bromides so obtained was converted to oxides and in turn converted to the corresponding chlorides. The dichloride was obtained from this mixture by fractional distillation. Pure dibromide and difluoride were prepared by converting pure dichloride to its oxide and treating with hydrobromic or hydrofluoric acid.

The three dihalides are liquids at ordinary temperatures and are readily soluble in the common organic solvents. They may be distilled under pressures below 0.01 mm. at temperatures between 100 and 150°. The fluoride is markedly sensitive to moisture.

Diphenyl germanium imine was prepared by the action of liquid ammonia on diphenyl germanium dichloride. It is a highly viscous liquid at ordinary temperatures. It is readily soluble in the common organic solvents and is hydrolyzed with extreme ease.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY, CASE SCHOOL OF APPLIED SCIENCE]

QUINAZOLINES. I. THE INTERACTION OF 2,4-DICHLOROQUINAZOLINE WITH SODIUM ALCOHOLATES AND SODIUM PHENATES WITH THE REPLACEMENT OF ONE HALOGEN TO FORM HALOGEN-OXYGEN ETHERS

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Since evodiamine and rutaecarpine, the alkaloids of *Evodia rutaecarpa*, have been shown to be derivatives of quinazolone[1] and since the quaternary salts of a few quinazolines have been found to have a lowering effect on the blood pressure,[2] it appears likely that other compounds of the quinazoline group might possess some desirable medicinal properties. It was during the course of a research now in progress in this Laboratory, the purpose of which was the preparation of a series of quinazoline derivatives for subsequent pharmacological testing,[3] that several anomalous compounds were obtained and a further investigation of these compounds was made because the quinazolines have an intrinsic interest of their own.

When 2,4-dichloroquinazoline (I) in alcohol is treated with sodium ethylate both halogens are replaced by ethoxy groups with the formation of 2,4-diethoxyquinazoline (V).[4] In attempting to prepare a similar ether of quinazoline with the phenolate of resorcinol in alcohol, several compounds were isolated from the reaction product which were found to differ from the expected ether. When phenol was substituted for resorcinol, it

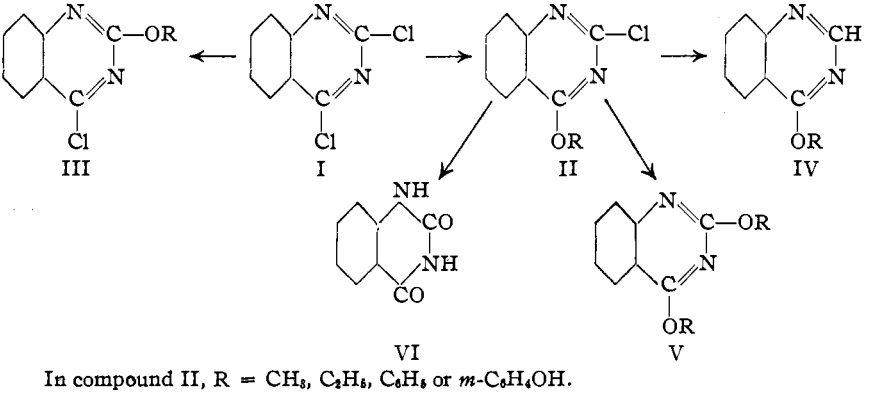
[1] Asahina, Manske and Robinson, *J. Chem. Soc.*, **129**, 1708 (1927).

[2] Gabriel and Colman, German Patent 161,401.

[3] The writers are indebted to Professor Marston Taylor Bogert for his suggestion that members of this group of compounds be prepared with this idea in mind.

