330 (1905).

[3] This Journal 27, 653 (1905).

and the analytical results are, therefore, rather poor, but the identity of the substance is well established by its reactions.

Nitrogen found, 12.21 and 12.37. Calculated for $C_{10}H_8O_4N_2$: N, 12.72.

6-Nitro Propionanthranilic Acid, $(6)O_2NC_6H_3\langle^{COOH\ (1)}_{NHCOC_2H_5\ (2)}$, separates from ethyl acetate in hard, glassy, colorless crystals, m. p. 218° (cor.). As stated above, acetic anhydride converts it into the anthranil.

Nitrogen found, 11.85. Calculated for $C_{10}H_{10}O_5N_2$: N, 11.76.

II. PREPARATION OF 3-ALKYL-4-QUINAZOLONES FROM ACYLANTHRANILS AND PRIMARY AMINES.

1. *2-Methyl-4-Quinazolones*[1] *from Acetanthranil.*

2-Methyl-4-quinazolone (2-Methyl-4-hydroxyquinazoline), $C_6H_4\langle^{N=C-CH_3}_{CO-NH} \rightleftharpoons C_6H_4\langle^{N=C-CH_3}_{C(OH)=N}$, was prepared by the action of ammonia upon acetanthranil. By carrying out the reaction in the cold, Anschütz, Schmidt and Greiffenberg[2] obtained acetanthranilamide as the chief product, which they changed to the quinazoline by the action of alkali, as described by Weddige[3].

2,3-Dimethyl-4-quinazolone, from acetanthranil and methylamine, melted at 72°-73° in the hydrated condition, and at 110° when anhydrous. It is identical with the "β,γ-dimethyl-δ-pseudooxychinazolin" obtained by Weddige[4] on methylating 2-methyl-4-hydroxyquinazoline. The suggestion made several years ago by Bogert and Gotthelf[5] that this substance was probably an oxygen ether, because of its low melting-point as compared with that of its 1,2-dimethyl isomer, was ill-advised, not only because it failed to give sufficient weight to Weddige's excellent proof of the structure of his product, but also because, as we have just shown, alkylation with alcohol, alkali and methyl iodide, almost invariably gives the N-methyl derivative. That Weddige was entirely correct in the structure which he assigned to his product, Bogert and Gotthelf were fully convinced before the publication of their second paper on the subject[6], for in the latter they described the various ethers obtained by the action of alcoholic alkali and methyl iodide upon hydroxyquinazolines as —NR derivatives. The production of Weddige's compound from the acetanthra-

[1] For the sake of simplicity, the term quinazolone is used throughout instead of ketodihydroquinazoline.

[2] Ber. 35, 3481 (1902).

[3] J. pr. Chem. (2) 36, 141 (1887).

[4] loc. cit.

[5] This Journal, 22, 533 (1900).

[6] This Journal, 23, 611 (1901).

nil and methylamine is a further corroboration which we are glad to furnish of the accuracy of his formula. The synthesis of the true methoxy isomer we hope to accomplish later.

2. *7-Nitro-2-Methyl-4-Quinazolones from 4-Nitro Acetanthranil.*

7-nitro-2-methyl-4-hydroxyquinazoline (*7-nitro-2-methyl-4-quinazolone*), $(7)O_2N.C_6H_3\langle \overset{N}{\underset{C(OH)}{}} = \overset{C-CH_3}{\underset{N}{}} \rangle \rightleftarrows (7)O_2N.C_6H_3\langle \overset{N}{\underset{CO-NH}{}} = \overset{C-CH_3}{} \rangle$,

has been previously described by Bogert and Steiner[1]. It was prepared from 4-nitro acetanthranil and ammonia, and melts at 275°-277° (cor.).

7-Nitro-2,3-dimethyl-4-quinazolone, from the same anthranil and methylamine, has also been reported by Bogert and Steiner[2]. It melts at 144°-145° (cor.).

7-Nitro-2-methyl-3-ethyl-4-quinazolone, from 4-nitroacetanthranil and ethylamine, melts at 175° (cor.).

Nitrogen found, 17.85. Calculated for $C_{11}H_{11}O_3N_3$: N, 18.00.

7-Nitro-2-methyl-3-isoamyl-4-quinazolone, from 4-nitro acetanthranil and isoamylamine, forms slender crystals, melting at 117-118°.

