Some Derivatives of 2-Methyl-3-phenyl-3H-4-quinazolone

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Abstract □ The preparation of isomeric acids and acid amides of 2-methyl-3-phenyl-3H-4-quinazolone and its benzene-substituted derivatives are described. A mechanism is suggested to account for the formation of 2-methyl-3H-4-quinazolone from the isomeric 3-(carboxyphenyl) acids by fusion with urea or the corresponding ammonium salts by distillation.

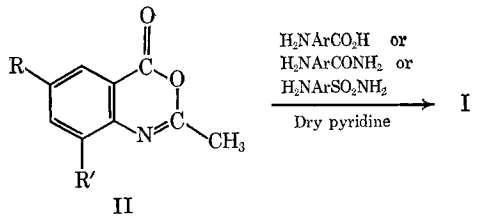
Keyphrases □ 2-Methyl-3-phenyl-3H-4-quinazolone derivatives—synthesis □ Antiepileptics, potential—synthesis

Although most antiepileptic drugs currently in use contain a carbonyl-nitrogen-carbonyl grouping, anticonvulsant activity is found also in simple amides such as 2-phenyl-2-hydroxypropionamide (1); and *N*-benzyl-β-chloropropionamide, which is an example of a methylene-nitrogen-carbonyl grouping (2). Furthermore, extensive screening of heterocyclic amides as well as noncyclic fragments of the barbiturate nucleus has furnished a lead to successful anticonvulsants as 2-phenylbutyramide and its *N*-methyl derivative (3).

Recently, a group of British investigators demonstrated the anticonvulsant activity of some 2-alkyl-3-aryl-3H-4-quinazolones, of which the 2-methyl-3-(*p*-bromophenyl) derivative has anticonvulsant activity comparable to the most potent anticonvulsant drugs (4).

Since the carbamoyl group appears in many CNS depressants and the sulfamoyl is characteristic of carbonic anhydrase inhibitors, it is of interest to introduce these groups into the phenyl radical of 2-methyl-3-phenyl-3H-4-quinazolone. Consequently, quinazolone derivatives of the general formula (I) have been prepared as potential anticonvulsants (Fig. 1).

For the synthesis of such compounds the following general reaction conditions were adopted (Scheme I).