[4] Abt, *J. prakt. Chem.*, [2] 39, 149 (1889).

was found that one of the reaction products was identical with one obtained when resorcinol was used. On further investigation by chemical analysis, molecular weight determination and chemical properties, the compound was found to be the monochloro-ethoxy derivative of quinazoline (II or III). That a compound with the formula II or III is formed is also shown by the fact that when it is treated with sodium ethylate in ethyl alcohol it yields the diethoxy derivative of quinazoline mentioned above. From this it is evident that one of the two chlorine atoms in dichloroquinazoline is more labile than the other. To establish the position of the unreacted halogen and thus decide whether the structural formula for the compound is best expressed by II or by III, an attempt was made to hydrolyze off the remaining chlorine atom by gently heating the chloro-ethoxy derivative with water. These attempts were not successful as either no hydrolysis took place after a short time or after continued heating both the chlorine atom and the ethoxy group were removed yielding benzoylene urea. The replacement of the halogen by hydrogen by treatment of the Grignard reagent with water was not successful, inasmuch as it was found impossible to bring about the formation of an RMgCl compound with the chloro-ethoxyquinazoline and magnesium. Nearly all of the original chloro-ethoxy derivative was recovered unchanged when the attempted reduction was carried out with (a) sodium amalgam and ether saturated with water, (b) sodium and ethyl alcohol, (c) sodium and ether saturated with water, (d) sodium and amyl alcohol, or (e) zinc, sodium hydroxide and ethyl alcohol; however, when reduced with (f) sodium and methyl alcohol in ether or (g) with zinc and acetic acid in ethyl alcohol, it yielded a product which was found to be identical with the 4-ethoxyquinazoline (IV) previously prepared by Bogert and May.[5] From this it is evident that the structure of the chloro-ethoxy derivative is best expressed by formula II and that the chlorine atom on postion 4 is more reactive than



In compound II, R = CH_3, C_2H_5, C_6H_5 or m-C_6H_4OH.

[5] Bogert and May, THIS JOURNAL, 31, 510 (1909).

the chlorine atom on position 2; that groups attached to carbon atom 4 are more labile than those on carbon atom 2 has been observed previously in the case of 4-methoxyquinazoline, which is easily hydrolyzed to 4-quinazolone, whereas 2-methoxyquinazoline required heating with concentrated hydrochloric acid in a sealed tube at 110–120° for one and one-half hours for a similar removal of the alkoxy group[5] and also in the greater ease with which the halogen is removed by hydrolysis from 4-chloroquinazoline as compared with the removal of halogen from 2-chloroquinazoline.[6]

In a similar manner it was found that it is possible to obtain the monochloromethoxyquinazoline. The monochloro-alkoxy derivatives are fairly soluble in petroleum ether; when the original reaction mixture in their preparation is recrystallized from this solvent, varying amounts of an insoluble by-product are obtained which consists almost entirely of the analogous monochlorophenoxy derivative and by varying the amount of phenol used in the reaction the yield of the chlorophenoxy derivative can be increased at the expense of the chloro-alkoxy derivative.

The reduction product of the chloromethoxy derivative was a light yellow oil with a pleasant odor, which did not crystallize on standing for a week in an ice box; whether it would have crystallized on longer standing is not known. However, the oil had characteristics which were the same as those given by Bogert and May[5] for 4-methoxyquinazoline prepared from 4-chloroquinazoline. When the chloromethoxy derivative is treated with sodium methylate in methyl alcohol it gives 2,4-dimethoxyquinazoline.[4]

These reactions for the replacement of but one of the two halogens by means of the presence of phenol appear to offer interesting possibilities in the case of quinazolines for the synthesis of mixed ethers and other similar compounds. Preliminary experiments have shown that this is possible and it is hoped to present these results in a later communication. The possibility of using phenol to repress the activity of the less reactive of two halogens in other types of compounds is also suggested.

Experimental Part

Preparation of 2,4-Dichloroquinazoline, $\overline{N{=}CClC_6H_4N{=}CCl}$ (I).[6,7]—In an acetylating flask were placed 15 g. of benzoylene urea (2,4-diketotetrahydroquinazoline),[8] 40 g. of phosphorus pentachloride and 20 cc. of phosphorus oxychloride and the mixture was refluxed on an oil-bath at 125° for about four hours. The clear brown liquid which results was poured slowly with stirring into 600 cc. of finely crushed ice. The precipitated dichloroquinazoline was immediately filtered off on a Büchner funnel, holding the remaining ice back in the beaker with a stirring rod. The precipitate was thoroughly pressed on the funnel, the aqueous filtrate was discarded and the residue dissolved in

[6] Gabriel and Stelzner, *Ber.*, **29**, 1300 (1896); Gabriel and Colman, *ibid.*, **38**, 3559 (1905).

