being used in the same manner as the Grignard reagent. The unfortunately low yields of carboxylic acids which we obtained upon carbonation are not due therefore to any absence of the intermediate lithium alkyl but to the formation of secondary products as already shown by Gilman and Van Ess.[9] The position of the alkyl sodium appears to be unique in that it lacks the reactivity necessary to complete the Wurtz reaction under these conditions, yet does not participate in the formation of secondary products with sodium caproate.

Data for a number of miscellaneous experiments are set down in Table VI. Many of these runs were made in an effort to locate some factor which would lead to increased yields of butylmalonic acid. Special mention can be made of (a) the effect of using over 100% excess of sodium sand—reaction No. 27—which resulted in a maximum yield of 57% of combined carboxylic acids; (b) the failure to obtain an improved yield of butylmalonic acid in No. 28 from the simultaneous presence of mercury, a test inspired by the higher yields of this acid in some of the experiments reported in the previous paper on the action of sodium on diamyl mercury; (c) the failure of the simultaneous presence of carbon dioxide to increase materially the yield of combined organic acids over what was obtained when the amyl chloride was first allowed to react until long after all evidence of reaction—judged by a temperature rise—had ceased; (d) the failure to note any marked increase in the yield of malonic acid in reaction No. 35 when amyl chloride was added to sodium in the presence of freshly prepared sodium caproate in order to test the validity of equation 4; (e) the continued constancy in the yields of butylmalonic acid in runs 27, 28, 29 and 35.

Conclusions

The Wurtz reaction can be interrupted at the intermediate organo-metallic stage if the alkyl halide is added to excess sodium at low or moderate temperatures. The reaction has been studied in some detail with *n*-amyl chloride and has been tested in a preliminary way with a number of other organic halides.

In the case of *n*-amyl chloride, caproic and butylmalonic acids were obtained upon carbonation. The yield of combined acids in one instance was as high as 56%.

The formation of the malonic acid by way of the monosodium compound has been shown to be unlikely.

Amylidene disodium is thermally more stable than amyl sodium.

CAMBRIDGE, MASS.

RECEIVED JUNE 12, 1936

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[9] Gilman and Van Ess, THIS JOURNAL, **55**, 1258 (1933).

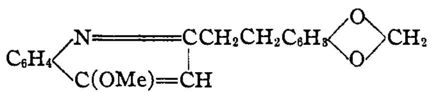
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

Researches on Quinazolines. XLIII. The Synthesis of a Quinazoline Derivative Structurally Analogous to Cusparine

BY DOMENICK PAPA[1] AND MARSTON TAYLOR BOGERT

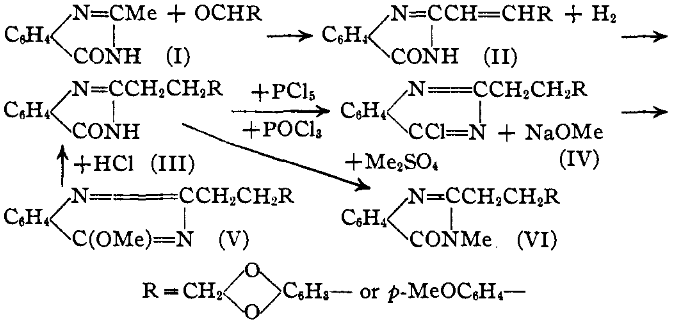
In a recent communication[2] from these Laboratories, there was described the synthesis of quinazoline derivatives akin structurally to the angostura alkaloids galipine and galipoline.[3]

The most important angostura alkaloid, however, is cusparine



The synthesis of its quinazoline analog is described in the following pages. The *p*-methoxyphenylethyl derivatives were also prepared, because they correspond, respectively to the galipoline and galipine analogs referred to above, but possess one less methoxyl group, and it seemed desirable therefore to include them in the series for pharmacological examination.