Scheme I

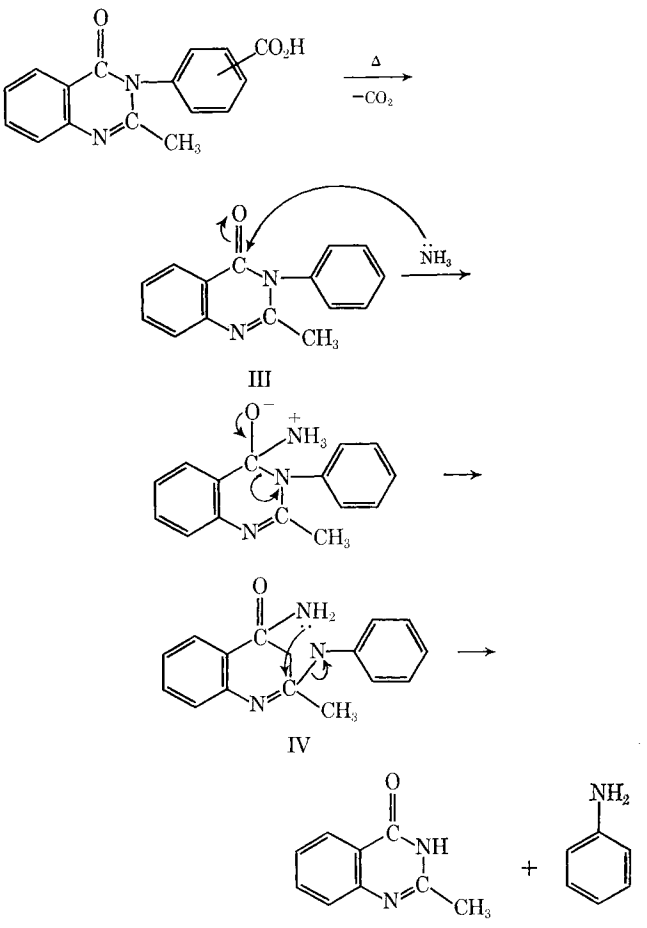
EXPERIMENTAL

Derivatives of 2-Methyl-3-phenyl-3H-4-quinazolone—*General Procedure*—Compounds I–X were prepared by suspending a mixture of equimolecular amounts of acetanthranil or its benzyl-substituted derivatives and the appropriate amino acid or amino amide in dry pyridine (2 g. pyridine/1 g. mixture) and refluxing for 1 hr. (5). The pyridine was then removed *in vacuo* and the resulting gummy mass or crystalline solid was recrystallized from the appropriate solvent (see Table I).

RESULTS AND DISCUSSION

The acids were prepared by condensing acylanthranils with *m*- and *p*-aminobenzoic acids, while the amides were obtained from the corresponding aminobenzamides by a similar condensation. Condensation of sulfanilamide with 6,8-dibromoacetanthranil afforded a quinazolone derivative with a *p*-sulfamoyl group. All attempts to prepare 2-methyl-3-(*p*-carbamoylphenyl)-3H-4-quinazolone or its *ortho* analog were abortive.

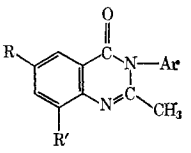
The synthesis of the acids listed in Table I was accomplished by condensing 2-methyl-3,1-benzoxaz-4-one or its benzyl-substituted derivatives (II) with isomers of anthranilic acid in dry pyridine. Attempts to convert the acids obtained to the corresponding amides *via* the application of the Cherbuliez method (6)—which consists in fusing the carboxylic acid with urea under pressure—did not give satisfactory results. Instead of affording the expected amides, 2-methyl-4-quinazolone was obtained. The constitution of which was established by mixed melting with an authentic sample prepared according to the method of Buzas and Hoffmann (7). The formation of 2-methyl-4-quinazolone probably takes place according to the following (Scheme II):



Scheme II

At the temperature (180–200°) at which the fusion is conducted, it is likely that decarboxylation of the isomeric acids occurs converting these into one compound (III). The carbonyl at Position 4 is then attacked by the ammonia—resulting from the de-

Table I—Derivatives of 2-Methyl-3-phenyl-3H-4-quinazolone



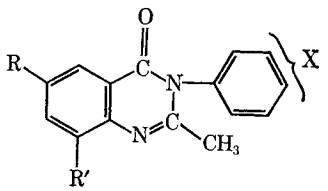
Compd.	Name	R	R′	Ar	Yield, %	Solvent of Crystallization[a]	M.p., °C,[b]	Formula	—Anal., %[c]— Calcd.	Found
I	2-Methyl-3-(*p*-carboxyphenyl)-6-bromo-3H-4-quinazolone	Br	H	*p*-carboxyphenyl	89	E	305	$C_{16}H_{11}BrN_2O_3$	C, 53.48 H, 3.06 N, 7.79	53.46 3.65 7.91
II	2-Methyl-3-(*m*-carboxyphenyl)-6,8-dibromo-3H-4-quinazolone	Br	Br	*m*-carboxyphenyl	96	E	286	$C_{16}H_{10}Br_2N_2O_3$	C, 43.83 H, 2.28 N, 6.39	44.09 2.99 6.15
III	2-Methyl-3-(*p*-carboxyphenyl)-6,8-dibromo-3H-4-quinazolone	Br	Br	*p*-carboxyphenyl	48.5	E	320	$C_{16}H_{10}Br_2N_2O_3$	C, 43.83 H, 2.28 N, 6.39	43.92 2.87 6.34
IV	2-Methyl-3-(*m*-carbamoylphenyl)-3H-4-quinazolone	H	H	*m*-carbamoylphenyl	50.1	A	225	$C_{16}H_{13}N_3O_2$	C, 68.81 H, 4.65 N, 15.05	68.28 4.71 14.75
V	2-Methyl-3-(*m*-carbamoylphenyl)-6-bromo-3H-4-quinazolone	Br	H	*m*-carbamoylphenyl	41.8	B	302	$C_{16}H_{12}N_3O_2Br$	C, 53.63 H, 3.35 N, 11.73	53.60 3.38 11.44
VI	2-Methyl-3-(*p*-carbamoylphenyl)-6-bromo-3H-4-quinazolone	Br	H	*p*-carbamoylphenyl	25.1	A	225	$C_{16}H_{12}BrN_3O_2$	C, 53.63 H, 3.35 N, 11.73	53.77 3.35 11.18
VIII	2-Methyl-3-(*m*-carbamoylphenyl)-6,8-dibromo-3H-4-quinazolone	Br	Br	*m*-carbamoylphenyl	50.3	B	295	$C_{16}H_{11}Br_2N_3O_2$	C, 43.93 H, 2.51 N, 9.61	44.25 2.55 9.16
VIII	2-Methyl-3-(*p*-carbamoylphenyl)-6,8-dibromo-3H-4-quinazolone	Br	Br	*p*-carbamoylphenyl	18.3	D	302	$C_{16}H_{11}Br_2N_3O_2$	C, 43.93 H, 2.51 N, 9.61	44.24 2.49 9.35
IX	2-Methyl-3-(*p*-sulfamoylphenyl)-6,8-dibromo-3H-4-quinazolone	Br	Br	*p*-sulfamoylphenyl	67.4	C	330	$C_{15}H_{11}Br_2N_3O_3S$	C, 38.05 H, 2.32 N, 8.87	38.17 2.33 8.80

