crystallized to constant melting point. The first fractions which made up most of the distillate gave acids melting at 62°, while the higher boiling fractions which were very small gave acids melting from 67 to 68°. The residue in the flask gave a very small amount of acid having a melting point of 76 to 78°. Though the datum is not quantitative the results indicate that palmitic acid is the main acid present, that stearic acid is in small amounts, and that arachidic acid is present in traces. This again is in agreement with cotton seed oil.

Summary

The oil from the seed of the Rose Mallow (*Hibiscus Moscheutos x H. coccineus*) has been analyzed. The composition of the oil is given in the table.

COMPOSITION OF THE OIL FROM THE SEED OF THE ROSE MALLOW

Glycerides of	
Oleic acid, %	33.12
Linolic acid, %	45.53
Satd. acids (chiefly palmitic with small amount of stearic and trace of arachidic), %	15.60
Unsaponifiable material, %	1.34

LEXINGTON, KENTUCKY RECEIVED JANUARY 15, 1935

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

Researches on Quinazolines. XXXIX. The Synthesis of Quinazoline Derivatives Structurally Analogous to the Angostura Alkaloids Galiopine and Galipine[1]

BY ELEANOR BEST MARR[2] AND MARSTON TAYLOR BOGERT

So many of our important alkaloids and other useful medicaments are derivatives of quinoline, isoquinoline or their hydrogenated cycles,[3] that it is surprising to find in the literature so little concerning the pharmacology of the closely related quinazoline derivatives, although quinazoline structurally may be considered as being simultaneously both a quinoline and an isoquinoline.

In fact, practically nothing appears to be known of the pharmacodynamics of quinazoline itself or its simple hydro derivatives, in spite of the fact that quinazoline, its 3,4-dihydro and 1,2,3,4-tetrahydro derivatives have been well known for many years. Further, these three bases are all soluble in water, the first forming a neutral solution and the other two giving alkaline ones.

In paving the way for a coöperative research in this field with some of our pharmacological friends, we have undertaken additional experimental work along the following lines: (1) Improvements in the preparation of quinazoline and its simple hydro derivatives, in order that these fundamental N-heterocycles may be available in sufficient quantities to justify a study of their physiological effects. (2) The synthesis and pharmacological examination of quinazoline derivatives of alkaloidal type, *i. e.*, structurally identical with familiar alkaloids, but containing the quinazoline in place of the quinoline or isoquinoline nucleus. This should give us a clue to whether similarity of molecular architecture is or is not a factor in determining physiological action in these types.

In the first of these two fields, we reported[4] a number of years ago, some modifications of the Riedel[5] process for the preparation of quinazoline. The present paper records a new and very satisfactory method for the production of the 3,4-dihydroquinazoline by the catalytic reduction of quinazoline. This is important, because 1,2,3,4-tetrahydroquinazoline is readily obtained by reducing the 3,4-dihydro derivative with sodium amalgam.[6]

The work in the alkaloidal field was prefaced by the synthesis of the 2-(β-phenethyl) derivatives, to learn what yields we might expect from the reactions contemplated and the most favorable conditions.

These syntheses are outlined below. In the introductory series, R was C_6H_5; in that which followed, it was $C_6H_3(OCH_3)_2$.

It will be observed that 2-(β-phenethyl)-4-quinazolone (III) was synthesized by two differ-

(1) Based upon the Dissertation submitted by Eleanor B. Marr, December, 1934, for the degree of Ph.D. under the Faculty of Pure Science, Columbia University, New York, N. Y., to which Dissertation the reader is referred for further experimental details and literature citations.—M. T. B.

(2) Ferguson Fellow in Chemistry, Columbia University, 1932–1934.

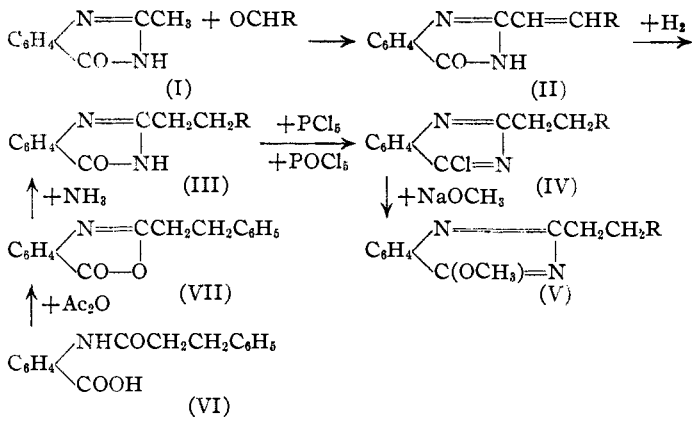
(3) See especially "Therapeutic Agents of the Quinoline Group," by W. V. von Oettingen, Chemical Catalog Co., N. Y., 1933.