Nitrogen found, 15.09. Calculated for $C_{14}H_{17}O_3N_3$: N, 15.27.

3. *5-Nitro-2-Methyl-4-Quinazolones from 6-Nitro Acetanthranil.*

The following have been described in previous papers.[3] They were prepared by condensing 6-nitro acetanthranil with ammonia, methyl- and ethylamine respectively.

5-Nitro-2-methyl-4-quinazolone (*5-nitro-2-methyl-4-hydroxyquinazoline*), $(5)O_2N.C_6H_3\langle \overset{N}{\underset{CO-NH}{}} = \overset{C-CH_3}{} \rangle \rightleftarrows (5)O_2N.C_6H_3\langle \overset{N}{\underset{C(OH)}{}} = \overset{C-CH_3}{\underset{N}{}} \rangle$,

melts with decomposition at 277°-279° (cor.).

5-Nitro-2,3-dimethyl-4-quinazolone melts at 203° (cor.). The *hydrochloride* precipitated when concentrated hydrochloric acid was added to an alcoholic solution of the quinazolone. It forms crystals which are small and granular in contradistinction to the long needles of the free quinazolone, and melts at 250° (uncor.). It is hydrolyzed by boiling water.

5-Nitro-2-methyl-3-ethyl-4-quinazolone melts at 208° (cor.).

Brom-5-nitro-2-methyl-4-quinazolone (*brom-5-nitro-2-methyl-4-hydroxyquinazoline*),

$(5)O_2N.C_6H_2Br\langle \overset{N}{\underset{CO-NH}{}} = \overset{C-CH_3}{} \rangle \rightleftarrows (5)O_2N.C_6H_2Br\langle \overset{N}{\underset{C(OH)}{}} = \overset{C-CH_3}{\underset{N}{}} \rangle$,

[1] This Journal, 27, 1330 (1905).

[2] Loc. cit.

[3] Bogert and Chambers; this Journal, 27, 649 (1905); Bogert and Seil, Ibid, 27, 1308.

has not been reported before. When 5-nitro-2-methyl-4-quinazolone was dissolved in the least possible amount of acetic anhydride and the calculated amount of bromine dissolved in the same solvent added, the reaction proceeded very rapidly as soon as the temperature rose slightly. Hydrogen bromide was evolved in large amount and the solution became clear and colorless. On adding more bromine, without further heating, the bromine was rapidly absorbed with evolution of other volatile products as well as hydrogen bromide. After taking up considerable bromine in this way, the solution became suddenly opaque and the bromquinazoline separated from the warm solution as a fine white heavy powder settling rapidly to the bottom of the beaker. Recrystallized from alcohol, it formed hard, compact crystals, which darkened at about 240° and did not melt at 340°.

Nitrogen found, 14.68. Calculated for $C_6H_6O_3N_3Br$: N, 14.78.

The peculiar manner in which one of us (Dr. Seil) was poisoned by the volatile products given off during this bromination has been described in a short paper just published[1].

The catalytic effect of acetic anhydride in brominating quinazolines was observed by us also in the case of 5-nitro-2-methyl-3-diacetamino-4-quinazolone[2], where the reaction proceeded much in the same way as described above[3].

4. *5-Nitro-2-Ethyl-4-Quinazolones from 6-Nitro Propionanthranil.*

This anthranil was condensed with ammonia, methyl- and ethylamine in much the same way as the above, with production of the following compounds:—

5-Nitro-2-ethyl-4-quinazolone (*5-nitro-2-ethyl-4-hydroxyquinazoline*), crystallizes well from dilute alcohol, and melts at approximately 240° (cor.). It resembles the homologous 2-methyl compound in general properties and solubilities, except that it is rather less soluble in water.

Nitrogen found, 19.31. Calculated for $C_{10}H_9O_3N_3$: N, 19.17.

5-Nitro-2-ethyl-3-methyl-4-quinazolone melts at 197°-198° (cor.).

Nitrogen found, 18.09. Calculated for $C_{11}H_{11}O_3N_3$: N, 18.00.

5-Nitro-2,3-diethyl-4-quinazolone melts at 181° (cor.).