[7] Bogert and Scatchard, THIS JOURNAL, **41**, 2061 (1919).

[8] Bogert and Scatchard, *ibid.*, **38**, 1612 (1916).

about 500 cc. of ether, using 50-cc. portions of ether at a time and filtering through the same funnel; a small amount of insoluble material remained and was discarded. The combined ether solutions were washed in a separatory funnel, first with dilute aqueous sodium carbonate and then with water. After drying the ether solution overnight with calcium chloride, the ether was removed by distillation from a water-bath, suction being applied at the end of the distillation to remove the last traces of ether. This product (12.4 g.) which remained in the distillation flask was slightly yellow but was found to be sufficiently pure for the syntheses described below. To obtain a very pure product it was dissolved in the minimum amount of boiling toluene, filtered hot, cooled, the crystals filtered with suction and washed with petroleum ether, in which it is insoluble; using the same quantities as above about 6 g. of recrystallized, colorless material was obtained; a further small amount was obtained by adding petroleum ether to the mother liquor; m. p. 120°. The compound must be used shortly after preparation as it gradually decomposes even when protected in a desiccator.

Preparation of 2-Chloro-4-ethoxyquinazoline, $\overline{N{=}COC_2H_5C_6H_4N{=}CCl}$ (II).— To 50 cc. of absolute ethyl alcohol in a small flask was added 0.7 g. of sodium, keeping the solution cool; when all of the sodium had reacted, 1.4 g. of phenol was added and then 3 g. of dichloroquinazoline slowly with stirring. The mixture was heated just to boiling and allowed to stand at room temperature overnight; it was then poured into 500 cc. of cold water, where it coagulated in fifteen to twenty minutes; the precipitate was filtered with suction, pressed thoroughly on the filter and recrystallized from petroleum ether, yielding 2.3 g. of colorless crystals; m. p. 92° (corr.). It is readily soluble in benzene, ether, carbon tetrachloride or acetone, fairly soluble in petroleum ether or alcohol, crystallizing well from the latter, and insoluble in water. When subjected to steam distillation a part of the compound volatilized into the distillate; the balance because of hydrolysis to benzoylene urea remained as a non-volatile residue. To determine the best proportions of sodium and phenol, the preparation was carried out as above in 50 cc. of alcohol with 2.5-g. portions of dichloroquinazoline; 0.5 g. of sodium and 2 g. of phenol gave 1 g. of product; 0.5 g. of sodium and 1 g. of phenol gave 2.5 g. of product; 1 g. of sodium and 4 g. of phenol gave 0.8 g. of product and 2.4 g. of chlorophenoxyquinazoline, which is insoluble in petroleum ether and which is described below; 0.5 g. of sodium and 4 g. of phenol gave 0.4 g. of product and 2.1 g. of chlorophenoxyquinazoline. Molecular weight determinations by depression of the freezing point were made with naphthalene as the solvent; the values of 227 and 229 were obtained; the calculated value is 208.5.

Anal. Calcd. for $C_{10}H_9ON_2Cl$: C, 57.55; H, 4.35; N, 13.4; Cl, 17.0. Found: C, 58.01; H, 4.40; N, 13.5; Cl, 17.1.