(4) Bogert and McColm, THIS JOURNAL, **49**, 2651 (1927).

(5) Riedel, German Patent 174,941 (1905).

(6) Gabriel, *Ber.*, **36**, 811 (1903).

ent methods, one beginning with 2-methyl-4-quinazolone (I) and the other with the hydro-

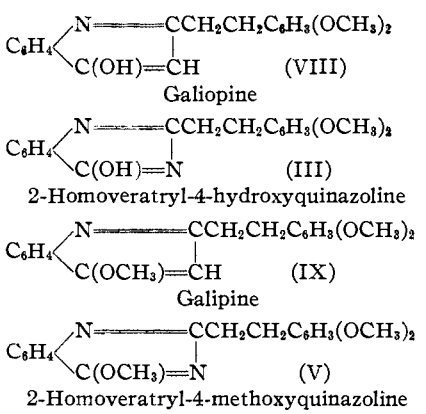


cinnamoyl anthranil (VII). The products of the two processes were identical. The second synthesis was used as a check on the first and to prove that in the reduction of the styryl derivative (II), the H saturated the side-chain only and did not enter the nucleus.

This latter fact is noteworthy, in view of the ease with which quinazoline itself adds two H to the miazine part of its molecule, with formation of the 3,4-dihydroquinazoline.

It has been observed frequently that a methyl group in position 2 is far more reactive than one at 4, probably because of its attachment to a carbon atom which is in alpha union with both heterocyclic nitrogens. On the other hand, halogens or ether groups at 4 are much more reactive than when at 2, behaving in the former case more like acyl halides and esters.

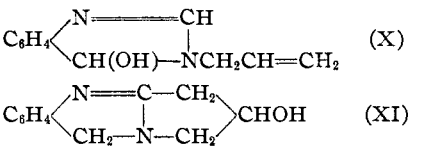
Of the new products thus synthesized, compounds (III) and (V) are structurally analogous to the angostura alkaloids galiopine (VIII) and galipine (IX), as a comparison of the constitutional formulas will show



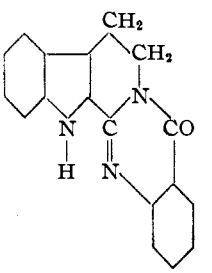
In nature a few alkaloids already have been discovered which contain the quinazoline nucleus.

Vasicine, the active principle of *Adhatoda vasica*, Nees, was isolated by Sen and Ghose[7] in 1924, and was assigned structure (X) by Späth and Nikawitz,[8] but both Reynolds and Robinson,[9] and Hanford, Liang and Adams,[10] have shown that this formula is not correct. Rây and his co-workers,[11] and Späth and Nikawitz, have suggested other formulas, of which Hanford, Liang and Adams prefer (XI).

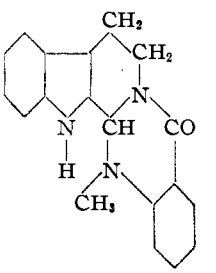
Peganine, which was isolated from the *Peganum harmala* in the laboratories of Merck & Company, has been shown to be identical with vasicine by Späth and Kuffner.[12]



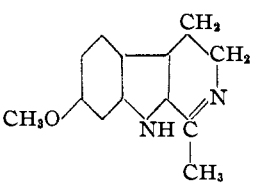
The constitution of Rutaecarpine (XII) and Evodiamine (XIII), the alkaloids of *Evodia rutaecarpa*, Benth. and Hook, has been established by the synthetic work of Asahina, Robinson and Manske.[13] The close relationship of their structures to that of certain of the harmala alkaloids will be seen on examination of the formulas



Rutaecarpine (XII)



Evodiamine (XIII)



Harmaline

(7) Seu and Ghose, *J. Indian Chem. Soc.*, **1**, 315 (1924).
(8) Späth and Nikawitz, *Ber.*, **67**, 45 (1934).
(9) Reynolds and Robinson, *Nature*, **134**, 142 (1934).
(10) Hanford, Liang and Adams, THIS JOURNAL, **56**, 2780 (1934).
(11) (a) De and Rây, *J. Indian Chem. Soc.*, **4**, 541 (1927); (b) Ghose, Krishna, Narang and Rây. *J. Chem. Soc.*, 2740 (1932); Rây and Narang, *J. Soc. Chem. Ind.*, **53**, 698 (1934).
(12) Späth and Kuffner, *Ber.*, **67**, 868 (1934).
(13) Asahina, Manske and Robinson, *J. Chem. Soc.*, 1708 (1927).

