Sulfanilamidoquinazolines

TELLIS A. MARTIN, ALLAN G. WHEELER, ROBERT F. MAJEWSKI, AND JOHN R. CORRIGAN

Mead Johnson Research Center, Evansville, Indiana 47721

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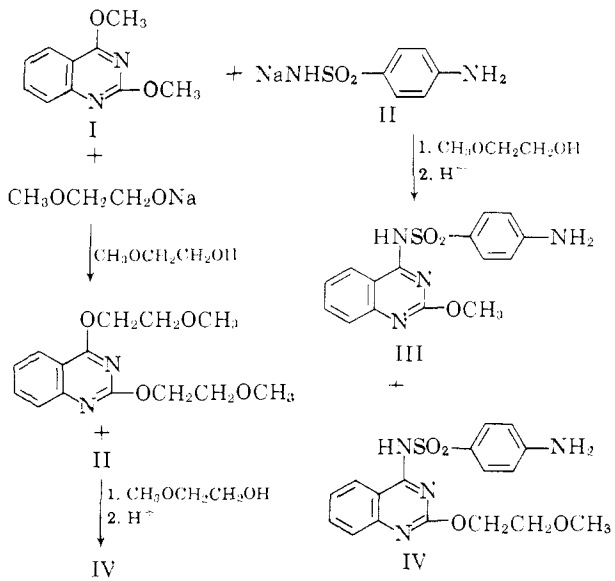
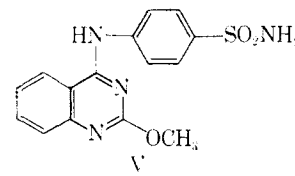
A long-acting sulfanilamide, 2-methoxy-4-sulfanilamidoquinazoline (III), was prepared[1] in low yield from 2,4-dimethoxyquinazoline (I) and sodium sulfanilamide (II) using 2-methoxyethanol as the reaction solvent. The present report deals with some of the results obtained during a study of the process described in the patent.[1] Gas chromatographic analysis of the reaction distillate showed substantially more than the theoretical 1 mole of methanol expected from the nucleophilic displacement of the reactive, ester-like, 4-methoxy group. Replacement of the less reactive 2-methoxy group by the solvent alcohol was considered a likely possibility, although such a replacement had not been previously reported. The formation of 2-(2-methoxyethoxy)-4-sulfanilamidoquinazoline (IV) was later confirmed by its subsequent isolation from process mother liquors. It was identical with the product formed from sodium sulfanilamide and 2,4-di(2-methoxyethoxy)quinazoline.



The latter compound was prepared by alcoholysis of I with 2-methoxyethanol. Here again the 2-methoxy group was replaced by the 2-methoxyethoxy group, contrary to literature indications. It has been reported[2] that replacement of an alkoxy group (OR) by a different alkoxy group (OR′) takes place only at position 4 of quinazoline with position 2 being unaffected. A literature search likewise failed to reveal any previous examples of alcoholysis of a 2-alkoxyquinazoline. On the other hand the ester-like character of 4-alkoxyquinazolines has been clearly demonstrated by hydrolysis,[3] alcoholysis,[2] and ammonolysis.[4] Armarego[5] states that a methoxy group in position 2, in contrast to position 4, hydrolyzes under more drastic conditions and undergoes nucleophilic displacement (*i.e.*, replacement with –NHR groups) with difficulty.

In addition to alcoholysis several other side reactions occurred involving I and II. Paper chromatography showed ten components in the reaction mixture. A prominent by-product was found to be 2-methoxyquinazolin-4(3H)-one. Hydrolytic cleavage of I by moisture or transmethylation to sulfanilamide and/or the solvent, by the 4-methoxy group, are possible explanations. Gas chromatography, however, did not show any 1,2-dimethoxyethane which would have resulted from methylation of the solvent.

Another by-product, N^4-(2-methoxy-4-quinazolyl)-sulfanilamide (V), an isomer of III, was identified by paper chromatographic and spectrophotometric comparison with an authentic sample of V, which had been



V

inadvertently obtained earlier in an attempt to prepare III by a modified procedure. This procedure involved the reaction, in liquid ammonia, between sulfanilamide and 2,4-dichloroquinazoline in the presence of 2 equiv. of lithium amide, followed by treatment of the resulting 2-chloro derivative with sodium methoxide. Compound V was also obtained by the reaction of sulfanilamide with 2,4-dichloroquinazoline in acetone, followed by the replacement of the 2-chloro group by methoxyl.

