[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE, CORVALLIS, OREGON]

Quinazolines. X. The Synthesis of Methyl 2,4-Dimethyl-6-quinazolyl Ketone[1]

BY JOHN SIEGLE AND BERT E. CHRISTENSEN

Both 8-acetyl-2,4-dimethylquinazoline[2] and its 7-acetyl isomer[3] react with aqueous formaldehyde at room temperature to yield extremely hygroscopic Mannich products. In spite of the known activities of the methyl ketones it is difficult to assign structures to these products in view of the activities of the methyl substituents (probably in 4-position) which permits 2,4-dimethylquinazoline[2] itself to yield a Mannich product.

In order to study the reactivities of the known acetyl substituted dimethylquinazolines as well as the properties of the amino alcohols derived therefrom, this laboratory prepared in addition the 6-acetyl isomer. The starting material for this sequence of reactions was *m*-tolunitrile which was converted to *m*-toluic acid and then to 4-nitro-*m*-toluic acid by well established procedures.

Permanganate oxidation of 4-nitro-*m*-toluic acid gave low yields; however, by changing to a solid dichromate oxidant and using the procedures given by Magidson[4] and later modified by Albert[5] for the oxidation of 2-chloro-4-nitrotoluene, reasonable yields of 4-nitroisophthalic acid were obtained.

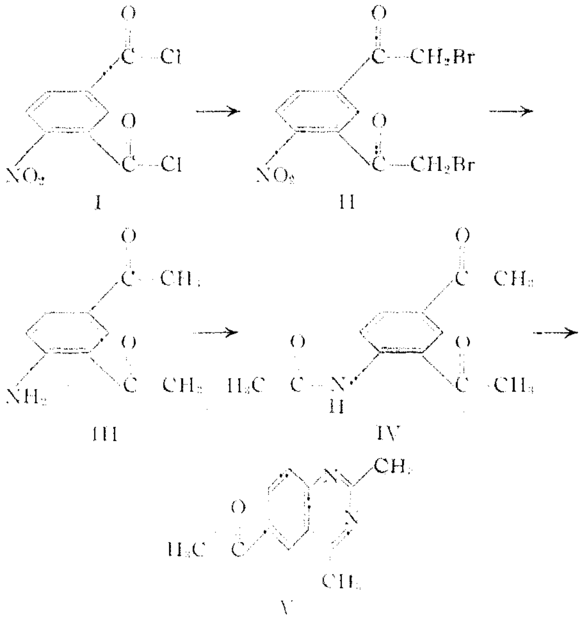

Fig. 1.

Treatment of the 4-nitroisophthalic acid with phosphorus pentachloride and phosphorus oxychloride mixtures gave the corresponding phthalyl chloride which was converted to 1-amino-2,4-diacetylbenzene by means of a procedure which Isensee successfully used to make 2-amino-1,3-diacetylbenzene.[2] This process involved the use of diazomethane to form the bromomethyl ketone which was then reduced with stannous chloride. These operations give much better yield than the older methods described by Ruggli and Gassenmeier.[6] Acylation of 1-amino-2,4-diacetylbenzene followed by cyclization yielded the final product 6-acetyl-2,4-dimethylquinazoline (see Fig. 1).

Experimental

4-Nitroisophthalyl Chloride.—Twenty grams of 4-nitroisophthalic acid, 40 ml. of phosphorus oxychloride and 80 g. of phosphorus pentachloride were refluxed for eight hours during which time the solution became red in color. The excess phosphorus pentachloride was removed by filtration using a sintered glass funnel.

The excess phosphorus oxychloride was then removed by vacuum distillation using a water aspirator, the residual liquid was cooled and then filtered to remove the remaining phosphorus pentachloride. The dark red filtrate was now dissolved in dry ether and used in the next step of the preparation.

An analytical sample was obtained by vacuum distillation of the crude red liquid acid chloride at a fraction of a mm. pressure. Under these conditions the acid chloride fraction distills between 145–150° as a light orange colored liquid. *Anal.* Calcd. for $C_8Cl_2H_3NO_4$: Cl, 28.6. Found: Cl, 28.7.

