

[CONTRIBUTION FROM THE MORLEY CHEMICAL LABORATORY, WESTERN RESERVE UNIVERSITY]

Quinazolines. VIII. The Methyl Esters of 1,3-Dimethylbenzoylene-urea-5-carboxylic Acid and 2,4-Dimethoxyquinazoline-5-carboxylic AcidBY N. A. LANGE, DOUGLAS C. CHISHOLM¹ AND J. LESTER SZABO

Scott and Cohen² prepared benzoylene-urea-5-carboxylic acid (2,4-diketo-1,2,3,4-tetrahydroquinazoline-5-carboxylic acid) (I). In reaction with dimethyl sulfate in alkaline solution, it yielded a product to which they assigned structure II. In previous studies of this method of alkylation of compounds of type I, it has been found that $\text{—NCH}_3\text{CO—}$ derivatives invariably are formed and not $\text{—N=COCH}_3\text{—}$ derivatives.³⁻⁵

A reinvestigation by the authors of the work of Scott and Cohen shows conclusively that their product is actually methyl 1,3-dimethylbenzoylene-urea-5-carboxylate (III). In confirmation of this claim, methyl 2,4-dimethoxyquinazoline-5-carboxylate (II) was prepared from I by the reaction with phosphorus pentachloride to yield the chloride of 2,4-dichloroquinazoline-5-carboxylic acid, followed by replacement of the halogen with

three methoxy groups through the use of sodium methoxide.

As was to be expected, it has been found that the quinazoline in question reacts tautomerically to yield either O,O- or N,N-dimethyl derivatives and Zeisel determinations have shown that the Scott-Cohen product conforms to structure III and ours to structure II.

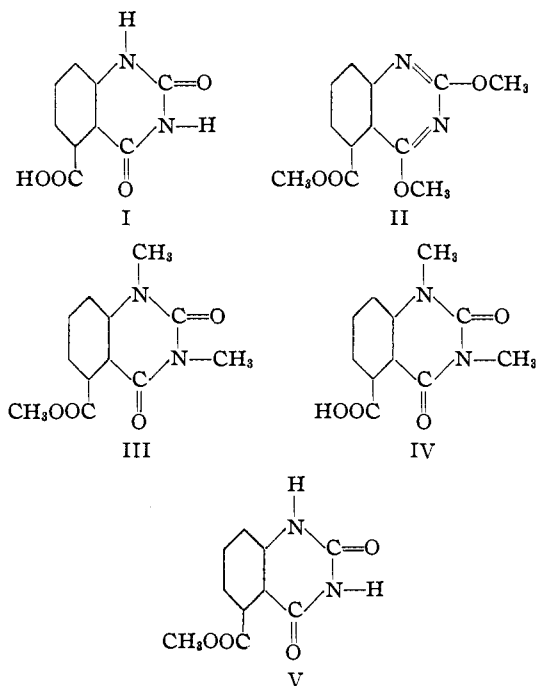
Experimental Part

Benzoylene-urea-5-carboxylic acid (2,4-diketo-1,2,3,4-tetrahydroquinazoline-5-carboxylic acid) (I) was prepared by the method of Scott and Cohen.² It forms colorless, shining, micro crystals, m. p. 346° (copper block, uncorr.). Scott and Cohen reported that this compound does not melt below 320° but sublimes slowly above 280°. The pH of a saturated aqueous solution of this acid was found to be 2.9 (quinhydrone electrode).

1,3-Dimethylbenzoylene-urea-5-carboxylic acid (1,3-dimethyl-2,4-diketo-1,2,3,4-tetrahydroquinazoline-5-carboxylic acid) (IV), prepared by the method of Scott and Cohen,² from I in alkaline solution and dimethyl sulfate, crystallized from dilute alcohol in minute needles, m. p. 318° (uncorr.). It is sparingly soluble in water or alcohol but dissolves in alkalis, from which it is precipitated unchanged on the addition of acids, even after prolonged boiling of the alkaline solution.

Methyl Benzoylene-urea-5-carboxylate (Methyl 2,4-diketo-1,2,3,4-tetrahydroquinazoline-5-carboxylate) (V).—Since the method described by Scott and Cohen for the preparation of III was found to proceed much slower than claimed and invariably resulted in a mixture of III and IV, experiments were made in the hope of improving their method of preparation. More satisfactory results were obtained by first esterifying the carboxyl group of I and then alkylating the two nitrogen atoms. Two grams of benzoylene-urea-5-carboxylic acid (I) was placed in a flask equipped with reflux condenser, 40 cc. of anhydrous methyl alcohol was added, and dry hydrogen chloride passed into the gently boiling mixture for four hours. The solution was allowed to cool while still passing in hydrogen chloride until it was completely saturated at room temperature; after standing overnight it was heated to boiling and more hydrogen chloride was passed in. On cooling, fine, colorless needles separated which were collected, washed with water, and dried; m. p. 318° (uncorr.). An extraction of this product with dilute sodium carbonate solution to remove any unreacted I, followed by crystallization of the undissolved residue from ethyl alcohol gave fine colorless needles of methyl benzoylene-urea-5-carboxylate (V), m. p. 307-309° (uncorr.). Scott and Cohen reported that this compound turns yellow at 180° and melts at 310-312°.

