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

Quinazolines. VI. The Alkylation of Benzoylene Urea

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The greater reactivity of substituents in the 4-position of quinazoline as compared with similar or like substituents in the 2-position has been demonstrated in previous papers.[1] When benzoylene urea (2,4-diketo-tetrahydroquinazoline) is alkylated with alkyl iodides in the presence of caustic alkalies a corresponding difference in the reactivities of the two imino hydrogen atoms present in this substance is noticed, the alkyl group invariably entering the 3-position before the 1-position is attacked. Thus, on methylation with methyl iodide, 1,3-dimethylbenzoylene urea is formed accompanied by a small amount of 3-methylbenzoylene urea, while with less exhaustive methylation, a good yield of the 3-methyl compound is easily obtained.[2]

The preparation of 1,3-diethylbenzoylene urea from benzoylene urea, alcoholic sodium hydroxide and ethyl iodide has been recorded.[3] No repetition of these results was realized, however, the products invariably being 3-ethylbenzoylene urea and unchanged benzoylene urea. 3-Ethylbenzoylene urea, originally produced by the oxidation of 2-thio-3-ethyltetrahydroquinazoline,[4] does not seem to have been prepared previously by direct alkylation, but by treating benzoylene urea (IV) with ethyl iodide and sodium hydroxide in dilute alcohol fair yields of the compound (V) are obtained.[5] It has been shown that on alkylating benzoylene urea (IV) dissolved in aqueous sodium hydroxide with dimethyl sulfate, 1,3-dimethylbenzoylene urea is formed; this experiment was repeated and the yield found to be practically the theoretical. By substituting diethyl sulfate for the dimethyl sulfate and employing a somewhat higher temperature, a poor yield of 1,3-diethylbenzoylene urea (I) was obtained, the remainder of the benzoylene urea being recovered unchanged.

The formation of 1-alkyl benzoylene ureas by direct alkylation of benzoylene urea is thus rendered improbable, since the resistance of the 1-position to alkylation is evidently weakened or overcome only after the 3-position is occupied. 1-Methylbenzoylene urea has been prepared from N-methylanthranilic acid,[6] and also by oxidizing the methiodide of 2,3-benzo-4-ketodihydroquinazoline.[7] On treating N-ethylanthranilic acid with isocyanic acid, or simply by fusing it with urea, 1-ethylbenzoylene urea (II) is formed. This substance is of interest because of its variable

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[1] Lange and Sheibley, THIS JOURNAL, **54**, 4305 (1932).

[2] Bogert and Scatchard, *ibid.*, **41**, 2062 (1919).

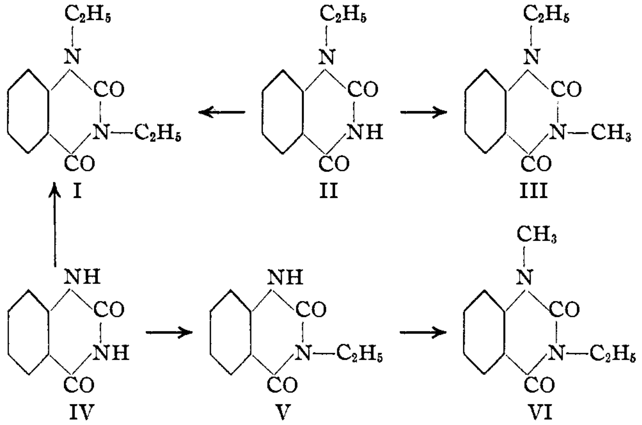
[3] Bogert and May, *ibid.*, **31**, 513 (1909).

[4] Söderbaum, *Ber.*, **23**, 2186 (1890); Busch, *J. prakt. Chem.*, [2] **51**, 136 (1895).

[5] Scott and Cohen, *J. Chem. Soc.*, **119**, 665 (1921).

[6] *Chemical Abstracts*, **11**, 578 (1917).

[7] Seide, *Ann.*, **440**, 319 (1925).



physical appearance and the ease with which it is alkylated. By reaction of (II) with ethyl iodide in the presence of alkali, pure 1,3-diethylbenzoylene urea (I) is obtained directly in good yield. In the same manner, using methyl iodide, a mixed dialkyl derivative, 1-ethyl-3-methylbenzoylene urea (III), is easily prepared; the isomeric compound, 1-methyl-3-ethylbenzoylene urea (VI), being arrived at by treating 3-ethylbenzoylene urea (V) with dimethyl sulfate. These mixed dialkyl benzoylene ureas possess properties intermediate between those of diethyl- and dimethyl-benzoylene urea; like the latter they are insoluble in solutions of the caustic alkalies, and in contrast to the isomeric mixed dialkoxyquinazolines,[1] they are unaffected by hydrochloric acid.