Preparation of 2-Chloro-4-methoxyquinazoline, $\overline{N{=}COCH_3C_6H_4N{=}CCl}$ (II).— This compound was prepared in a methyl alcohol solution in a manner similar to the preparation of the analogous chloro-ethoxy derivative as described above; 2.5 g. of product after recrystallization from petroleum ether was obtained from 0.7 g. of sodium, 50 cc. of methyl alcohol, 1.4 g. of phenol and 3 g. of dichloroquinazoline; it forms colorless crystals from petroleum ether or alcohol; m. p. 99–100° (corr.). It is readily soluble in benzene, ether, carbon tetrachloride or acetone, fairly soluble in petroleum ether, methyl alcohol or ethyl alcohol, and insoluble in water; it is volatile with steam but with partial decomposition into the non-volatile benzoylene urea. A molecular weight determination by the Rast method[9] using camphor for the solvent gave a value of 191; the calculated molecular weight is 194.5.

[9] Rast, *Ber.*, **55**, 1051, 3727 (1922).

Anal. Calcd. for $C_9H_7ON_2Cl$: C, 55.52; H, 3.63; Cl, 18.2. Found: C, 56.28; H, 3.79; Cl, 18.4.

Preparation of 2-Chloro-4-phenoxyquinazoline, $\overline{N=COC_6H_4C_6H_4N=CCl}$ (II).—This compound was obtained by allowing 0.95 g. of sodium to react completely with an excess of molten phenol; then 8 g. of powdered dichloroquinazoline was mixed with the solid phenol-sodium phenate, which gradually liquefied during the mixing; after standing overnight the reaction mixture was poured into 700 cc. of cold water, when a viscous oil separated; this oil solidified and became granular after the aqueous solution was made slightly alkaline with sodium hydroxide; the solid residue was removed by filtration, washed with water and recrystallized from alcohol; 4.5 g. of colorless crystals was obtained; 2.1 g. of this compound was also obtained from the interaction of 0.5 g. of sodium, 4 g. of phenol and 2.5 g. of dichloroquinazoline in 50 cc. of ethyl alcohol, as described under the preparation of the chloro-ethoxy derivative. The compound is fairly soluble in ethyl alcohol, methyl alcohol, acetone, benzene or ethyl acetate, slightly soluble in ether or chloroform, insoluble in petroleum ether or water; m. p. 121° (corr.).

Anal. Calcd. for $C_{14}H_9ON_2Cl$: Cl, 13.8. Found: Cl, 13.9.

Preparation of 2-Chloro-4-resorcinoxyquinazoline, $\overline{N=C(OC_6H_4OH)C_6H_4N=CCl}$ (II).—Fifty cc. of absolute ethyl alcohol was treated with 2.5 g. of sodium; after all of the sodium had reacted, 16 g. of resorcinol was added and then 9 g. of dichloroquinazoline was added slowly in small portions during three hours; after standing overnight, the brown colored solution was poured into one liter of water, the mixture made neutral to litmus, the precipitate allowed to coagulate, filtered, washed with water and dried on a suction filter. The air-dried material (9.5 g.) was extracted with boiling petroleum ether, which removed 2.5 g. of chloro-ethoxyquinazoline; the residue of 7 g. was almost completely soluble in boiling alcohol, from which colorless crystals of 2-chloro-4-resorcinoxyquinazoline separated on cooling; m. p. 171–172° (corr.). The solubilities of this compound are like those of the corresponding chlorophenoxy derivative described above.

Anal. Calcd. for $C_{14}H_9O_2N_2Cl$: C, 61.65; H, 3.33. Found: C, 61.78; H, 3.46.

Preparation of 2,4-Diethoxyquinazoline (V).—Thirty cc. of absolute ethyl alcohol was treated with 0.3 g. of sodium; after all of the sodium had reacted, 2 g. of chloroethoxyquinazoline was added; the solution was warmed gently for five to ten minutes and allowed to stand at room temperature overnight, when about 0.5 g. of sodium chloride separated and was removed by filtration. The filtrate was treated with water, which precipitated 1.8 g. of diethoxyquinazoline; after filtering and drying, it was recrystallized from alcohol, yielding colorless crystals; m. p. 55° (corr.). Although this melting point is 4° higher than that of the diethoxyquinazoline as reported by Bogert and May,[5] there is no doubt as to the identity of the two products, since a sample of the material obtained by their method of preparation also showed a melting point of 55° (corr.) and when the two preparations were mixed the melting point remained unchanged; examination of the two products under a polarizing microscope showed the same angle of extinction in each case.