The steps involved in these syntheses were the following



Experimental

2-*p*-Methoxystyryl-4-quinazolone (II).—A mixture of 5 g. of 2-methyl-4-quinazolone (I) and 4.5 g. of *p*-anisaldehyde was heated for two hours at 170–175°. It liquefied after half an hour of heating and at the end of two hours

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[1] Fritzsche Fellow in Organic Chemistry, Columbia University, 1935–1936.

[2] Marr and Bogert, THIS JOURNAL, **57**, 729 (1935).

[3] Through an unfortunate error in proofreading, this alkaloid appears in that article as "galiopine."—M. T. B.

was semi-solid. When cold, it was pulverized, boiled with 10 cc. of 96% ethyl alcohol, to remove unchanged initial materials, and crystallized twice from glacial acetic acid in the presence of Norite. The product was a pale yellow crystalline solid, m. p. 284–285° (corr.); yield 80%. For analysis, it was dried for two hours at 110°.

Anal. Calcd. for $C_{17}H_{14}O_2N_2$: C, 73.34; H, 5.05. Found: C, 73.47; H, 4.97.

2 - (3′,4′ - Methylenedioxystyryl) - 4 - quinazolone (II) was prepared from 2-methyl-4-quinazolone (I) and piperonal, as described by Bogert and Beal,[4] except that the crude product was purified as recorded above, and then appeared as a crystalline solid of very pale yellowish cast, m. p. 316–317° (corr.) with decomposition; yield 64%. Bogert and Beal reported a m. p. of 305°. Dried at 110°, it was analyzed with the following results.

Anal. Calcd. for $C_{17}H_{12}O_3N_2$: C, 69.94; H, 4.15. Found: C, 70.11; H, 4.35.

2-(beta-*p*-Anisylethyl)-4-quinazolone (III), prepared by the same process as the next compound, formed colorless lustrous crystals, m. p. 213–214° (corr.); yield 90%. For analysis, it was dried to constant weight at 110°.

Anal. Calcd. for $C_{17}H_{16}O_2N_2$: C, 72.85; H, 5.76. Found: C, 72.73; H, 5.47.

2-(beta-3′,4′-Methylenedioxyphenylethyl)-4-quinazolone (III).—The styryl compound (II) was reduced catalytically by the process used by Marr and Bogert[2] for the reduction of 2-styryl-4-quinazolone, except that the crude product was washed first with water and then with 50% ethanol. From 4 g. of the styryl derivative (II), 500 cc. of 96% ethanol, and 150 g. of 3% sodium amalgam, there was obtained 3.49 g. (85%) of a colorless crude product, m. p. 238.5° (corr.), which was recrystallized by careful dilution of its hot alcoholic solution, and then melted at 239–240° (corr.). For analysis, it was dried to constant weight at 110°.

Anal. Calcd. for $C_{17}H_{14}O_3N_2$: C, 69.38; H, 4.78. Found: C, 69.40; H, 4.77.

2-(beta-*p*-Anisylethyl)-4-chloroquinazoline (IV).—In the main, the procedure followed was similar to that used by Marr and Bogert[2] for the production of 2-phenylethyl-4-chloroquinazoline. A mixture of 2 g. of the 4-quinazolone derivative (III), 1.4 g. of phosphorus pentachloride, and 25 cc. of phosphorus oxychloride, was refluxed for ten hours. The cooled solution was poured upon cracked ice, immediately extracted with ether, the ether extract washed with dilute sodium carbonate solution, then with water, dried over calcium chloride and the ether evaporated. There was thus obtained 0.75 g. of yellow crystals, m. p. 125–128° (corr.), containing halogen.

No analysis was attempted, because the instability of the product rendered it unlikely that an analytically pure compound could be obtained.

For successful results in this preparation, the following precautions must be observed: (a) the initial quinazolone must be pure, dry, and finely pulverized; (b) the phosphorus oxychloride must be distilled just before use and collected under carefully maintained anhydrous conditions (the product used in our experiments was colorless, transparent, and boiled at 107.4–107.7° (corr.)); (c) the apparatus should be washed thoroughly with water, alcohol, and ether, and dried for twelve hours at 110°; (d) the heating period of ten hours must be continuous; (e) the temperature must not be permitted to rise above 115° for any length of time, or considerable decomposition will occur; (f) the rate of evaporation of the ether influences the physical state of the residue, for too rapid evaporation tends to leave an oil which solidifies only with difficulty.