Some further work on the nucleophilic displacement of the 4-methoxy group of I by sulfonamide anions has shown that the benzenesulfonamide anion reacts with I to give the expected yield of the 4-benzenesulfonamido derivative while the N-methylbenzenesulfonamide anion produces little, if any, product. The primary benzenesulfonamide anion permits the splitting out of methanol, as Bretschneider and Klötzer[6] point out for an analogous reaction of sulfanilamide anion with trimethoxy-*s*-triazine, while the N-methylbenzenesulfonamide anion does not.

Antibacterial Results.—The antibacterial activities of III, its N^4-acetyl derivative, and several related compounds, have been reported.[7] Recently the antibacterial activity of IV was determined and found to be inferior to III.

Acute Toxicities.—The acute toxicities for 2-methoxy-4-sulfanilamidoquinazoline (III) and its isomer, N^4-(2-methoxy-4-quinazolyl)sulfanilamide (V), were determined in groups of 10 male albino mice[8] weighing 17 to 30 g. A sodium salt solution of each compound in N-saline was administered intravenously at a rate of 0.3 ml./min. The pH of the III solution was 8.5–9.0 and of the V solution was 12–12.5.

(1) F. A. Grunwald, Belgian Patent 603,719 (Dec. 5, 1961); British Patent 920,019 (March 6, 1963).
(2) N. A. Lange and F. E. Sheibley, *J. Am. Chem. Soc.*, **54**, 1305 (1932).
(3) M. T. Bogert and C. E. May, *ibid.*, **31**, 507 (1909).
(4) N. J. Leonard and D. Y. Curtin, *J. Org. Chem.*, **11**, 341 (1946).
(5) W. L. F. Armarego in "Advances in Heterocyclic Chemistry," Vol. 1, A. R. Katritzky, Ed., Academic Press, New York, N. Y., 1963, p. 253.
(6) H. Bretschneider and W. Klötzer, U. S. Patent 2,774,756 (Dec. 18, 1956).
(7) E. F. Harrison and J. H. Weikel, Jr., *Antimicrobial Agents Chemotherapy*, 546 (1963).
(8) Swiss Webster strain of mice obtained from Laboratory Supply Co., Indianapolis, Ind.

A median lethal dose (LD_{50}) for III was 460 mg./kg. (432–490) with a median toxic dose (TD_{50}) of 24 mg./kg. (20.0–28.8).[9] The LD_{50} for V was 320 mg./kg. (264.4–387.2) and the TD_{50} was 12 mg./kg. (9.2–15.7).

Ataxia (2/10) at 18 mg./kg. was the minimal toxic effect observed with III and occurred about 23 min. after treatment. Additional effects at the highest dose level that was not lethal to 20 mice (400 mg./kg.) consisted of depression and an increase in respiratory depth within 2 min. after treatment. These effects were followed by Straub's tail reaction, opisthotonos, and clonic convulsions accompanied by a rolling movement. Deaths at 440- and 500-mg./kg. dose levels were apparently the result of respiratory failure and started to occur 14 min. after drug administration.

The minimal toxic response to V was also ataxia which occurred at 7 mg./kg. (2/10) within 2 min. after treatment. Responses to V at the highest dose level that was not lethal to 10 mice (150 mg./kg.) and at lethal dose levels (300 and 400 mg./kg.) were similar to those observed with III at corresponding levels of toxicity. The onset of clonic convulsions was slightly faster with V. Recovery from side effects was evident within 15–20 hr. after treatment with either III or V.

Experimental[10]

2-Methoxy-4-sulfanilamidoquinazoline (III).[1]—Metallic sodium (121 g., 5.26 g.-atoms) was carefully dissolved in 2 l. of methanol in a 12-l. flask. The reaction system was purged with nitrogen and 4.7 l. of 2-methoxyethanol (Fisher, purified), 903 g. (5.26 moles) of sulfanilamide, and 1 kg. (5.26 moles) of 2,4-dimethoxyquinazoline[3] were added with stirring to the solution. The mixture was heated to reflux (84°) and maintained at this temperature for 72 hr.[11] After cooling to 10–20°, 850 ml. of 6 *N* HCl was added over 1.5 hr. The crude product was collected, washed with 1 l. of methanol, and dried; yield, 721 g. (41.5%). Efficient slurrying of the crude product with warm methanol gave 706 g. (40.6%) of off-white product, m.p. 227–228°.

Anal. Calcd. for $C_{15}H_{14}N_4O_3S$: N, 16.96; S, 9.71. Found: N, 16.93; S, 9.58.

