after filtering, the alkali solutions were acidified with acetic acid, when the cyanamide separated either as an oil or as a solid.

Summary

Bromate in alkaline solution is an efficient reagent for desulfurization of thioureas. Owing to decomposition by heat thioureas often give varied melting points; they are best recrystallized from toluene.

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QUINAZOLINES. IV. ALCOHOLYSIS IN THE QUINAZOLINE SERIES AND THE PREPARATION OF SOME MIXED DIETHERS OF QUINAZOLINE

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In the course of some experiments with 2,4-dichloroquinazoline it was observed that one of the two chlorine atoms present in this compound undergoes substitution more readily than the other, and that under proper conditions monochloroquinazolines only are formed. By converting these monochloro derivatives into known compounds, the location of the entering groups was ascertained and the more reactive chlorine atom assigned to the 4-position.[1]

When warm alcoholic solutions of 2,4-dichloroquinazoline are treated with potassium cyanide or other salts of weak acids, 2-chloro-4-ethoxyquinazoline is formed. In order to explain this it was assumed that in such solutions of 2,4-dichloroquinazoline there exists an equilibrium between the chlorine at the 4-position and the solvent, thus

$$C_8H_4N_2Cl_2 + C_2H_5OH \rightleftharpoons C_8H_4N_2ClOC_2H_5 + HCl$$

and that with conditions providing for the speedy removal of the hydrogen chloride formed, as does the presence of salts of weak acids, the reaction to the right is favored.[2] This mechanism is not limited to the alcohols, however, for on merely shaking 2,4-dichloroquinazoline with aqueous sodium hydroxide, 2-chloro-4-ketodihydroquinazoline results.[3]

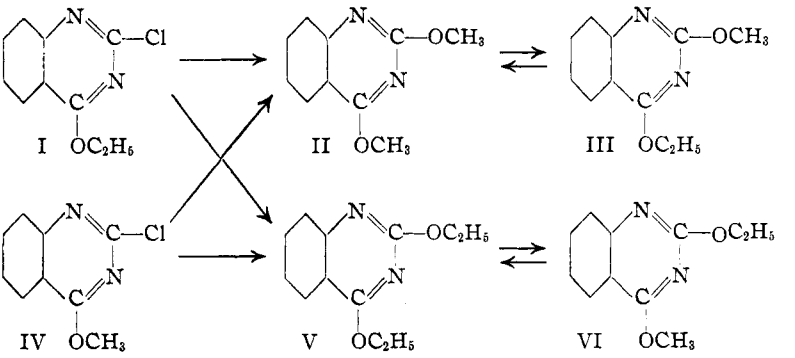
The formation of 2,4-diethoxyquinazoline (V) from 2-chloro-4-ethoxyquinazoline (I) and alcoholic sodium ethylate was described in an earlier paper.[4] This and the corresponding reaction between 2-chloro-4-methoxyquinazoline (IV) and methyl alcoholic sodium methylate to give 2,4-dimethoxyquinazoline (II) indicated that mixed diethers of the types III and VI might be prepared by treating 2-chloro-4-ethoxy- and 2-chloro-4-

[1] Lange, Roush and Asbeck, THIS JOURNAL, **52**, 3696 (1930).

[2] Lange and Sheibley, *ibid.*, **53**, 3867 (1931).

[3] British Patent 287,179.

[4] THIS JOURNAL, **52**, 3700 (1930).

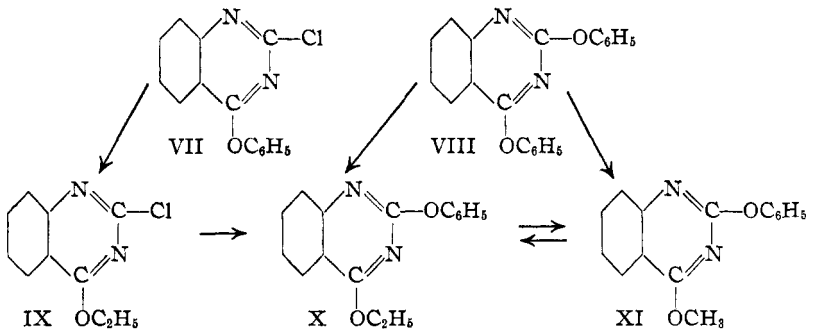


methoxyquinazolines (I and IV) with sodium methylate and sodium ethylate, respectively. Preliminary experiments in this direction, however, soon indicated that the characteristic reactivity of the 4-position in quinazoline was not by any means confined to halogen substituents only. 2-Chloro-4-methoxyquinazoline (IV) was allowed to react with sodium ethylate in alcohol, but the product was 2,4-diethoxyquinazoline (V) instead of the expected 2-ethoxy-4-methoxy derivative (VI). Similarly, sodium methylate in methyl alcohol converted 2-chloro-4-ethoxyquinazoline (I) into 2,4-dimethoxyquinazoline (II). These unexpected results suggested that perhaps in alcoholic solutions of 4-alkoxyquinazolines there exists an equilibrium between the 4-alkoxy group and the solvent, similar in form to the expression already proposed for 2,4-dichloroquinazoline, and such that under alkaline conditions the alcohol present in decided excess almost wholly determines the nature of the product.