1,3-Diazoacetyl-4-nitrobenzene.—Five hundred and seventy ml. of ether and 170 ml. of 40% potassium hydroxide were stirred in a liter erlenmeyer flask which was cooled with a Dry Ice–acetone-bath. Fifty-seven grams of N-nitrosomethylurea was then added slowly and after solution was completed the yellow ethereal layer was separated and dried over potassium hydroxide pellets for four to six hours. The dried diazomethane solution was then transferred to a three necked flask equipped with mechanical stirrer, dropping funnel, and provided with a Dry Ice–acetone-bath.

One-half of the acid chloride solution prepared in the preceding operation (half portions were run for reasons of safety) was diluted to 125 ml. with dry ether and then added slowly to the diazomethane solution. The precipitate which separated was removed by filtration: crude yield, 9 g., 73%. This product was immediately suspended in ether for use in the next operation.

1,3-Dibromoacetyl-4-nitrobenzene.—In a 3-liter erlenmeyer flask equipped with dropping funnel and mechanical stirrer were placed 1-liter of ether and 18.0 g. of the crude diazoketone from the preceding run. After the formation of a uniform suspension approximately 50–70 ml. of 48% hydrobromic acid was added dropwise with stirring. This was continued until further addition of the hydrobromic acid no longer caused gas evolution. The ethereal solution was separated and ether removed leaving a yellow-orange residue. This was dissolved in a small excess of hot chloroform, decolorized with charcoal, filtered and then reprecipitated by addition of petroleum ether; yield 11.6 g., 33.4% (based on the nitroisophthalic acid), m. p.

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(2) Isensee and Christensen, THIS JOURNAL, **70**, 4061 (1948).

(3) Christensen, Graham and Griffith, *ibid.*, **67**, 2001 (1945).

(4) Magidson and Grigerowski, *Ber.*, **66**, 869 (1933).

(5) Albert and Linnell, *J. Soc. Chem. Ind.*, **55**, 54T (1936).

(6) Ruggli and Gassenmeier, *Helv. Chim. Acta*, **22**, 496 (1939).

104–105°. A white analytical sample was prepared by three precipitations from chloroform using petroleum ether and decolorizing with charcoal. *Anal.* Calcd. for $C_{10}H_7Br_2NO_4$: C, 32.9; H, 1.92; Br, 43.8. Found: C, 32.5; H, 1.88; Br, 43.5, 43.6, 43.9.

4-Amino-1,3-diacetylbenzene.—1,3-Dibromoacetyl-4-nitrobenzene (7.6 g.), 38 g. of stannous chloride dihydrate and 290 ml. of concentrated hydrochloric acid were stirred on a water-bath. After two and one-half hours the solution became yellow; the reaction mixture was then poured into 500 ml. of water and the resultant mixture made very basic with concentrated sodium hydroxide and then set aside in a refrigerator. A long yellow needled crystalline product was removed by filtration and recrystallized from water, yield 2.9 g., 78%, m. p. 139–140°. *Anal.* Calcd. for $C_{10}H_{11}NO_2$: C, 67.7; H, 6.21; N, 7.92. Found: C, 67.8; H, 6.46; N, 8.06.

4-Acetamino-1,3-diacetylbenzene.—A flask containing 1 g. of 4-amino-1,3-diacetylbenzene, 2.25 g. of acetic anhydride was placed in an oven at 42–46° overnight. The amino ketone went into solution, and the solution was poured into a small amount of water. An oily material which slowly crystallized separated, and after neutralization of the solution with sodium carbonate was removed by filtration. The precipitate was recrystallized from *n*-heptane as long colorless needles, yield 1.1 g. (88%), m. p. 127–128°. *Anal.* Calcd. for $C_{12}H_{13}NO_3$: C, 65.6; H, 5.93; N, 6.40. Found: C, 65.75; H, 5.99; N, 6.44.

6-Acetyl-2,4-dimethylaquinazoline.—A solution containing 1 g. of 4-acetamino-1,3-diacetylbenzene in 25 ml. of absolute alcohol was saturated with ammonia and then placed in a bomb. The bomb was maintained in an oven at 100–105° for seven and one-half hours. The yellow alcoholic reaction product was evaporated before a fan to dryness. A yellow residue was obtained which was dissolved in *n*-heptane, decolorized with charcoal and then recrystallized; yield 0.72 g. (76%) of white crystalline powder, m. p. 92°. *Anal.* Calcd. for $C_{12}H_{12}N_2O$: C, 71.9; H, 6.00; N, 14. Found: C, 71.6; H, 5.93; N, 13.7.