2 - (beta - 3′,4′ - Methylenedioxyphenylethyl) - 4 - chloroquinazoline (IV), prepared like the above *p*-anisyl derivative, was obtained as an orange oil, which refused to congeal; yield 0.85 g., from 2 g. of initial quinazolone (III); qualitative test for halogen, positive.

2 - (beta - *p* - Anisylethyl) - 4 - methoxyquinazoline (V), prepared as described for the next compound, gave 0.3 g. of colorless crystals, m. p. 84.5–85.5° (corr.), from 0.75 g. of the chloro derivative (IV).

Anal. Calcd. for $C_{18}H_{18}O_2N_2$: C, 73.47; H, 6.17. Found: C, 73.41; H, 5.93.

Refluxed for thirty minutes with concentrated hydrochloric acid, a clear solution resulted, from which 2-(beta-*p*-anisylethyl)-4-quinazolone (III) was precipitated by dilution, m. p. 209–212° (corr.). Recrystallized from absolute alcohol, the m. p. was raised to 212–213°. Mixed with a sample of the anisylethyl-4-quinazolone (III) (m. p. 213–214°, corr.), synthesized as noted above, the m. p. was 212–213.5° (corr.).

2 - (beta - 3′,4′ - Methylenedioxyphenylethyl) - 4 - methoxyquinazoline (V).—To a solution of 0.85 g. of the chloro compound (IV) in 15 cc. of absolute methanol, there was added a sodium methylate solution prepared from 0.14 g. of sodium and 10 cc. of absolute methanol. After standing for twenty-four hours in a stoppered flask, the solution was filtered and the filtrate diluted. Yellow crystals (0.6 g.) separated after eighteen hours. These were digested with Norite in absolute ethanol solution, the mixture filtered hot and the filtrate diluted carefully. An emulsion formed which, after cooling overnight and heating again, separated crystals. Washed with dilute ethanol and dried in a vacuum desiccator, they melted at 67–68° (corr.).

Anal. Calcd. for $C_{16}H_{16}O_3N_2$: C, 70.10; H, 5.25. Found: C, 70.04; H, 4.86.

Hydrolyzed by concentrated hydrochloric acid, the corresponding quinazolone (III) was obtained, m. p. 239–240° (corr.). Mixed with a sample of the synthetic quinazolone (III) (m. p. 239–240°, corr.), the m. p. was 238.5–239.5° (corr.).

2-(beta-*p*-Anisylethyl)-3-methyl-4-quinazolone (VI).—The anisylethyl-4-quinazolone (III) was dissolved in sodium hydroxide solution and treated with dimethyl sulfate. The crude product was crystallized from diluted alcohol and then formed small colorless needles, m. p. 118–118.5° (corr.), which were not hydrolyzed by digestion with concentrated hydrochloric acid.

Anal. Calcd. for $C_{16}H_{18}O_2N_2$: C, 73.47; H, 6.17. Found: C, 73.81; H, 6.10.

2 - (beta - 3′,4′ - Methylenedioxyphenylethyl) - 3 - methyl-4-quinazolone (VI), prepared similarly, crystallized in long, thin needles which melted sharply at 94–94.5°

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[4] Bogert and Beal, THIS JOURNAL, **34**, 522 (1912).

(corr.), and were not hydrolyzed by digestion with concentrated hydrochloric acid.

Anal. Calcd. for $C_{18}H_{16}O_3N_2$: C, 70.10; H, 5.25. Found: C, 70.20; H, 5.17.

2,3-Dimethyl-4-quinazolone.—Incidentally this compound was also prepared from 2-methyl-4-quinazolone (I), by the same method as the two just reported above. It was obtained in thin colorless needles, m. p. 111–111.5° (corr.), which were not hydrolyzed when boiled with concentrated hydrochloric acid. Bogert and Seil[5] obtained it by the action of methylamine upon acetanthranil and gave its m. p. as 110°.