From the views just presented it was reasonable to infer that 2,4-diethoxyquinazoline (V), say, on treatment with sodium methylate, would give the desired 2-ethoxy-4-methoxyquinazoline (VI). This was found to be the case, and a corresponding treatment of 2,4-dimethoxyquinazoline (II) with sodium ethylate resulted in the formation of the isomeric 2-methoxy-4-ethoxyquinazoline (III). These mixed quinazoline dialkyl ethers are colorless crystalline solids with properties intermediate between those of diethoxy and dimethoxyquinazolines, and possess the characteristic pleasant fruit-like odor which is especially pronounced in the case of the dimethoxy derivative. The alcoholysis leading to their formation is reversible, for on treating them with sodium dissolved in the alcohols corresponding with their 2-substituents, the initial dialkoxy compounds were again obtained. Thus 2-ethoxy-4-methoxyquinazoline (VI) and sodium ethylate in alcohol gave 2,4-diethoxyquinazoline (V), and 2-methoxy-4-ethoxyquinazoline (III) in methyl alcohol in the presence of sodium methylate was transformed into 2,4-dimethoxyquinazoline (II).[5]

[5] Compare Johnson and Guest, THIS JOURNAL, **32**, 1280 (1910); also Reid, *Am. Chem. J.*, **45**, 487 (1911).

A corresponding behavior was observed with 4-phenoxyquinazolines. The product of the action of alcoholic sodium ethylate on 2-chloro-4-phenoxyquinazoline (VII) was 2-chloro-4-ethoxyquinazoline (IX) and not the mixed diether, 2-ethoxy-4-phenoxyquinazoline. A similar treatment of 2,4-diphenoxyquinazoline (VIII)[6] produced the now expected mixed diether, 2-phenoxy-4-ethoxyquinazoline (X), which was also obtained by adding 2-chloro-4-ethoxyquinazoline (IX) to sodium dissolved in molten phenol. The failure of phenol, under these conditions, to replace the 4-ethoxy group with a phenoxy group is in accord with the thesis put forward previously[7] to the effect that sodium phenate, in alcoholic solutions of 2,4-dichloroquinazoline, does not act as an acid remover as do sodium alcoholates, but reacts directly with the 4-chlorine atom, splitting out sodium chloride and forming 2-chloro-4-phenoxyquinazoline. By employing methyl alcohol and acting on 2,4-diphenoxyquinazoline (VIII) with sodium methylate, the analogous 2-phenoxy-4-methoxyquinazoline (XI) was prepared. This substance, treated with alcoholic sodium ethylate, reverted to the known (from IX) 2-phenoxy-4-ethoxyquinazoline (X), which action is also reversible, the ethoxy derivative (X) giving the methoxy derivative (XI) again, through the action of sodium methylate.



When the treatment with sodium alcoholates leading to these changes is prolonged, hydrolysis ensues and alkali-soluble derivatives of 4-keto-dihydroquinazoline result. These products are being studied and will be described in a subsequent communication. In a search for water-soluble substances, a di-β-hydroxy derivative of 2,4-diethoxyquinazoline was prepared and is included as a matter of record.

All melting points given in this paper are corrected.

Experimental Part

The alcoholysis of the chloro-alkoxyquinazolines (I, IV) was effected by warming them almost to the boiling point in an alcoholic solution of sodium alcoholate, then al-

[6] U. S. Patent 1,758,792.