Experimental

N-Hydrocinnamoylanthranilic Acid (VI).—Hydrocinnamic acid, prepared most conveniently by the Clemmensen reduction of cinnamic acid,[14] was converted into its chloride,[15] and the latter condensed with anthranilic acid, in chilled anhydrous ether solution. The anthranilic acid hydrochloride which separated was filtered out, the ethereal filtrate evaporated, and the crude product purified by recrystallization, first from benzene, and then from dilute alcohol (1:1) in the presence of Norite. The pure product appeared in colorless slender prisms, m. p. 138.7–139.7° (corr.), soluble in alcohol, ethyl acetate or benzene, but practically insoluble in water, or in petroleum ether.

Anal. Calcd. for $C_{16}H_{15}O_3N$: C, 71.34; H, 5.62. Found: C, 71.69; H, 5.59.

3,4-Dihydroquinazoline.—To a solution of 8 g. of quinazoline in 150 cc. of 96% ethyl alcohol, there was added 0.2 g. of Adams platinum oxide catalyst, and the reduction was carried out at 26° with hydrogen at an initial pressure of 29.2 lb. per sq. in. After three hours, the absorption of hydrogen ceased and the pressure fell to 24.2 lb. This drop in pressure of 5 lb. agrees with that calculated (5.2 lb.) for the absorption of one mole of hydrogen.

The crude product was recrystallized from benzene to a constant m. p. of 126.5–127.5° (corr.), in accord with the literature. After the first recrystallization, the m. p. was 125.5–126.5° (corr.) and the yield 6 g.

Like quinazoline itself and its 1,2,3,4-tetrahydro derivative, this compound also is sensitive to air and light, and slowly darkens and decomposes on standing.

The hydrochloride, prepared by passing dry hydrogen chloride into a dry benzene solution of the base, formed small colorless crystals, m. p. 231–234°.

Picrate.—Fine yellow needles, melting with decomposition at 219–220° (corr.). The m. p. is recorded in the literature[16] as about 215°.

3,4-Dihydroquinazoline has been prepared by other investigators,[17] but the methods they employed seem to us less satisfactory than the one described above. The yields obtained by this catalytic hydrogenation process are greatly influenced by the purity of the initial quinazoline. If the latter is being purified by crystallization from petroleum ether, the presence of any sulfur in this solvent may result in a product which, although possessing the correct melting point, nevertheless may retain sufficient sulfur to affect the activity of the catalyst.

As noted above, under the conditions of our experiments, only one mole of hydrogen was added to the quinazoline molecule, and the absorption of hydrogen then ceased quite sharply. It is, of course, quite possible that, under different conditions, *e. g.*, higher temperatures and pressures, other catalysts, etc., more extensive hydrogenation will result. However, Itomi[18] found that by the electrolytic reduction of 3-phenyl-4-quinazolone, hydrogen could be added only to the miazine portion of the molecule.

The difference in the ease of hydrogenation between the 1,2 and the 3,4 unsaturations is probably due to the amidine configuration of the CH group in position 2.

2-(β-Phenethyl)-4-quinazolone (III).—A solution of 5.3 g. of 2-styryl-4-quinazolone (II), prepared as described by Bogert and Beal,[19] in 500 cc. of 96% ethyl alcohol, was heated under a reflux and treated with 200 g. of 2.5% sodium amalgam in small portions. After heating for seven hours, the solution was left overnight at room temperature, then decanted from the mercury, filtered, the filtrate diluted with 500 cc. of water and acidified with acetic acid. Small colorless crystals separated. These were removed and washed with water; yield, 4.8 g. From the mother liquor, 0.3 g. more was recovered. This crude product was purified by recrystallization from dilute alcohol, from 96% alcohol, and finally from ethyl acetate, when it formed long colorless silky needles, m. p. 209.5–210.5° (corr.). Dried to constant weight at 105°, it gave the following figures on analysis:

Anal. Calcd. for $C_{16}H_{14}ON_2$: C, 76.76; H, 5.64. Found: C, 76.13; H, 5.61.

