MODIFIED TOTAL SYNTHESIS OF ARBORINE, GLYCOSMININE, AND GLOMERINE BY CONDENSATION OF SULFINAMIDE ANHYDRIDE WITH THIOAMIDES

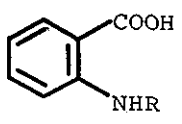
Tetsuji Kametani*, Chu Van Loc, Masataka Ihara, and Keiichiro Fukumoto

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

Treatment of the sulfinamide anhydrides (3 and 4), prepared from anthranilic acids (1 and 2), with thioamides gave the corresponding 4-quinazolone derivatives. This reaction was applied to the synthesis of arborine (5), glycosminine (6), glomerine (7), 2-methyl-4-quinazolone (8), and 4-quinazolone (9).

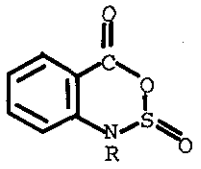
We have recently carried out the total syntheses of quinazolone alkaloids by condensation of the sulfinamide anhydrides (3 and 4), prepared from anthranilic acids (1 and 2) and thionyl chloride, with either imines[1,2] or amides[3,4]. However, the yields obtained in the syntheses of arborine (5), glycosminine (6), and glomerine (7) were not so high (54.5 %, 39.5 %, and 43.4 %, respectively)[3,4] We now report a modified synthesis of the alkaloids (5 ~ 7) and

other quinazolone derivatives (8 and 9) by condensation of the sulfinamide anhydrides (3 and 4) with thioamides. The sulfinamide anhydride (4), prepared from N-methylanthranilic acid (2) and thionyl chloride in dry boiling benzene[2,3], was treated with an equimolar amount of thiophenylacetamide in dry benzene overnight at room temperature to give, in 66 % yield, arborine (5)[5], an alkaloid isolated from the leaves of Glycosmis arborea.



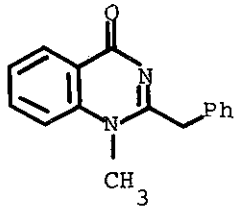
(1) R = H

(2) R = Me

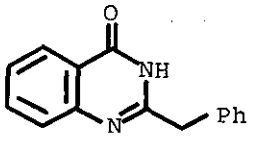


(3) R = H

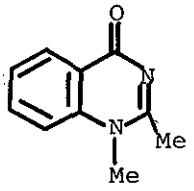
(4) R = Me



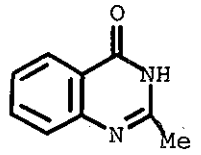
(5)



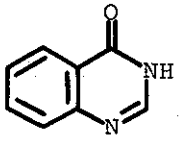
(6)



(7)



(8)



(9)

Glycosminine (6)[6], a minor alkaloid from G. arborea, was also synthesized in 52.3 % yield by treatment of the sulfinamide anhydride (3) with thiophenylacetamide. Similarly, reaction of the sulfinamide anhydride (4) with thioacetamide gave, in 57.8 % yield, glomerine (7)[7] (found in Glomeris marginata). Thioacetamide also reacted with the sulfinamide anhydride (3) to afford, in 68.9 % yield, 2-methyl-4-quinazolone (8)[8], mp 234 - 236° (lit[8]., mp 236°), ν_{max} ($CHCl_3$) 1670 cm^{-1} (C = O); δ ($CDCl_3$) 2.63 (3H, s, CH_3), 7.3 ∿ 8.0 (3H, m, ArH), 8.73 (1H, d, J = 8Hz, C_5-H), m/e 160 (M^+). However, when acetamide was treated with the sulfinamide anhydride (3), the compound (8) was obtained in only 36 % yield. Condensation of the sulfinamide anhydride (3) with thioformamide afforded 4-quinazolone (9)[9] in 41.7 % yield. It may be thus concluded that thiophenylacetamide and thioacetamide, being much more easily dissolved than phenylacetamide and acetamide in nonprotic solvent such as benzene, are more suitable as starting materials in the synthesis of arborine (5), glycosminine (6), and glomerine (7).

Thus we have succeeded in devising a new effective method which can be applied in the synthesis of various quinazolone alkaloids.

EXPERIMENTAL

Melting points were measured with a Yanagimoto micro melting point apparatus (MP S2) and are uncorrected. Nmr spectra were taken with a JNM-PMX-60 spectrometer (with tetramethylsilane as internal reference), ir spectra with a Hitachi 215 spectrophotometer,

and mass spectra with a Hitachi M-52G spectrometer.

Arborine (5). —— A mixture of N-methylanthranilic acid (2) (100 mg) and thionyl chloride (500 mg) in dry benzene (10 ml) was refluxed for 2 hr. The solvent and the excess of the reagent were then evaporated under reduced pressure at 25° to leave the sulfinamide anhydride (4) as an oil, to which was added a solution of thiophenylacetamide (100 mg) in dry benzene (150 ml). The resulting mixture was set aside overnight at room temperature, washed with 10 % aqueous potassium carbonate solution and water successively, and dried over Na_2SO_4. After evaporation of the solvent, the residue was submitted to silica gel chromatography with methylene chloride-n-hexane (1 : 1) as eluent to give arborine (5) (110 mg), mp 154 - 156° (lit[5]., mp 155 - 156°), whose ir and nmr spectral data were identical with those reported[3].