Found: C, 57.97; H, 5.01; N, 17.19. Calculated for $C_{12}H_{13}O_3N_3$: C, 58.29; H, 4.85; N, 17.00.

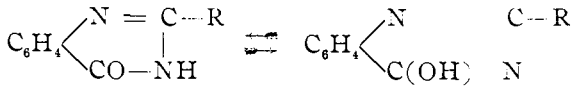
[1] This Journal, **29**, 239.

[2] This Journal, **28**, 888 (1906).

[3] A misprint occurs in the article referred to. The melting point of the brominated quinazolone is given as 110°, instead of which the compound melts roughly in the neighborhood of 170°.

III. ALKYLATION OF 4-HYDROXYQUINAZOLINES (4-QUINAZOLONES) WITH ALCOHOL, ALKALI AND ALKYL IODIDES.

Quinazolines were used of the type



where R was either methyl or ethyl, and the alkylation was carried out either in sealed tubes or at the ordinary pressure, using methyl, ethyl and isoamyl iodides.

In Sealed Tubes.—The quinazoline was mixed with the appropriate alcohol (methyl alcohol for methyl iodide, ethyl alcohol for ethyl iodide) containing the calculated amount of sodium alcoholate, a slight excess of alkyl iodide was added, and the mixture heated in sealed tubes for three to five hours at 140-150°. On opening the cooled tube at the close of the reaction, there was invariably considerable pressure evident, apparently due to the formation of ether, and indications of more or less decomposition, as the tube contents were colored with carbonaceous material and liberated iodine. By extracting with boiling alcohol and treating the solution with bone black, a pure product could usually be obtained. The mother-liquor from these first crystals carried most of the iodine. It was decolorized by sulphur dioxide and a second crop of crystals obtained.

At Ordinary Pressure.—The mixture of quinazoline, alcohol, alkali and alkyl iodide, was boiled gently under a reflux condenser until neutral to litmus. No charring or liberation of iodine occurred, and clean products were the rule.

1. *Methylation.*

Methylation of 5-nitro-2-methyl-4-hydroxyquinazoline.—Three grams of the quinazoline were dissolved in 20 cc. of methyl alcohol, the calculated amount of potassium hydroxide added, and then a slight excess of methyl iodide. The mixture was heated in a sealed tube for four to five hours at 150°. On opening the tube, considerable pressure appeared. The lower end of the tube was filled with needle-like crystals, slightly colored by tar and by iodine. The latter was largely removed by potassium hydroxide solution. By extracting with hot alcohol, treating with bone-black, and recrystallizing from alcohol, the chief product was separated in a pure state. It proved to be identical with the 5-nitro-2,3-dimethyl-4-quinazolone prepared from 6-nitro acetanthranil and methylamine.

Found: C, 54.61 and 54.39; H, 4.21 and 4.25; N, 19.36 and 19.29. Calculated for $C_{10}H_9O_3N_3$: C, 54.79; H, 4.11; N, 19.17.

The experiment was repeated several times, not only in sealed tubes, but also at ordinary pressure, and in every case the product was the N-methyl derivative. An attempt was made to separate the potassium salt of the hydroxyquinazoline by adding an excess of strong potassium hydroxide

solution to a solution of the quinazoline in the same alkali. The salt crystallized out, but could not be freed from excess of alkali without suffering partial hydrolysis. Efforts to obtain the silver salt were also unsuccessful.

In one of the sealed tube experiments noted above, we isolated a small amount of a white crystalline substance, melting above 300°, which was difficultly soluble in alcohol, and left no ash on incineration. It was not formed in sufficient amount to analyze or identify.

Methylation of 5-nitro-2-ethyl-4-hydroxyquinazoline gave invariably the N-methyl derivative, whether the reaction was carried out in sealed tubes or at ordinary pressure. In the latter case the reaction was rapid, the product separating after a few minutes boiling. On recrystallization from alcohol, it gave the beautiful, long, prismatic crystals characteristic of 5-nitro-2-ethyl-3-methyl-4-quinazolone. The melting-point of the product, however, was slightly low, 193°-194°, instead of 196°-197°, and this could not be changed by recrystallization. It was probably due to a trace of difficultly removable impurity.

Nitrogen found, 18.16. Calculated for $C_{11}H_{11}O_3N_3$: N, 18.00.

