Some 4-Quinazolinones

A. Mendel

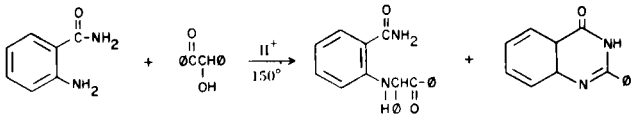
Contribution No. 813 from the Central Research Laboratories,
3M Company, St. Paul, Minnesota 55133

Received August 12, 1976

The acid catalyzed reaction of anthranilamide with benzoin was studied under two conditions. Condensation at 150° gave known I plus unexpected quinazolinone II. In refluxing benzene (azeotropic water removal), the reactants yielded imine III. The acid catalyzed and uncatalyzed 150° reaction of III was examined by both ir and tlc. Both benzoic acid and II were formed in each case. Triethyl orthoformate with I gave quinazolinone IV while this ester with III formed II, benzaldehyde and benzoic acid.

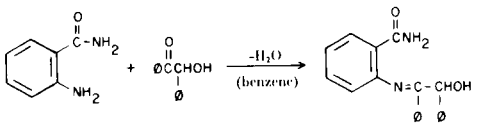
J. Heterocyclic Chem., **14**, 153 (1977).

The preparation of *o*-(α-benzoylbenzylamino)benzamide (I) by the acid catalyzed condensation of anthranilamide with benzoin (1) resulted in low yields of I. Thin-layer chromatography (tlc) of the mother liquor showed a second component which was then isolated by column chromatography and identified as 2-phenyl-4(3*H*)quinazolinone (II) by independent synthesis.



I II

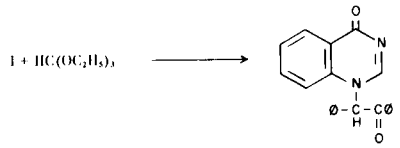
In an attempt to increase the yield of compound I, anthranilamide was heated with benzoin under mild, azeotropic conditions (refluxing benzene). Instead of the expected product I however, a new material was formed which was assigned structure III based on elemental, ir and nmr analyses. The formation of imines in the Voigt reaction has been reviewed (2).



III

The thermal (150°) reaction, both uncatalyzed, and acid catalyzed, of imine III was studied by ir and by tlc. Compound II with benzoic acid were formed in each case and no amide (I) formation was detected (tlc).

Reaction of compound I with triethyl orthoformate gave the proposed 1-(α-benzoylbenzyl)-4(1*H*)quinazolinone (IV), whereas compound III reacted with triethyl orthoformate under similar conditions to give a mixture of compound II, benzaldehyde and benzoic acid.



IV

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H Nmr spectra were recorded in deuteriochloroform unless stated otherwise. TMS was used as the internal standard on a Varian A-60 spectrometer. Ir measurements were taken with a Perkin-Elmer Model 21 spectrophotometer.

Progress of reactions was monitored by withdrawing, using open-end melting point capillary tubes, microgram amounts of the reaction mixture and examining it with tlc. Tlc was done on microscope slides coated with Woelm GF silica gel. Visualization was by ultraviolet light followed by iodine and starch techniques (3). Column chromatography was executed on Mallinckrodt silicic acid (No. 2847) and elution was monitored by tlc.

Preparation of I using Hydrochloric Acid.

A mixture of 18.8 g. (0.089 mole) of benzoin and 12 g. (0.088 mole) of anthranilamide was moistened with two drops of concentrated hydrochloric acid and the product was heated for forty-five minutes in a preheated and 150° maintained oil bath. The amber

melt was poured into ethanol and this cooled solution deposited 5.65 g. (19%) of I, m.p. 182-189°; lit. (1) m.p. 185-188°.

Tlc examination of the ethanol mother liquor showed two other components. Accordingly, this liquor was concentrated (rotary evaporator) and the residue, dissolved in chloroform, was column chromatographed. Chloroform elution gave small amounts of yellow oils whose R_f values were the same as that of benzoin. These oils were discarded. Continued elution of the column with 2% ethanol in chloroform and finally 5% ethanol in chloroform gave yellow to orange solid which on recrystallization from acetone gave 3 g. (15%) of white compound II, m.p. 234-236°; lit. (4) m.p. 238°, identical (ir) with a sample independently prepared from anthranilamide and benzaldehyde, followed by activated manganese dioxide (5) oxidation in place of potassium permanganate-acetone (4). Admixture of II with this authentic sample did not give a depressed melting point (m.p. 238-239°).

Preparation of I using *p*-Toluenesulfonic Acid (PTSA).

An intimate mixture of 12.5 g. (0.06 mole) of benzoin, 8 g. (0.06 mole) of anthranilamide and 1 g. of PTSA was heated for forty-five minutes in a preheated and 150° maintained oil bath. The resulting cooled glass was heated with about 250 ml. of benzene and allowed to stand one day, to give on filtration 4 g. (20.5%) of white I, m.p., 179-184°.