Anal. Calcd. for $C_{12}H_{14}O_2N_2$: C, 66.02; H, 6.47. Found: C, 66.33; H, 6.62.

Preparation of 2,4-Dimethoxyquinazoline (V).—This compound was prepared by the interaction of chloromethoxyquinazoline and sodium methylate in methyl alcohol in the same manner as the diethoxy derivative described above. Three grams of chloromethoxyquinazoline and 0.4 g. of sodium in 30 cc. of absolute methyl alcohol gave about 0.9 g. of sodium chloride and 2.7 g. of the dimethoxy derivative, which was recrystallized from alcohol; m. p. 75° (corr.); Bogert and Scatchard[7,8] reported a melting point of 74° for dimethoxyquinazoline but a sample prepared by their method when

carefully purified was found to melt at 75°; an examination under a polarizing microscope and a mixed melting point determination of the two products proved their identity.

Anal. Calcd. for $C_{10}H_{10}O_2N_2$: C, 63.12; H, 5.30. Found: C, 63.25; H, 5.38.

Preparation of 4-Ethoxyquinazoline (IV).—To 6 g. of chloro-ethoxyquinazoline (1 mol) dissolved in 50 cc. of absolute ether were added 0.67 g. of sodium (1 mol) in small pieces and then 0.93 g. methyl alcohol (1 mol); the sodium gradually reacted with the alcohol and after three days at room temperature the sodium chloride was removed by filtration, the ether removed from the filtrate by distillation from a water-bath, suction being applied at the end of the distillation; the light yellow oil which remained was poured on a watch glass and partly solidified on standing for a week in an ice box; the colorless crystals (1 g.) were filtered with suction, pressed between filter paper to remove adhering oil and were recrystallized with much difficulty from alcohol; m. p. 45–48°. A better yield of the same product was obtained when 3.6 g. of chloro-ethoxyquinazoline was dissolved in 150 cc. of alcohol, 15 g. of zinc dust added and 25 cc. of glacial acetic acid added slowly with mechanical stirring; after standing at room temperature for twenty-four hours, the mixture was filtered to remove the excess of zinc and the filtrate poured into 500 cc. of cold water; the unreduced chloro-ethoxyquinazoline which precipitated was collected and recrystallized for recovery. The dilute alcoholic solution was made slightly basic by the addition of sufficient sodium hydroxide solution, which precipitated zinc hydroxide; the filtered solution (about 600 cc.) was then extracted with ether, the extract dried overnight with calcium chloride and the ether removed by distillation from a water-bath. The yellow oil which remained was distilled with steam the distillate extracted with ether, the ether solution dried with calcium chloride and the ether removed by distillation on a water-bath, removing the last traces of ether under a vacuum. As soon as the residual oil with a pleasant odor was poured on a watch glass it began to crystallize until the mass was almost completely solid; the material thus obtained was pressed between filter paper to remove traces of adhering oil and had a melting point of 46–48° (corr.); mixed with a known sample of 4-ethoxyquinazoline (m. p. 47–49°) prepared by the method of Bogert and May,[5] the mixture showed a melting point of 47–48°. Without further purification, this material obtained by the reduction with zinc and acetic acid was used for analysis.

Anal. Calcd. for $C_{10}H_{10}ON_2$: C, 68.93; H, 5.79. Found: C, 69.07; H, 5.81.

Reduction of 2-Chloro-4-methoxyquinazoline and 2-Chloro-4-phenoxyquinazoline.—These reductions were made in alcohol with zinc and acetic acid as described above under the reduction of the analogous chloro-ethoxy derivative and in each case gave yellow-brown oils which did not crystallize on standing in a cold place; the product from the chloromethoxy derivative had a pleasant odor, whereas that from the chlorophenoxy derivative had a very disagreeable odor. Material of sufficient purity for analysis was not obtained.