Glycosminine (6). —— To the sulfinamide anhydride (3), prepared from anthranilic acid (1) (100 mg) and thionyl chloride (500 mg), was added a solution of thiophenylacetamide (110 mg) in dry benzene (150 ml). The resulting mixture was set aside overnight at room temperature and then evaporated to yield a residue, whose solution in 5 % ethanolic sodium hydroxide (100 ml) was allowed to stand at room temperature for 3 hr in order to hydrolyse the dimer resulting from the sulfinamide anhydride. After evaporation of ethanol under reduced pressure at 25°, the residue was dissolved in chloroform. The chloroform solution was washed with water, dried over Na_2SO_4 and evaporated to give a residue which was recrystallized from chloroform to afford glycosminine (6) as colorless crystals (90 mg), mp 248 - 249° (lit[3]., mp 247 - 249°),

whose ir and nmr spectral data were identical with those reported[3].

Glomerine (7). —— To the sulfinamide anhydride (4), prepared from N-methylanthranilic acid (150 mg), was added a solution of thioacetamide (74.5 mg) in dry benzene (150 ml). The resulting mixture was set aside overnight at room temperature and then evaporated to leave a residue which was dissolved in chloroform. The resulting solution was washed with 10 % aqueous potassium carbonate solution, water, dried over Na_2SO_4 and evaporated to yield a residue, whose recrystallization from ethyl acetate gave glomerine (7) as yellow needles (100 mg), mp 203 - 205° (lit[7]., mp 204 - 205°), whose ir and nmr spectral data were identical with those reported.[4,5]

2-Methyl-4-quinazolone (8). —— a) From Thioacetamide. To the sulfinamide anhydride (3), prepared from anthranilic acid (1) (100 mg), was added a solution of thioacetamide (54 mg) in dry benzene (140 ml). The resulting mixture was set aside overnight at room temperature and then evaporated to leave a residue, whose solution in 5 % ethanolic sodium hydroxide (100 ml) was allowed to stand at room temperature for 3 hr. After evaporation of the solvent, the residue was dissolved in chloroform. The resulting solution was washed with water, dried over Na_2SO_4, and evaporated to yield a residue which was recrystallized from chloroform to give 2-methyl-4-quinazolone (8) (80 mg) as yellow crystals, mp 235 - 236° (lit[8]., mp 236°), ir ($CHCl_3$) 1670 cm^{-1} (C = O); nmr ($CDCl_3$) δ 2.63 (3H, s, CH_3), 7.3 - 8.0 (3H, m, ArH), 8.73 (1H, d, J = 8Hz, C_5-H), mass spectrum m/e 160 (M^+). b) From Acetamide. To the sulfinamide anhydride (3), prepared from anthranilic acid (1) (100 mg), was added a solution of acetamide (43 mg) in dry

benzene (160 ml). The resulting mixture was set aside overnight at room temperature. Work-up as above, followed by recrystallization from chloroform, afforded yellow crystals (42 mg), identical with 2-methyl-4-quinazolone (8) previously obtained.

4-Quinazolone (9). —— To the sulfinamide anhydride (3), prepared from anthranilic acid (1) (400 mg), was added a solution of thioformamide (178 mg) in dry benzene (300 ml). The resulting mixture was set aside overnight at room temperature. After evaporation of the solvent, the residue was dissolved in 5 % ethanolic sodium hydroxide solution (200 ml). The solution was allowed to stand at room temperature for 3 hr and then evaporated under reduced pressure at 25° to leave a residue which was dissolved in chloroform. The resulting solution was washed with a small amount of a saturated aqueous solution of calcium chloride. The chloroform layer was then dried over Na_2SO_4 and evaporated to yield a residue which was recrystallized from ethanol to give 4-quinazolone (9) as colorless needles (178 mg), mp, 209 - 211° (lit[9]., mp 212°), ir ($CHCl_3$) 1675 cm^{-1} (C = O); mass spectrum m/e 146 (M^+).

ACKNOWLEDGEMENTS

We thank Mrs. R. Kobayashi, Miss M. Tanno, Miss Yuko Kato, Miss Kumi Katsuma, Miss Kaoru Kikuchi, Miss Junko Okazaki for spectral measurements and for aid in the preparation of the manuscript.

REFERENCES

1. T. Kametani, T. Higa, K. Fukumoto, and M. Koizumi, Heterocycles, 1976, 4, 23.
2. T. Kametani, T. Higa, C. V. Loc, M. Ihara, M. Koizumi, and K. Fukumoto, J. Amer. Chem. Soc., 1976, 98, 6186.
3. T. Kametani, C. V. Loc, T. Higa, M. Koizumi, M. Ihara, and K. Fukumoto, J. Amer. Chem. Soc., 1977, 99, 2306.
4. T. Kametani, C. V. Loc, T. Higa, M. Ihara, and K. Fukumoto, J. Chem. Soc. Perkin I, 1977, 2347.
5. D. Chakravarti, R. N. Chakravarti, L. A. Cohen, B. Dasgupta, S. Datta, and H. K. Miller, Tetrahedron, 1961, 16, 224.
6. S. C. Pakrashi, J. Bhattacharyya, L. F. Johnson, and H. Budzikiewicz, Tetrahedron, 1963, 19, 1011.
7. H. Schildknecht, W. F. Wenneis, K. H. Weiss, and U. Maschwitz, Z. Naturforsch., 1966, B21, 121.
8. E. Ziegler, W. Steiger, and Th. Kappe, Monatsh., 1969, 100, 150.
9. St. Niementowski, J. prakt. Chem., 1895, [2] 51, 566

Received, 10th August, 1978