All melting points given in this paper are corrected.

Experimental Part

Preparation of 1-Ethylbenzoylene Urea (II).—Ten grams of N-ethylanthranilic acid[8] (m. p. 154.5°) was covered with 250 cc. of water and 5.3 cc. of glacial acetic acid added. The mixture was warmed slightly and allowed to cool. It was then stirred mechanically at a rate sufficient to keep the solid matter in suspension, and a solution of 7 g. of potassium cyanate in 20 cc. of water added during the course of ten minutes, meanwhile disintegrating with a glass rod the clots of solid material that formed. At the end of one-half hour of continuous stirring, 100 g. of flaked sodium hydroxide was slowly added in small portions during a further hour of stirring, the solution clarifying at first and finally becoming an opaque white. The reaction mixture was allowed to stand overnight in running water at 10° when an oily emulsion resulted, from which on stirring gently a mixture of sodium salts crystallized; this was filtered off with weak suction but was not washed. The moist precipitate was dissolved in 250 cc. of water. the solution filtered and heated almost to the boiling point. It was then made just acid with acetic acid, the 9.3 g. of precipitated needle-like crystals that separated being collected and dried. Further acidification of the filtrate yielded 0.5 g. of N-ethylanthranilic acid. The dried precipitate was extracted with 100 cc. of alcohol in two portions, warming the first extract but decanting the second without warming. The

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(8) Houben and Brassert. *Ber.*, **39**, 3237 (1906).

finely granular, insoluble residue that remained settled rapidly in the alcoholic media, no difficulty being experienced in these operations. This residue, 5.8 g., was crystallized from about 300 cc. of boiling alcohol, in which it is sparingly soluble and dissolves to a turbid solution. In this manner 3.5 g. of fine granular crystals of 1-ethylbenzoylene urea. m. p. 215–217°, was obtained. The substance is sparingly soluble in acetone and is unaffected by hot concentrated hydrochloric acid. It is soluble in concentrated sulfuric acid and readily soluble in warm aniline, separating slowly from the latter solvent in thick tabular crystals. When concentrated solutions of it in hot alcohol are rapidly cooled the compound crystallizes in feathery needles which soon fill the whole solution and then, after about fifteen minutes, settle into the more compact granular variety; dilute solutions on gradual cooling develop large square crystals. From its solution in normal sodium hydroxide dilute hydrochloric acid precipitates the substance in microscopic needles which retain their form for months. On inspissating the initial alcoholic extracts a small amount of 1-ethylbenzoylene urea separated; after further concentration N-ethylanthranilic acid crystallized, 4.5 g. of the latter compound being recovered in this way.

1-Ethylbenzoylene urea was also obtained by heating a finely powdered mixture of equal weights of N-ethylanthranilic acid and urea at 150° for one hour, cooling, and washing the solidified melt with hot water, when it remelted. On cooling it again became solid and was dissolved in hot alcohol and allowed to crystallize, the 1-ethyl compound separating first.

Anal. Calcd. for $C_{10}H_{10}O_2N_2$: C, 63.12; H, 5.30. Found: C, 63.22; H, 5.46.

Preparation of 1,3-Diethylbenzoylene Urea (I).—(a) To 0.2 g. of potassium hydroxide dissolved in 25 cc. of alcohol was added 0.5 g. of 1-ethylbenzoylene urea and 0.5 cc. of ethyl iodide. The mixture was refluxed gently on a steam-bath for four hours and finally evaporated to dryness. The residue was warmed with dilute hydrochloric acid, washed with water, dried and then shaken with normal sodium hydroxide solution. The solution was diluted with water, the residue removed by filtration and again washed and dried. Crystallization from alcohol yielded about 0.4 g. of small white needles, m. p. 110–111°, soluble in concentrated sulfuric acid. Long needles were obtained from dilute alcohol, and rods on slow crystallization.