The benzene filtrate was column chromatographed. Elution with benzene gave small amounts of oils which were discarded. Subsequent elution with ether gave 1.5 g. (11.4%) of off white II, m.p. 237-238°.

Benzoin *N*-(*o*-carbamoylphenyl)imine (III).

A mixture of 10.6 g. (0.05 mole) of benzoin, 6.8 g. (0.05 mole) of anthranilamide, 200 mg. of PTSA, and 100 ml. of benzene was mechanically stirred and refluxed under a water trap for one day. The resulting solid was collected by filtration and washed (benzene) to give 14.4 g. of dry off-white solid, m.p. 182-187° whose tlc pattern and ir spectrum differed with those respectively of compound I. This product was purified by Soxhlet extraction with 2-propanol to afford 12 g. (73%) of white crystalline III, m.p. 202-211°; ir (Nujol): 2.8 and 3.0-3.15 (OH, NH_2), 6.08 (C=O of amide) μm; nmr (DMSO-d_6): δ 4.96 (d, 1H, singlet on addition of deuterium oxide), 5.72 (d, 1H, disappears on addition of deuterium oxide), 6.3 ~ 8.0 (m, 16H, 14 aromatic H and NH_2).

Anal. Calcd. for $C_{21}H_{18}N_2O_2$: C, 76.4; H, 5.5; N, 8.5. Found: C, 76.2; H, 5.5; N, 8.6.

Reaction of III with Triethyl Orthoformate.

A magnetically stirred mixture of 10 g. of III with 50 ml. of triethyl orthoformate was refluxed for about sixty-four hours during which time solution occurred. The product was concentrated (rotary evaporator, 75°/water aspirator pressure) to leave a viscous yellow residue. It was dissolved in about 50 ml. of benzene and chromatographed on 300 g. of silicic acid (Mallinckrodt, No. 2847). Elution with benzene gave traces of oils which were discarded. Further elution with dichloromethane gave a small amount of yellow oil which was identified by its ir spectrum to be benzaldehyde. Continued elution with dichloromethane gave 68 mg. of a white solid, m.p. 117-118°, which was identified by its ir spectrum to be benzoic acid. Elution of the column with chloroform gave an additional small quantity of benzoic acid (ir, tlc); final elution with up to fifteen percent ether in chloroform led to 5.4 g. of white, crystalline II, m.p. 236.5-237.5°, identified by ir and nmr.

Reaction of I with Triethyl Orthoformate.

Triethyl orthoformate (15 ml.) with compound I (3.4 g.) was magnetically stirred and refluxed (drying tube protected) for forty-three hours during which time solution occurred and a new precipitate formed. Tlc also indicated no remaining starting material. The cooled product was filtered. The precipitate was recrystallized from absolute alcohol to give 2.3 g. of off-white solid, m.p. 225-227°; ir (Nujol): no NH or OH absorption, 5.90 (C=O), 6.08 (C=O of amide) μm; nmr (DMSO-d_6): δ 7.26 (S, 1CH), 7.0-8.4 (m, 14 Aromatic H).

Anal. Calcd. for $C_{22}H_{16}N_2O_2$: C, 77.6; H, 4.7; N, 8.2. Found: C, 77.7; H, 4.8; N, 8.2.

Thermal Treatment of Compound III.

About 200 mg. of the imine contained in a test tube, was kept in a 150° oil bath for sixteen hours. The test tube contained an upper zone of sublimate, which was shown (ir) to be benzoic acid, and a lower zone of sublimate which was shown (ir, tlc) to be compound II. The non-sublimed residue was identified by ir and tlc to be compound II.

Results identical to those above were obtained when a drop of concentrated hydrochloric acid was added to the imine.

Acknowledgments.

The author is indebted to Mr. J. G. Gagnon for the microanalyses, to Mr. W. E. Breneman and Mr. T. L. Morris for the ir spectra and to Mr. J. W. Westberg for the nmr spectra, and also to Mr. G. J. Lillquist for interpretation of the spectral data.

REFERENCES AND NOTES

(1) J. A. Moore, G. J. Sutherland, R. Sowerby, E. G. Kelly, S. Palermo and W. Webster, *J. Org. Chem.*, **34**, 887 (1969).

(2) C. L. Stevens, P. M. Pillai, M. E. Munk and K. G. Taylor, in "Mechanisms of Molecular Migrations," Vol. 3, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N.Y., 1971, p. 271.

(3) E. Stahl, "Drug Analysis by Chromatography and Microscopy," Ann Arbor Science, Ann Arbor, Michigan, 1973.

(4) T. A. K. Smith and H. Stephen, *Tetrahedron*, **1**, 38 (1957).

(5) Beacon Chemical Industries, Inc., Cambridge, Mass.