[7] Lange and Sheibley, THIS JOURNAL, **53**, 3868 (1931).

lowing the solution to stand at room temperature overnight, filtering from the precipitated sodium chloride and pouring the filtrate into water. Warming on the steam-bath for an hour an alcoholic solution of sodium alcoholate and dimethoxy- or diethoxyquinazoline and then precipitating the product by pouring into water gave the mixed dialkoxy derivatives (III, VI) formed by alcoholysis of the group in position 4. Such mixed diethers are hydrolyzed to benzoylene urea by boiling their alcoholic solutions with a few drops of concentrated hydrochloric acid. 2-Chloro-4-phenoxyquinazoline was converted into 2-chloro-4-ethoxyquinazoline by allowing a mixture of the former and sodium alcoholate in alcohol to stand overnight at room temperature and then warming slightly, the ethoxy derivative (IX) crystallizing out directly on cooling. When, however, this reaction mixture was heated immediately instead of first being allowed to stand overnight, impure diethoxyquinazoline (V) and not 2-chloro-4-ethoxyquinazoline resulted. The 2-phenoxy-4-alkoxyquinazolines (X, XI) were prepared by warming on the steam-bath a mixture of 2,4-diphenoxyquinazoline and sodium alcoholate in alcohol for one to two hours, or until all of the diphenoxyquinazoline had dissolved and no solid separated on cooling, after which the solution was poured into water and allowed to coagulate. The compounds obtained by alcoholysis, their properties and the yields of the crude precipitated products obtained are given in Table I.

Preparation of 2-Phenoxy-4-ethoxyquinazoline (X) from 2-Chloro-4-ethoxyquinazoline (IX).—Ten grams of phenol in which 0.4 g. of sodium had been dissolved was treated with 1.8 g. of 2-chloro-4-ethoxyquinazoline, and the mixture warmed on a steam-bath for two hours. After standing overnight it was poured into about 100 cc. of water, sodium hydroxide solution was added to dissolve the excess phenol, and the heavy oil which had separated soon became solid. This was filtered, dried and weighed 2.2 g. Crystallization from alcohol gave small yellow-tinged tabular crystals, m. p. 107–108°.

Anal. Calcd. for $C_{16}H_{14}O_2N_2$: C, 72.15; H, 5.30. Found: C, 72.58; H, 5.43.

Preparation of 2,4-Diphenoxyquinazoline (VIII).—About 30 g. of warm molten phenol was treated with 0.8 g. of sodium. After all of the sodium had reacted, the mixture was heated to 130° in an oil-bath and 3 g. of 2,4-dichloroquinazoline added slowly with stirring. It was then heated at 170° for one hour and allowed to stand overnight, when it solidified. The solid mass was stirred with 200 cc. of water, and strong sodium hydroxide solution added until the excess phenol had dissolved and the residual oil solidified. The product was filtered and washed, first with dilute acetic acid and then with water, and weighed 4.1 g. after drying. Crystallized from acetone followed by a recrystallization from glacial acetic acid, it formed small rhomb-shaped crystals, m. p. 160–161°, which are sparingly soluble in alcohol, and very sparingly soluble in ether. On boiling with dilute hydrochloric acid (1:1) it is decomposed into phenol and benzoylene urea. Boiling with alcoholic aniline does not affect it.

Anal. Calcd. for $C_{20}H_{14}O_2N_2$: C, 76.40; H, 4.49. Found: C, 76.09; H, 4.63.

Preparation of $\overline{N{=}C(OCH_2CH_2OH)C_6H_4N{=}C}OCH_2CH_2OH$, 2,4-Di-β-hydroxyethoxyquinazoline.—This compound is fairly soluble in water and glycol, rendering its isolation difficult. Two grams of 2,4-dichloroquinazoline was added to 0.5 g. of sodium dissolved in 25 cc. of freshly distilled glycol, and the mixture was heated on a steam-bath for two hours. After diluting with 150 cc. of water the solution was made acid with acetic acid, and filtered from any oily droplets which had separated. About 25 g. of salt was stirred into the filtrate, ammonia was added in slight excess over the acidity, and the resulting brine heated on the steam-bath for one hour. On aspirating air over the surface of this liquid for some days, white crystalline crusts separated; these were removed and the aspirating of air over the surface of the mother liquors was continued. The total solids thus obtained were dried and combined, and extracted with about 100