In a second series of experiments, 10 g. of the finely powdered styrylquinazolone was suspended in 150 cc. of 96% ethyl alcohol and reduced by a current of hydrogen, in the presence of 0.1 g. of the Adams platinum oxide catalyst, and at an initial pressure of 25.8 lb. The absorption of hydrogen proceeded slowly and ceased after three hours, when the pressure had fallen to 23.8 lb. The fall in pressure calculated for the absorption of one molecule of hydrogen is 3.3 lb. On working up the product, there were isolated 7.4 g. of unchanged initial material, and 1.4 g. of the 2-phenethyl-4-quinazolone, identical with that obtained by the sodium amalgam reduction. One reason for the poor yield by this catalytic reduction is probably the slight solubility of both the styryl derivative and its reduction product in alcohol at the temperature employed (*i. e.*, that of the room).

Bogert and Beal[20] found that this styrylquinazolone could not be successfully reduced by hydriodic acid and red phosphorus.

This same 2-phenethyl-4-quinazolone was obtained from hydrocinnamoylanthranilic acid as follows.

The hydrocinnamoylanthranilic acid (VI) was dehydrated to the anthranil (VII) by digestion with excess of acetic anhydride. After distilling off the acetic acid and most of the excess of acetic anhydride, the residual concentrate, without separation of the anthranil, was added gradually to an excess of concentrated ammonium hydroxide solution heated just to the boiling point. When all was in solution, some 10% potassium hydroxide solution was added and the boiling continued for an hour. When the mixture was cold, the crystals were removed, washed with water and dried; m. p. 205.5–207°; yield, 97%. Recrystallized from 96% alcohol, ethyl acetate, and finally dilute (1:1) alcohol, the product formed long colorless silky needles, m. p. 208.5–209.5° (corr.); mixed m. p. 209–210° (corr.).

Anal. Calcd. for $C_{16}H_{14}O_2N_2$: C, 76.76; H, 5.64. Found: C, 76.99; H, 5.68.

2-Phenethyl-4-chloroquinazoline (IV) was obtained as a pale yellow oil, by the combined action of phosphorus

(14) Reid and Mitchell, THIS JOURNAL, **53**, 325 (1931).
(15) Mohr, *J. prakt. Chem.*, [2] **71**, 323 (1905).
(16) Gabriel and Jansen, *Ber.*, **23**, 2814 (1890).
(17) Gabriel and Jansen, *ibid.*, **23**, 2813 (1890); **24**, 3097 (1891).
(18) Itomi, *Mem. Coll. Sci. Kyoto Imp. Univ.*, **13A**, 311 (1930).
(19) Bogert, Beal and Amend, THIS JOURNAL, **32**, 1657 (1910).
(20) Bogert and Beal, *ibid.*, **34**, 516 (1912).

trichloride and phosphorus oxychloride upon the quinazolone (III); yield nearly 50%. The preparation proved to be a rather tricky one. The quinazolone and the apparatus must be perfectly dry, the phosphorus oxychloride freshly distilled, and the temperature kept below 120°.

2-Phenethyl-4-methoxyquinazoline (V), from the above chloro derivative and sodium methylate, in absolute methanol solution; purified by crystallization from dilute (1:1) ethyl alcohol, it formed colorless needles, m. p. 58.5–59.8° (corr.), which were dried to constant weight and analyzed.

Anal. Calcd. for $C_{17}H_{16}ON_2$: C, 77.23; H, 6.10. Found: C, 77.09; H, 5.74.

Boiled with concentrated hydrochloric acid, this ether was hydrolyzed to 2-(β-phenethyl)-4-quinazolone.