Preparation of Benzoylene Urea (VI) by Hydrolysis of Chloromethoxyquinazoline.—Three grams of chloromethoxyquinazoline was suspended in 150 cc. of distilled water, warmed on the steam-bath for five hours, filtered, the insoluble portion washed with water, then with alcohol and dried; it was a white product which did not melt below 300°; it was submitted to analysis without further purification. The filtrate above gave a distinct test for chlorides and had a slight odor of methyl anthranilate.

Anal. Calcd. for $C_8H_6O_2N_2$: C, 59.22; H, 3.73. Found: C, 59.49; H, 3.87. Hydrolysis of chloro-ethoxyquinazoline similarly gave the same product.

Summary

A study has been made of the interaction of 2,4-dichloroquinazoline with sodium alcoholates in the presence of phenol and resorcinol and it was

found possible to replace but one of the two halogen atoms with an OR group (where R is either an alkyl or an aryl radical). The structure of the resulting compounds has been determined and shows that the halogen attached to the carbon atom at position 4 is more reactive than the halogen atom on carbon atom 2. Recrystallization of dichloroquinazoline from toluene or toluene plus petroleum ether yields a very pure product; these solvents are superior to benzene (which had been previously used in the preparation) because of the greater temperature coefficient of solubility. The following new compounds have been prepared: 2-chloro-4-methoxyquinazoline, 2-chloro-4-ethoxyquinazoline, 2-chloro-4-phenoxyquinazoline and 2-chloro-4-resorcinoxyquinazoline.

CLEVELAND, OHIO

[CONTRIBUTION FROM THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY, MELLON INSTITUTE OF INDUSTRIAL RESEARCH, UNIVERSITY OF PITTSBURGH]

THE PREPARATION OF CERTAIN GAMMA-LACTONES

BY WILLIAM L. NELSON AND LEONARD H. CRETCHER

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Gamma-butyrolactone was prepared by a method which involves (1) the condensation of the sodium salt of ethyl malonate with β-chloro-ethylvinyl ether to form ethyl vinyloxyethylmalonate,[1] (2) saponification of the ester, (3) liberation of the free acid with simultaneous hydrolysis and liberation of acetaldehyde to form β-hydroxyethylmalonic acid, (4) pyrogenic decomposition to the lactone of γ-hydroxybutyric acid. The alpha-substituted ethyl and propyl butyrolactones were prepared in the same manner from the corresponding alkyl malonic esters.

Fittig and Chanlarow[2] prepared the α-ethyl derivative by hydrolysis of ethyl β-hydroxyethylacetoacetate. The unsubstituted lactone has been prepared by a variety of methods.[3]

It is interesting to note that in Fittig's description of α-ethyl butyrolactone he stated that a clear, approximately saturated water solution of the lactone on warming in the hand became clouded and remained so when placed in hot water until a temperature between 80–90° was reached, whereupon the second phase disappeared to reappear upon slight lowering of the temperature. When cooled more strongly, the solution again became clear. We have repeated Fittig's experiment with the same result. So far as the authors are aware, this is the first mention in the literature of a

[1] Cretcher, Koch and Pittenger, THIS JOURNAL, **47**, 1173 (1925).

[2] Fittig and Chanlarow, *Ann.*, **226**, 327 (1884).

[3] (a) Frühling, *Monatsh.*, **3**, 700 (1882); (b) Michael, *Ber.*, **34**, 4053 (1901); (c) Henry, *Bull. soc. chim.*, [2] **45**, 341 (1886); (d) Bentley, Haworth and Perkin, *J. Chem. Soc.*, **69**, 168 (1896); (e) Willstätter, *Ber.*, **35**, 619 (1902); (f) Fittig and Roder, *Ann.*, **227**, 23 (1885); (g) Marvel and Birkhimer, THIS JOURNAL, **51**, 260 (1929).