(b) One gram of benzoylene urea was dissolved in 30 cc. of normal sodium hydroxide solution and 2 cc. of diethyl sulfate added. The mixture was heated on a water-bath, adding small amounts of diethyl sulfate as needed and small pellets of solid sodium hydroxide whenever the liquid became acid. After heating for about twelve hours the additions of diethyl sulfate were discontinued and further heating on the steam-bath finally destroyed any diethyl sulfate that remained; the alkaline mixture was then poured into 100 cc. of water, thus causing a considerable increase in the amount of precipitate that had formed throughout the heating period. After standing overnight the precipitate was filtered off, dried and weighed 0.4 g. Crystallization from alcohol yielded 0.2 g. of a product identical with the 1,3-diethylbenzoylene urea already described. The filtrate from the precipitate was acidified with hydrochloric acid and on standing deposited 0.65 g. of unchanged benzoylene urea.

Anal. Calcd. for $C_{12}H_{14}O_2N_2$: C, 66.02; H, 6.47. Found: C, 66.10; H, 6.59.

Preparation of 1-Ethyl-3-methylbenzoylene Urea (III).—One gram of 1-ethylbenzoylene urea and 0.5 cc. of methyl iodide were added to 25 cc. of methyl alcohol containing 0.4 g. of potassium hydroxide, and the mixture was heated on a steam-bath for five hours. On allowing it to cool a mush of needles separated; these were redissolved by warming and the solution was evaporated to dryness. The residue, after being treated successively with dilute hydrochloric acid and sodium hydroxide as described in the preparation of diethylbenzoylene urea above, weighed 1.0 g. Crystallization from alcohol was easily effected, 0.8 g. of short white needles, m. p. 138–139°, being obtained in the first crop. The compound is soluble in concentrated sulfuric acid.

Anal. Calcd. for $C_{11}H_{12}O_2N_2$: C, 64.67; H, 5.93. Found: C, 64.65; H, 5.94.

Preparation of 3-Ethylbenzoylene Urea (V).—This compound was prepared by substituting alcoholic ethyl iodide for methyl alcoholic methyl iodide and following the directions of Bogert and Scatchard[2] for the preparation of 3-methylbenzoylene urea. A yield of 1 g. was obtained from 2 g. of benzoylene urea and 0.5 g. of sodium hydroxide in 62.5 cc. of dilute alcohol (1:1), using 2.2 g. of ethyl iodide and heating on a water-bath for four and one-half hours. After several recrystallizations from alcohol, fine needles. m. p. 197.5–198.5°, were obtained which are soluble in concentrated sulfuric acid.

Anal. Calcd. for $C_{10}H_{10}O_2N_2$: C, 63.12; H, 5.30. Found: C, 63.46; H, 5.29.

Preparation of 1-Methyl-3-ethylbenzoylene Urea (VI).—One gram of 3-ethylbenzoylene urea was dissolved in 25 cc. of normal sodium hydroxide, about 2 cc. of dimethyl sulfate was added and the mixture allowed to stand at 25° with occasional shaking. Within an hour the solution was opaque with a precipitate of fine needles. After standing for thirty-six hours or so, it was heated on a water-bath to destroy any traces of dimethyl sulfate and then allowed to cool, the liquid being still alkaline. The precipitate was removed by filtration, dried and weighed 1.2 g. Successive treatments, with dilute hydrochloric acid and sodium hydroxide in the manner already described for the isolation of the other dialkyl derivatives, reduced its weight to 1 g. Crystallization from alcohol gave about 0.9 g. of long, slender white needles which soften around 110° and melt at 133–134°. This substance, like the other alkyl derivatives, is also soluble in concentrated sulfuric acid.

Anal. Calcd. for $C_{11}H_{12}O_2N_2$: C, 64.67; H, 5.93. Found: C, 64.91; H, 5.49.

Summary

Direct alkylation of benzoylene urea with alkyl iodides leads to the formation of 3-alkyl and, to a limited extent, 1,3-dialkyl benzoylene ureas. 1-Alkyl benzoylene ureas are best prepared by treating N-alkyl anthranilic acids with isocyanic acid or urea. 1,3-Dialkyl benzoylene ureas result from treatment of benzoylene urea with the lower alkyl sulfates or, better, by alkylating 1- or 3-alkyl benzoylene ureas with the appropriate reagents. Mixed dialkyl derivatives can be obtained by selective alkylation, using the latter method. The following new compounds have been prepared: 1-ethylbenzoylene urea, 1-ethyl-3-methylbenzoylene urea, and 1-methyl-3-ethylbenzoylene urea.

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