2-(2-Methoxyethoxy)-4-sulfanilamidoquinazoline (IV) Monohydrate.[1]—This compound was first isolated, with difficulty, in 10% crude yield from the mother liquors of III. It was identical with material synthesized as follows for confirmation of structure. 2,4-Di(2-methoxyethoxy)quinazoline (10.8 g., 0.0388 mole), 8.22 g. (0.042 mole) of sodium sulfanilamide, and 80 ml. of 2-methoxyethanol were heated at 85–90° for 1 week. The reaction mixture was concentrated, the residue was dissolved in water, and the aqueous solution was washed with ether and acidified to produce 9 g. (59%)[12] of tan solid. Four recrystallizations from 50% aqueous 2-methoxyethanol gave a cream solid of m.p. 129.5–138° (a sample dried at 85–90° *in vacuo* presumably lost water of crystallization because the melting point rose to *ca.* 182°).

Anal. Calcd. for $C_{17}H_{18}N_4O_4S \cdot H_2O$: C, 52.03; H, 5.14; N, 14.28; S, 8.17; H_2O, 4.58. Found: C, 52.42; H, 5.33; N, 14.38; S, 8.30; H_2O, 4.22.

N^4-Acetyl-N^1-[2-(2-methoxyethoxy)-4-quinazolyl]sulfanilamide.—The two samples of IV with acetic anhydride gave the same N^4-acetyl derivative, m.p. 210.5–212° after sintering at 190°.

Anal. Calcd. for $C_{19}H_{20}N_4O_5S$: C, 54.80; H, 4.84; N, 13.45; S, 7.70. Found: C, 54.54; H, 5.08; N, 13.12; S, 7.86.

The n.m.r. spectra of this compound and IV were consistent with the structures.

2-Methoxyquinazolin-4(3H)-one was obtained in approximately 12% yield from III reaction mother liquors. It gave no melting point depression when mixed with an authentic sample prepared according to the literature,[13] m.p. 229–230°.

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90; OCH_3, 17.60. Found: C, 61.54; H, 4.66; N, 16.07; OCH_3, 17.73.

2,4-Di(2-methoxyethoxy)quinazoline. A.—A mixture of 19 g. (0.1 mole) of 2,4-dimethoxyquinazoline and 190 ml. of 2-methoxyethanol containing 2.7 g. (0.117 g.-atom) of dissolved sodium was stirred and heated at 85° for 3 hr. The solution was concentrated under reduced pressure, diluted with 100 ml. of water to separate a red oil, and extracted with ether (three 100-ml. portions). The ether extract was dried and concentrated to yield 3.7 g. (13%) of solid. Recrystallization from ethyl acetate–Skellysolve B (1:8) gave a white product, m.p. 45–46°.

Anal. Calcd. for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.06. Found: C, 60.72; H, 6.59; N, 9.98.

The product was identical with that prepared in 43% yield from 2,4-dichloroquinazoline and sodium 2-methoxyethylate (method B).

2-(2-Methoxyethoxy)quinazolin-4(3H)-one was precipitated from the aqueous mother liquor of the above preparation (method B) by neutralization with acetic acid. A tan solid, weighing 4.6 g. (21%), was obtained. Three recrystallizations from ethyl acetate gave a white product, m.p. 117.5–118.5°.

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 60.20; H, 5.54; N, 12.73.

N^4-(2-Chloro-4-quinazolyl)sulfanilamide.—Lithium amide was prepared by slowly adding 1.6 g. (0.23 g.-atom) of lithium wire to 200 ml. of liquid ammonia containing 0.2 g. of ferric nitrate. Sulfanilamide, 17.2 g. (0.1 mole), was then added portionwise to the lithium amide suspension, followed by 19.9 g. (0.1 mole) of 2,4-dichloroquinazoline. The resulting mixture was allowed to stir for 2.25 hr. and the liquid ammonia was then evaporated with the aid of a steam bath. The solid residue was mixed with 200 ml. of water and a small amount of undissolved solid was filtered off. Acidification of the filtrate with acetic acid precipitated a solid which was collected and dried at room temperature. The solid was then triturated with methanol and dried at 55°; crude yield, 20.8 g. (62%). A sample recrystallized twice from 70% aqueous dimethylformamide gave the purified compound. Attempts to melt the compound resulted in evolution of HCl with no melting up to 360°. However, when a sample was introduced in a bath at about 260°, melting occurred immediately with decomposition.

Anal. Calcd. for $C_{14}H_{11}ClN_4O_2S$: C, 50.22; H, 3.31; Cl, 10.59. Found: C, 50.11; H, 3.49; Cl, 10.40.