This ester (V) is best prepared by treating the acid (I)



(1) At the Chemical Laboratory of the Case School of Applied Science.

(2) Scott and Cohen, *J. Chem. Soc.*, **119**, 664 (1921).

(3) Scott and Cohen have here inadvertently applied the erroneous term "hydantoin" to quinazoline derivatives which, in fact, contain one more ring carbon than the hydantoins.

(4) Lange and Sheibley, *THIS JOURNAL*, **55**, 2113 (1933).

(5) Bogert and Seil, *ibid.*, **29**, 526 (1907).

with thionyl chloride to form the carboxylic acid chloride, thus avoiding the introduction of halogen into the ring at the 2,4-positions, which occurs when phosphorus pentachloride is used.⁶ The acid chloride on treatment with anhydrous methyl alcohol gave the desired ester (V). To 8 g. of the quinazoline carboxylic acid (I) 100 cc. of thionyl chloride was added and the mixture refluxed for three and one-half hours, after which it was allowed to stand overnight. The excess thionyl chloride was decanted from residual solids and the latter placed in a desiccator containing calcium chloride and alkali. This crude material formed colorless clusters of thin plates and micro prisms which darkened when heated to 300° and melted at 331–332° (uncorr.) with decomposition. Attempts to recrystallize this material were not successful because of its insolubility in hot or cold chloroform, carbon tetrachloride, benzene, xylene, anisole or thionyl chloride. On titration with standard silver nitrate solution the chlorine content indicated a purity of 90% acid chloride. Refluxing this product with various anhydrous alcohols and with ammonia gave products which were purified by recrystallization but not analyzed and which are most likely the following derivatives: methyl ester, colorless, thin, micro, needle-like plates, m. p. 318°; ethyl ester, colorless, thin, micro, needle-like plates, m. p. 297–299°; benzyl ester, colorless, shining, thin, irregular plates, m. p. 257–261°; amide, colorless, cotton-like, micro needles, m. p. 359°, this last, when mixed with the carboxylic acid (I) gave a melting point of 338°. These melting points are uncorrected.

Methyl 1,3-Dimethylbenzoylene-urea-5-carboxylate (Methyl 1,3-Dimethyl-2,4-diketo-1,2,3,4-tetrahydroquinazoline-5-carboxylate) (III).—Four grams of the crude acid chloride and 150 cc. of anhydrous methyl alcohol were refluxed several hours, a part of the material remaining undissolved. The mixture was placed in a refrigerator overnight and the undissolved solids filtered off and partially dried. The 4.6 g. of crude ester (V) obtained in this way was dissolved in a solution of 4 g. of potassium hydroxide in 30 cc. of water, and 4.5 g. of dimethyl sulfate added with vigorous shaking. This mixture was allowed to stand overnight at room temperature and then placed in a refrigerator. The crystalline material which separated was filtered off, washed with water and dried; yield about 1 g. Crystallization from a small amount of methyl alcohol gave a product which is not volatile with steam and

which forms very long (sometimes 3–4 cm.), colorless needles, m. p. 144.4–145.5° (corr.). Scott and Cohen² reported a melting point of 144° for this product. It is unaffected by boiling for a short time with hydrochloric acid; prolonged boiling, however, causes gradual hydrolysis of the ester group.

Anal. Calcd. for $C_{11}H_9O_3N_2(OCH_3)$: CH_3O , 12.50. Found: CH_3O , 12.38, 12.61.

Methyl 2,4-Dimethoxyquinazoline-5-carboxylate (II).—One gram of pure benzoylene-urea-5-carboxylic acid (I), 5 g. of phosphorus pentachloride, and 1.4 cc. of phosphorus oxychloride in an acetylating flask were refluxed in an oil-bath until all of the carboxylic acid had dissolved. The excess of phosphorus halides was removed under reduced pressure and the dark brown liquid residue became viscous on cooling. To this residue a solution of 0.4 g. of metallic sodium in 8 cc. of anhydrous methyl alcohol was added gradually with shaking and cooling in running water. The viscous material dissolved slowly and sodium chloride gradually precipitated. The undissolved material was removed by filtration, and from the filtrate small, pale yellow plates began to separate. The mixture was cooled thoroughly and the separated material collected. A single crystallization of this product from methyl alcohol gave 1 g. of colorless plates, m. p. 134.5–135.5° (corr.). The cautious addition of water to the alcoholic solution increases the amount which separates on crystallization. This compound is not volatile with steam. It is partially demethylated on boiling with dilute hydrochloric acid with the formation of the benzoylene-ureacarboxylic methyl ester (V), identified by determining the melting point of a mixture with a known sample of the ester.

Anal. Calcd. for $C_9H_9ON_2(OCH_3)_3$: C, 58.05; H, 4.87; CH_3O , 37.51. Found: C, 58.40; H, 4.97; CH_3O , 37.40.

Summary

Methyl 2,4-dimethoxyquinazoline-5-carboxylate has been synthesized and found to possess properties expected for a compound of this structure. It also has been shown that a compound previously assigned this constitution is actually the isomeric methyl 1,3-dimethylbenzoylene-urea-5-carboxylate.

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(6) Abt, *J. prakt. Chem.*, [2] **39**, 150 (1889).