[a] A, acetone; B, pyridineethanol; C, acetone-methanol-dimethyl-formamide; D, dimethylformamide-ethanol; E, ethanol. [b] Melting points are uncorrected. [c] Analyses performed by Janssen Pharma-ceutica, Beer se, Belgium.

composition of urea—with the consequent formation of (IV) which then undergoes ring closure by internal addition followed by the elimination of aniline.

It may be seen from the foregoing that the suggested scheme besides accounting for the formation of 2-methyl-4-quinazolone, gives a reasonable answer to the production of aniline in the course of the fusion.

Several other attempts were made to prepare the amides listed in Table I. Thus treatment of the corresponding esters with ammonia either aqueous or alcoholic was unsuccessful and the esters were recovered unchanged. Likewise, distillation of the ammonium salts of the parent acids proved to be unsatisfactory. Similarly, no success attended an attempt to prepare the amide from the corresponding acid chloride. However, preparation of the amides of Table I was accomplished by condensing amino-amides with acetanthranil or its benzyl-substituted derivatives in dry pyridine.



I

R = H or Br; R′ = H or Br; R and R′ may be the same or different; X = *m*-or *p*-: COOH or $CONH_2$, or *p*-SO_2NH_2

Figure 1

2-Methyl-4H-3,1-benzoxaz-4-one (acetanthranil), its 6-bromo derivative, and the 6,8-dibromo compound were prepared according to the method of Bogert (8) in an overall yield of 86, 73. and 94%, respectively.

The isomeric aminobenzamides were prepared from the corresponding nitrobenzoyl chlorides by ammonolysis followed by reduction of the nitroamides thus obtained with ferrous sulfate and ammonia according to the method of Jacobs and Heidelberger (9).

The compounds in Table I have been submitted for a general pharmacological screening for possible anticonvulsant action and/or other biological activity. The results obtained will be the subject of a subsequent communication.

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COMMUNICATIONS

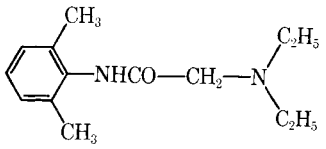
Disproportionation of Lidocaine Sulfate Dihydrate in Certain Organic Solvents

Keyphrases ☐ Lidocaine sulfate dihydrate—synthesis ☐ Disproportionation, organic solvents—lidocaine sulfate dihydrate ☐ IR spectrophotometry—identity

Sir:

The disproportionation of lidocaine[1] sulfate dihydrate into the bisulfate and amine base has been observed.

$$[XYLH]_2SO_4 \cdot 2H_2O \longrightarrow XYL + [XYL]HSO_4 + 2H_2O$$

where XYL = lidocaine 

It was this reaction that presented difficulty in the preparation of lidocaine sulfate. Such a disproportionation was suspected when attempts to prepare the sulfate in the presence of acetone yielded only the bisulfate. The sulfate was ultimately synthesized utilizing a suitable mixed organic solvent system, namely, 95% ethanol and ethyl ether.