N^4-(2-Methoxy-4-quinazolyl)sulfanilamide (V) was originally prepared by heating under reflux for 26 hr. a mixture of 6.8 g. (0.02 mole) of the above crude chloro intermediate and 125 ml. of methanol containing 2 g. (0.087 g.-atom) of dissolved sodium. The solution was cooled and acidified with 17 ml. of acetic acid to give a white precipitate which was collected, washed with methanol, and dried overnight at 50–55°; yield, 4.8 g. (72%).

Anal. Calcd. for $C_{15}H_{14}N_4O_3S$: C, 54.53; H, 4.27; N, 16.96; S, 9.71. Found: C, 54.50; H, 4.51; N, 16.97; S, 9.75.

V was also obtained as follows. A mixture of 19.9 g. (0.1 mole) of 2,4-dichloroquinazoline, 34.4 g. (0.2 mole) of sulfanilamide, and 250 ml. of acetone was stirred to give a pale yellow solution as the temperature rose to 35°. After 5 hr. a solid had formed. The solvent was removed *in vacuo*. A stirred mixture of the residual solid and 450 ml. of methanol containing 23 g. (1.0 g.-atom) of dissolved sodium was heated under reflux for 20 hr., filtered to remove insoluble material, and the filtrate was acidified to precipitate 6.5 g. (20%) of V. Recrystallization from di-

(9) Median lethal and toxic doses were calculated according to the method of J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exptl. Therap.*, **96**, 99 (1949).

(10) The melting points are corrected (Thomas–Hoover capillary apparatus). We gratefully acknowledge the cooperation of Dr. Lewis J. Throop, Messrs. John G. Schmidt, Clarence Kennedy, and Charles M. Combs of our Control Laboratories for the analytical, chromatographic, and instrumental data. The infrared spectra of all the described compounds were consistent with the assigned structures.

(11) In another run using only 2-methoxyethanol as the solvent the temperature was raised to 110°, following the reaction period, and the distillate was collected. Approximately 10% of the solvent volume was distilled. Gas chromatographic analysis of the distillate showed 1.4 equiv. of methanol indicating partial displacement of the 2-methoxy group.

(12) Alcoholysis of the 2-alkoxy group could not lead to by-products; therefore, a relatively higher yield than in the case of III was obtained.

(13) R. H. McKee, *J. prakt. Chem.*, [2] **84**, 821 (1912); *Chem. Abstr.*, **6**, 991 (1912).

methylformamide–water gave an off-white solid, m.p. 228.5–230.5° dec. (resolidifies at *ca.* 232° and remelts at *ca.* 286.5–289°).

Anal. Found: C, 54.62; H, 4.29; N, 16.89.

This product was shown to be identical with the original sample by mixture melting point and infrared spectrum, and by spectrophotometric and paper chromatographic comparisons. Compound V gave a negative Bratton–Marshall test.

N-(2-Methoxy-4-quinazolyl)benzenesulfonamide was prepared from I and sodium benzenesulfonamide in 27% yield by the procedure given for III; m.p. 230–232°.

Anal. Calcd. for $C_{15}H_{13}N_3O_3S$: N, 13.30; S, 10.17. Found: N, 13.11; S, 10.25.

When a similar reaction was run with sodium N-methylbenzenesulfonamide and I, no product was isolated. The only crystalline solid isolated was 2-methoxyquinazolin-4(3H)-one.

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Reactions between Orthoesters and Organic Nitrogen Compounds. VI.[1] Arylhydrazines

C. RUNTI AND C. NISI

Pharmaceutical Chemistry Department, University of Trieste, Trieste, Italy

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The reaction between ethyl orthoformate (EOF) and hydrazines has not yet been thoroughly investigated.[2–4] It is known that hydrazine hydrate itself gives 4-amino-4H-1,2,4-triazole[2] and that the reaction between EOF and phenylhydrazine, in the presence of acetic acid, produces N-formylhydrazine and 1,5-diphenylformazan.[3,4] We have therefore studied systematically the reactivity of the arylhydrazines with EOF and other orthoesters.

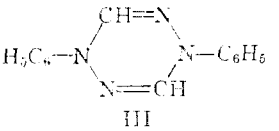
2-Nitro-, 4-nitro-, and 2,4-dinitrophenylhydrazine and their hydrochlorides react with EOF and other orthoesters to produce arylhydrazones of the ethyl esters of the corresponding carboxylic acids (I)[5] (Table I). In some cases, with EOF, the corresponding hydrazidines, *i.e.*, the N,N′-bis(arylamino)formamidines (II), may also be formed as by-products.