TABLE I

TRANSFORMATIONS OF 2,4-QUINAZOLINE ETHERS BY ALCOHOLYSIS

Starting material Quinazoline	G.	Sodium, g.	Abs. alc., cc.	Water, cc.	Product formed Quinazoline	G.	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
2-Chloro-4-ethoxy-(I)	3	0.4	30 Me	150	2,4-Dimethoxy-(II)[a]	2.2	75	$C_{10}H_{10}O_2N_2$	63.12	63.26	5.30	5.15
2-Chloro-4-methoxy-(IV)	3	.4	30 Et	150	2,4-Diethoxy-(V)[a]	2.7	55	$C_{12}H_{14}O_2N_2$	66.02	66.51	6.47	6.45
										66.45		5.99
2,4-Dimethoxy-(II)	1	.15	25 Et	80	2-Methoxy-4-ethoxy-(III)[b]	0.95	57– 58	$C_{11}H_{12}O_2N_2$	64.67	65.02	5.93	6.05
2,4-Diethoxy-(V)	1	.15	25 Me	80	2-Ethoxy-4-methoxy-(VI)[c]	0.9	61– 62	$C_{11}H_{12}O_2N_2$	64.67	64.61	5.93	5.86
2-Chloro-4-phenoxy-(VII)	1.9	2	10 Et	0	2-Chloro-4-ethoxy-(IX)[d]	1.5	90– 92	$C_{10}H_9ON_2Cl$*	57.55	58.07	4.35	4.63
								* Calcd.: Cl, 17.0. Found: C, 17.2				
2,4-Diphenoxy-(VIII)	1	.1	30 Et	100	2-Phenoxy-4-ethoxy-(X)[e]	0.6	107–108	$C_{16}H_{14}O_2N_2$	72.15	...	5.30	..
2,4-Diphenoxy-(VIII)	1	.1	30 Me	100	2-Phenoxy-4-methoxy-(XI)[f]	0.85	139.5	$C_{15}H_{12}O_2N_2$				
								Calcd.: N, 11.11. Found: N, 11.30				

[a] Further identified by mixed melting points with known specimens of dimethoxy- and diethoxyquinazolines.

[b] Fine white matted needles from dilute alcohol. The substance depresses the melting point of diethoxyquinazoline and is converted into dimethoxyquinazoline on warming with methyl alcoholic sodium methylate.

[c] Flat glistening needles from dilute alcohol. This substance also depresses the melting point of diethoxyquinazoline into which it is again converted on warming with alcoholic sodium ethylate.

[d] This compound is difficult to purify when prepared by this method. Its identity was established by mixed melting points with known specimens of chloroethoxyquinazoline, and by its conversion into 2-phenoxy-4-ethoxyquinazoline.

[e] Colorless, minute glistening prisms from alcohol. Mixed with the product from chloroethoxyquinazoline and sodium phenate the melting point was unchanged. Treatment with sodium methylate converts the substance into 2-phenoxy-4-methoxyquinazoline. The same product (X) was also obtained when alcoholic potassium hydroxide was substituted for sodium ethylate.

[f] Microscopic hair-like needles from acetone or alcohol, sparingly soluble in the latter. On warming for fifteen minutes with a slight excess of sodium ethylate in absolute alcohol, 2-phenoxy-4-ethoxyquinazoline is formed.

cc. of boiling alcohol. The mixture resulting was allowed to stand and the insoluble residue of salt removed by filtration. The inspissated alcoholic extract, on standing, slowly deposited glistening granular crystals, m. p. 153–154°. The substance is fairly soluble in water on warming, to a solution having a bitter taste, and from which it may be recrystallized.

. *Anal.* Calcd. for $C_{12}H_{14}O_4N_2$: C, 57.57; H, 5.64. Found: C, 57.81; H, 6.03; C, 58.18; H, 5.99; C, 58.02; H, 5.28.

Preparation of $\overline{N{=}C(OCH_2CH_2OCOCH_3)C_6H_4N{=}C}OCH_2CH_2OCOCH_3$, the Diacetyl Derivative of 2,4-Di-β-hydroxyethoxyquinazoline.—This acetylation was effected by boiling 1.9 g. of the dihydroxy derivative with an excess of acetic anhydride in the presence of anhydrous sodium acetate for two hours, then pouring into water and neutralizing the acidity with sodium carbonate when, after standing in cold water for an hour, the separated oil solidified. It was filtered, washed with water and crystallized from alcohol or dilute alcohol, yielding 1.4 g. of crystals, m. p. 65–66°.

Anal. Calcd. for $C_{16}H_{18}O_6N_2$: C, 57.46; H, 5.43. Found: C, 57.31; H, 5.34.

Summary

Mixed 2,4-diethers of quinazoline have been prepared by acting on 2,4-dialkoxyquinazolines with sodium alcoholates in alcohols other than those used in obtaining the original dialkoxy compounds. The replacement of an alkoxy (OR) by a different alkoxy (OR′) takes place only at the 4-position, the 2-substituent being unaffected. The transposition is reversible, the mixed diethers being readily converted into the respective dialkoxy derivatives again by employing the proper alcohols. The reaction has been extended to 4-phenoxyquinazolines, these being easily transformed into 4-alkoxy compounds which are further transformable, except that in this case the replacement of phenoxy by alkoxy is irreversible. The following new quinazolines have been prepared: 2-methoxy-4-ethoxy-, 2-ethoxy-4-methoxy-, 2-phenoxy-4-methoxy-, 2-phenoxy-4-ethoxy- and 2,4-di-β-hydroxyethoxyquinazoline and its diacetyl derivative.

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