2-(3',4'-Dimethoxystyryl)-4-quinazolone (II).—A mixture of 8.5 g. of veratraldehyde with 8 g. of 2-methyl-4-quinazolone was heated at 180–185°. After about two and one-half hours, the evolution of steam ceased. The mixture, liquid at first, partially solidified at the end of the first hour. The melt was dissolved in about 500 cc. of Cellosolve, 400 cc. of hot alcohol added, and the mixture cooled. The crystals which separated were removed, washed with a mixture of the same solvents, then with alcohol, and dried; yield, 10.9 g. of pale yellow crystals, m. p. 265–266°, with softening at about 264°. Purified by crystallization from Cellosolve, alcohol, or a mixture of the two, and decolorized by Norite, the compound was secured in fine pale yellow needles, m. p. 268–269° (corr.), nearly insoluble in glacial acetic acid, ethyl acetate, chloroform, acetone or benzene, in the cold and not much more soluble hot. The product was also difficultly soluble in hot ethyl alcohol, but dissolved more freely in hot isoamyl alcohol or in hot Cellosolve.

Anal. Calcd. for $C_{18}H_{16}O_3N_2$: C, 70.10; H, 5.23. Found: C, 70.57; H, 5.20.

2-Homoveratryl-4-quinazolone (III).—A suspension of 4 g. of the styryl derivative (II) in 500 cc. of 96% ethyl alcohol was heated under a reflux and reduced by the gradual addition of 150 g. of 3% sodium amalgam, after which the solution of the sodium salt was acidified and concentrated. The yield of crude product, m. p. 208.5–209.5° (corr.), was 92%. Recrystallized from ethyl alcohol and then from ethyl acetate, it formed long slender colorless needles, m. p. 209–210° (corr.).

Anal. Calcd. for $C_{18}H_{18}O_3N_2$: C, 69.64; H, 5.85. Found: C, 69.53; H, 5.51.

2-Homoveratryl-4-chloroquinazoline (IV) was prepared from the last-mentioned compound (III) by the action of a mixture of phosphorus oxychloride and phosphorus pentachloride. The crude product was obtained from ether solution in small pale yellow needles, m. p. 116–118°, easily soluble in ethyl alcohol or benzene, but only slightly in petroleum ether. Without further purification or analysis, this crude product was used direct for the synthesis of the

2-Homoveratryl-4-methoxyquinazoline (V), by dissolving it in absolute methanol and subjecting it to the action of sodium methylate for seventeen hours at room temperature. The yield of crude compound, m. p. 91–95°, from 0.55 g. of the chloroquinazoline was 0.42 g. Decolorized by Norite and crystallized from dilute (1:1) ethyl alcohol, it formed long slender flat colorless crystals, m. p. 96.3–97.3° (corr.).

Anal. Calcd. for $C_{19}H_{20}O_3N_2$: C, 70.33; H, 6.22. Found: C, 70.73; H, 6.58.

Boiled for a short time with concentrated hydrochloric acid, it was hydrolyzed to 2-homoveratryl-4-quinazolone.

Summary

1. Quinazoline derivatives have been synthesized, structurally analogous to the angostura alkaloids galiopine and galipine, for the purpose of comparing the physiological effects of the two series.

2. Incidentally, several other new quinazoline derivatives are described, and some old ones have been prepared by new methods.

NEW YORK, N. Y. RECEIVED JANUARY 21, 1935

[CONTRIBUTION FROM THE COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY]

A Study of Acid Degradation

BY MELVIN S. NEWMAN[1]

In degradation of α-bromo acid azides by the method of Curtius,[2] it has been found that, instead of amines, aldehydes and ketones are formed in accordance with the outline

$$R_1R_2CHCOOH \xrightarrow{(1)\ Br_2} R_1R_2CBrCOOH \xrightarrow{(2)\ SOCl_2} R_1R_2CBrCOCl \xrightarrow{(3)\ NaN_3} R_1R_2CBrCON_3 \xrightarrow{(4)\ \text{heat}} R_1R_2CBrNCO \xrightarrow{(5)\ HOH} R_1R_2CBrNH_2 \xrightarrow{(6)\ HOH} R_1COR_2$$

It is obvious that through this procedure aldehydes result from mono-substituted and ketones from di-substituted acetic acids.

This method of acid degradation had previously been suggested by von Braun,[3,4] but as the same scheme was independently evolved by the author at approximately the same time, Professor von Braun has graciously welcomed coöperation in this field.[5]

(1) National Research Council Fellow in Chemistry.

(2) Curtius, *J. prakt. Chem.*, [2] **50**, 275 (1894).

(3) Von Braun, *Petroleum Z.*, **28**, 50 (1932).

(4) Von Braun, *Ber.*, **67**, 218 (1934).

(5) Private communication.