Summary

1. 2-Methyl-4-quinazolone has been condensed with *p*-anisaldehyde and with piperonal to the corresponding styryl derivatives, and the olefin bond of the latter has been saturated by catalytic hydrogenation.

2. These substituted 2-phenylethyl-4-quinazolones have been converted into the corresponding substituted 2-phenylethyl-4-chloro and 4-methoxy quinazolines, of which the 2-(beta-3′,4′-methylene dioxyphenylethyl)-4-methoxyquinazoline is the quinazoline analog of the angostura alkaloid cusparine.

3. The substituted 2-phenylethyl-3-methyl-4-quinazolones were also synthesized, to learn in what respects these N-methyl derivatives differed from their O-methyl isomers.

4. The pharmacological properties of these compounds have not yet been studied.

NEW YORK, N. Y. RECEIVED JULY 10, 1936

(5) Bogert and Seil, THIS JOURNAL, **29**, 531 (1907).

[CONTRIBUTION FROM THE LABORATORIES OF CHEMISTRY AND PHYSICS, AMHERST COLLEGE]

A Sensitive Manostat for Low Pressures and its Application to the Adsorption of Hydrogen and Deuterium on Copper

BY THEODORE SOLLER, SEYMORE GOLDWASSER AND RALPH A. BEEBE

In the course of experiments conducted in the Amherst[1] Laboratory of Chemistry on the rates of hydrogen and deuterium adsorption on copper at gas pressures in the region of 2 mm., it became apparent that rate data were needed under conditions of constant pressure. The most sensitive manostat described in the literature is that of Huntress and Hershberg[2] who claim control of pressure to ±0.15 mm. Because this amount of variation was prohibitive for work at 1 to 2 mm. total pressure, a new automatic manostat has been developed which regulates the pressure to better than ±0.005 mm. and is applicable to all pressures. Provision has also been made for the continuous reading of the volume of gas entering the system during the course of adsorption. With the new manostatic technique it has been possible to investigate in detail the relative rates of adsorption of the two hydrogen isotopes on copper at low pressures. At 0° we have found a marked difference in the rates of adsorption of hydrogen and deuterium under identical conditions. Moreover, the temperature inversion in the ratio H_2/D_2 adsorbed has again been observed. This inversion has been found previously by Beebe *et al.*[1] and more recently has been predicted by Pease and Wheeler[3] from a statistical mechanical approach to the problem.

A. The Manostat

The general plan of the control mechanism is as follows. A slight decrease in the pressure of the system causes the mirror of the differential manometer to be tilted downward in such a way as to throw a light beam onto a photo-electric cell. Working through an amplifier, this cell actuates the solenoid which opens the mercury valve, thereby admitting a small amount of gas to the system. The admission of this gas causes a slight increase of the pressure and the valve is closed *via* the mirror, the photo-electric cell, and the solenoid, thus completing the cycle.

The Differential Manometer.—A modified form of the mercury manometer described by Johnson and Harrison[4] was used. To eliminate the rather troublesome task of fusing the platinum strip into a glass roller rod, a 1.6 mm. steel rod was substituted. The platinum strip was then easily attached by spot welding. Three leveling screws supporting the whole float and mirror mechanism made the device more readily adjustable. The whole manometer was placed in a small water thermostat, control of which was necessary to ±0.1° to prevent undue change in the volume of the mercury supporting the glass float. Because a quick response to pressure change was essential, the dead-beat feature of the manometer of Johnson and Harrison was sacrificed by using a 10-mm. tube to connect the mer-

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(1) Beebe, Low, Wildner and Goldwasser, THIS JOURNAL, **57**, 2527 (1935).

(2) Huntress and Hershberg, *Ind. Eng. Chem., Anal. Ed.*, **5**, 145 (1933). The authors also include a complete review of the subject up to 1933.

(3) Pease and Wheeler, *ibid.*, THIS JOURNAL, **58**, 1665 (1936).

(4) Johnson and Harrison, *J. Sci. Instruments*, **6**, 305 (1929).