The presence of the ethoxy group in I is proved by their reactivity with aniline and with arylhydrazines. In this case compounds II are produced again.

I II

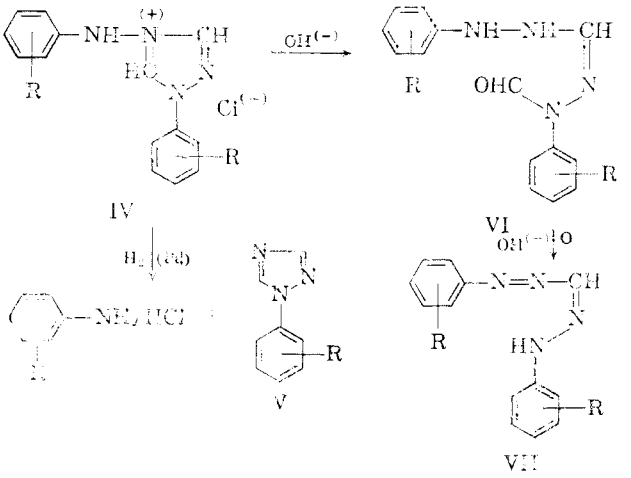
Phenylhydrazine and the tolylhydrazine hydrochlorides present, however, a completely different behavior. Two products were isolated by reaction between excess EOF and phenylhydrazine hydrochloride: the first (m.p. 198–198.5°) corresponds to the already known 1,4-dihydro-1,4-diphenyl-1,2,4,5-tetrazine (III); the second, obtained as the main product, melts at 210° dec. and has the molecular formula $C_{14}H_{13}ClN_4$. It is slightly soluble in water, contains ionic chloride, and yields a nitrate (m.p. 167.5–168°) which is hardly soluble in water. It is impossible to isolate the corresponding base, even under mild reaction conditions (Ag_2O).

For the second product the following considerations supported the structure 4-anilino-1-phenyl-1H-1,2,4-triazolium (4) chloride (IV, R = H). (a) By hydrogenolysis with palladium on carbon in ethanol, aniline hydrochloride and 1-phenyl-1H-1,2,4-triazole (V, R = H) are obtained. (b) By the action of aqueous ammonia on IV (R = H) a hydrolysis product, $C_{14}H_{14}N_4O$, m.p. 163.5–164° dec., is obtained. Elementary analysis and the presence of an absorption band at 1676 cm.$^{-1}$ in the infrared spectrum led us to assign the structure of N-(anilino)-N′-(formylanilino)formamidine (VI, R = H) to the compound. Further evidence was given by oxidizing VI (R = H) with hydrogen peroxide in alkaline medium, whereby 1,5-diphenylformazan (VII, R = H) was obtained.



III

Quite similar results were obtained starting from *p*-tolylhydrazine hydrochloride and EOF. Even in this case the structure was confirmed by a series of similar reactions. Compounds IV so obtained are



listed in Table II.

The structure of compounds IV is rather unexpected, since they are triazolium derivatives in which a quaternary nitrogen is bound to an arylamino group. They present in the infrared spectrum a rather broad absorption band at 1810 cm.$^{-1}$, attributable to the structural element $\geq N^+$-H (immonium band).[6] The compounds possess surface-active properties (concentration 4 mg./100 ml. at 25°), even though much lower than an equiconcentrated solution of dodecyl-*p*-tolyltrimethylammonium methylsulfate.[7]

(1) Paper V of this series: C. Runti, C. Nisi, and L. Sindellari, *Ann. Chim.*, **51**, 719 (1961).

(2) R. Stollé, *J. prakt. Chem.*, [2] **68**, 467 (1903); see also C. F. Allen and A. Bell, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 96.

(3) L. Claisen, *Ann.*, **287**, 360 (1895).

(4) R. v. Walther, *J. prakt. Chem.*, [2] **53**, 475 (1896).

(5) Only two examples of compounds of this type, obtained by E. Schmidt [*Ber.*, **47**, 2545 (1914)] by reaction between phenylhydrazine hydrochloride and an imino ether, are mentioned in literature, to our knowledge. Generally imino ethers and arylhydrazines react to give formazans and/or amidrazones [see A. W. Nineham, *Chem. Rev.*, **55**, 355 (1955)].

(6) B. Witkop, J. B. Patrick, and H. M. Kissman, *Chem. Ber.*, **85**, 949 (1952); see J. T. Potts, *Chem. Rev.*, **61**, 87 (1961).

(7) Desogen®.