Lidocaine Sulfate Dihydrate—Fifty-two grams (0.22 mole) of lidocaine base was dissolved in 125 ml. of ether. To 50 ml. of 95% ethanol previously cooled in an ice-water bath was added slowly, 5.3 ml. (9.8 g.; 0.1 mole) of concentrated sulfuric acid. The acid-alcohol mixture was added dropwise to the ether solution of the base under vigorous magnetic stirring. After complete addition, the precipitate was isolated by filtration and washed with several portions of ether. A yield of 56.8 g. (93%) was obtained. Recrystallization from 15% ethanol in benzene by cooling from 30 to 10° gave colorless crystals, m.p. 106–108°.[2] IR spectrum[3] showed S-O str. at 1125 cm.$^{-1}$ [lit. 1125–1080 cm.$^{-1}$ (1)].

Anal.[4]—Calcd. for $C_{28}H_{50}N_4O_8S$ (602.80): C, 55.79; H, 8.36; N, 9.30; S, 5.32; XYL, 77.75; H_2O, 5.97%; mol. wt., 603. Found: C, 55.99; H, 8.61; N, 9.07; S, 5.60; XYL, 77.52; H_2O, 6.09%; mol. wt., 618.

Supplementary Data—Assay (2) of lidocaine bisulfate, m.p. 218–220° [lit. 210–212° (3)], for lidocaine base gave the following results: Calcd., 70.50%; Found, 70.22%. IR spectrum showed S-O str. at 1180 and 1070 cm.$^{-1}$ [lit. 1190–1160 and 1080–1015 cm.$^{-1}$ (1)]. The pH of a 2% solution in saline of lidocaine sulfate dihydrate and lidocaine bisulfate was 5.5 and 2.7, respectively. Melting point determination on lidocaine base gave the value of 67–69° [lit. 66–69° (4, 5)].

Disproportionation Reaction Procedure—The solvents used were absolute ethanol, acetone, benzene, carbon tetrachloride, chloroform, ether, and water. Five grams (0.0083 mole) of lidocaine sulfate dihydrate was placed in 200 ml. of solvent contained in a 500-ml. stoppered flask and mixed well. After 3 days at room temperature the mixture was filtered. In the case of the solvents acetone and chloroform, in which a visible reaction had taken place, the weight and melting point of the precipitate formed was obtained. In the case of the other solvents in which no visible reaction appeared, the filtrate was evaporated to dryness over a steam bath. The weight and melting point was obtained on the residue. Further confirmation of the recovered sulfate and the reaction products lidocaine base and bisulfate was obtained by IR spectra.

Results—The sulfate was completely soluble in absolute ethanol and water. No precipitation occurred upon standing for 3 days. Upon evaporation of the filtrate the unreacted sulfate was recovered in both cases, m.p. 106–108°; recovery 4.8 g. (96%).

In benzene, carbon tetrachloride, and ether there was no visible evidence of a reaction taking place. The sulfate appeared to be insoluble in these solvents. Evaporation of the filtrates gave a 5–11% yield of lidocaine base indicating a limited disproportionation.

[1] Xylocaine (Lidocaine USP), Astra Pharmaceutical Products, Inc., Worcester, Mass.
[2] All melting point values corrected, using a Mel-Temp apparatus.
[3] Perkin-Elmer model 137B, KBr.

[4] Microanalyses involving C, H, and N were performed by Schwarzkopf Laboratories, Woodside, N. Y. All other analyses were performed by our Analytical Laboratories. Sulfur, gravimetric as barium sulfate; lidocaine base, alkaline (NH_4OH) chloroform extraction, nonaqueous perchloric acid titration (2); water, Karl Fischer method; molecular weight, classical method with Fisher apparatus, Beckman thermometer.