Methylation of 7-nitro-2-methyl-4-hydroxyquinazoline.—This was carried out only at ordinary pressure, and the product was in every case the N-methyl derivative, identical with that obtained from 4-nitro acetanthranil and methylamine.

An effort was made to prepare certain of the salts of 7-nitro-2-methyl-4-hydroxyquinazoline. The potassium salt was precipitated in good crystalline condition by the addition of concentrated potassium hydroxide to its aqueous solution, but we could not separate or purify it satisfactorily. Attempts to prepare a lead salt by various methods were likewise futile.

2. *Ethylation.*

Ethylation of 5-nitro-2-methyl-4-hydroxyquinazoline.—Most of the reactions carried out in sealed tubes gave a crude product melting in the neighborhood of 230°, which on recrystallization turned out to be only the unchanged quinazoline. But from one tube, run seemingly in just the same way as the others, there was obtained a crystalline compound melting at 164°-165°. This substance was easily secured in large yield when the reaction was carried out at ordinary pressure. It is evidently the ethoxy derivative. Recrystallized from alcohol, it melted sharply at 161° (cor.), and repeated crystallization from alcohol failed to change it to its —NR isomer (m. p. 208° cor.).

Nitrogen found, 18.24. Calculated for $C_{11}H_{11}O_3N_3$: N, 18.00.

The formation of the N-ethyl isomer was not observed in any of the reactions, the products being the oxygen ether and unethylated quinazoline. The oxygen ether was boiled for half an hour with isoamyl iodide, to see

whether the N-amyl quinazolone would be formed and ethyl iodide split off[1], but no such change occurred.

Ethylation of 5-nitro-2-ethyl-4-hydroxyquinazoline.—When the alkylation was carried out at atmospheric pressure, good crystals were obtained, melting sharply at 148-149°, which proved to be the ethoxy compound. On recrystallization from alcohol, they were rearranged completely to the N-ethyl isomer (m. p. 180°-181°). The product from the sealed tubes melted at 166°-167°, and was a mixture of the —OR and —NR isomers, for on recrystallization from alcohol it gave the pure oxygen ether. That this was due to a rearrangement and not to a fractional crystallization seems clear from the fact that there was no loss in the weight of the crystalline material separated and there were no other products in the mother-liquor. This oxygen ether is, therefore, less stable than its methyl homologue.

Nitrogen found, 17.14 and 16.98. Calculated for $C_{12}H_{13}O_3N_3$: N, 17.00.

Ethylation of 7-nitro-2-methyl-4-hydroxyquinazoline gave similar results. The reaction was conducted at ordinary pressure and the only products were the oxygen ether and unchanged quinazoline. The oxygen ether melts at 105°-106° (cor.), while the isomeric N-ethyl compound has a melting-point of 175° (cor.). Recrystallized from alcohol, it showed no inclination to pass into its isomer, resembling in this respect the corresponding 5-nitro compound.

Nitrogen found, 17.95. Calculated for $C_{11}H_{11}O_3N_3$: N, 18.00.

3. *Amylation.*

Amylation of 7-nitro-2-methyl-4-hydroxyquinazoline.—The experiments were conducted both at ordinary pressure and in sealed tubes at 150°. Ethyl alcohol was used as the solvent. In all cases the chief products were the oxygen ether and unchanged quinazoline. The latter was easily removed by washing with dilute alkali. The pure isoamyloxy compound forms large, flat plates, which melt at 104° (cor.), and no rearrangement is effected by boiling alcohol.

Nitrogen found, 15.41. Calculated for $C_{14}H_{17}O_3N_3$: N, 15.27.

Organic Laboratory, Columbia University.
December, 1906.

[CONTRIBUTIONS FROM THE HAVEMEYER CHEMICAL LABORATORY, NEW YORK UNIVERSITY.]

ON THE PRINCIPLE OF OPTICAL SUPERPOSITION. II

BY M. A. ROSANOFF.

Received February 26, 1907.

In my first paper on the subject[2] I showed that the universally accepted

[1] Compare Knorr; *Ann.*, **236**, 87, (1887).

[2] This Journal, **28**, 525 (1906); Z. physik. Chem., **56**, 565 (1906.) To the bibliography mentioned in that paper should be added: Percy Frankland and Price, J. Chem. Soc., **1897**, 266-268.