Summary

Directions for the synthesis of methyl 2,4-dimethyl-6-quinazolyl ketone from 4-nitroisophthalic acid are given.

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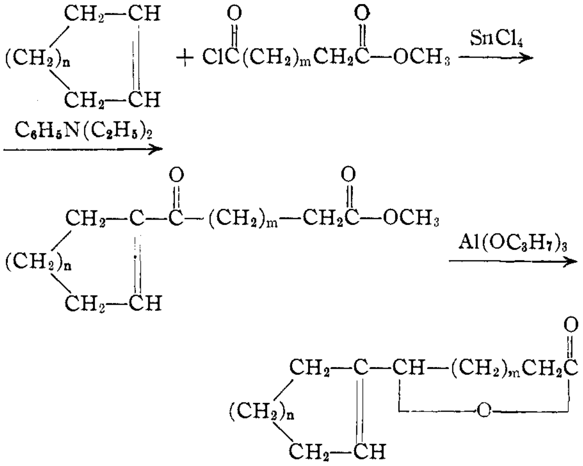
[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

The Synthesis of Some Cycloalkenyl-substituted Butyro- and Valerolactones[1]

BY JAMES ENGLISH, JR., AND JASON E. DAYAN[2]

As a part of the general problem of the study of compounds structurally related to auxin a,[3] we have prepared a series of four lactones containing unsaturation in the position corresponding to that proposed by Kögl[4] for the auxins. The method of synthesis is illustrated below; *n* and *m* were chosen as 1 and 2, in order to give representatives of both the cyclohexene and cyclopentene series, and of both γ- and δ-lactones in each case.



Reactions analogous to the first step, a modification of the procedure developed by Darzens,[5] have been carried out by Rapson and Robinson[6] and by Lapides.[7] In both cases, poor yields of unsaturated keto-esters were reported; in the present instance, despite extensive experimentation, the maximum yields of pure keto esters obtained was 30–35%. The use of less than equimolar amounts of stannic chloride[8] and low reaction temperatures seemed to be the most important precautions necessary for optimum yields. The ultraviolet absorption spectra exhibited maxima at 234–240 mμ corresponding to that predicted[9] for compounds of the proposed structure. The reduction of the keto acids proceeded smoothly with high yields of γ-lactones; the yields were considerably lower and more variable in the case of the δ-lactones and seemed to depend on the use of a carefully fractionated starting material.

The unsaturated lactones prepared were found to undergo extensive decomposition in the presence of traces of acid and colored compounds were produced also on saponification with alcoholic alkali. We have been unable to isolate the free hydroxy acids corresponding to the lactones reported in Table II, due, apparently, to production of colored acidic products that are reconvertible to the original lactones only in poor yields. Crystalline pseudo-benzylthiouronium salts of the hydroxy acids were readily obtained.

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[1] Taken in part from the thesis submitted by Jason E. Dayan to the faculty of the Graduate School of Yale University, in partial fulfillment of the requirement for the degree of Doctor of Philosophy.

[2] General Aniline Works, Rensselaer, New York.

[3] J. English, Jr., and L. J. Lapides, THIS JOURNAL, **65**, 2466 (1944); J. English, Jr., and J. Delafield Gregory, *ibid.*, **69**, 2123 (1948); J. English, Jr., G. W. Barber and L. J. Lapides, *ibid.*, **70**, 2859 (1949).

[4] F. Kögl and H. Erxleben, *Z. physiol. Chem.*, **235**, 181 (1935).

[5] G. Darzens, *Compt. rend.*, **150**, 707 (1910); **151**, 758 (1911).

[6] Rapson and R. Robinson, *J. Chem. Soc.*, 1285 (1935).

[7] Lapides, Ph.D. Thesis, Yale University, 1944.

[8] Cologne and Moslavi, *Bull. soc. chim.*, **6**, 335 (1939).

[9] Woodward, THIS JOURNAL, **63**, 1123 (1941)