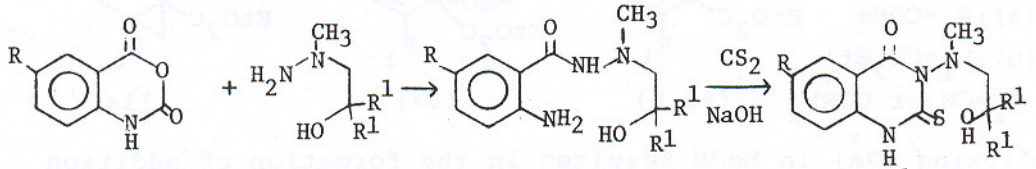
R1545A

PREPARATION OF NOVEL HETEROCYCLIC SYSTEMS FROM ISATOIC ANHYDRIDES

Shyam Sunder and Norton P. Peet

Pharmaceutical R&D-Medicinal Chemistry, The Dow Chemical Company, Bldg. 219, 9550 Zionsville Rd., Indianapolis, IN 46268

Isatoic anhydride (1a) and 5-chloroisatoic anhydride (1b) were treated with 2-(1-methylhydrazino)ethanol (2a) to produce 2-aminobenzoic acid 2-(2-hydroxyethyl)-2-methylhydrazide (3a) and its 5-chloro analog 3b, respectively. Treatment of 3a and 3b with carbon disulfide gave, respectively, 2,3-dihydro-3[(2-hydroxyethyl)methylamino]-2-thioxo-4(1H)-quinazolinone (4a) and its 6-chloro analog 4b. In similar fashion, the dimethyl analogs of 4a and 4b (4c and 4d) were prepared from the isatoic anhydrides and 1-(1-

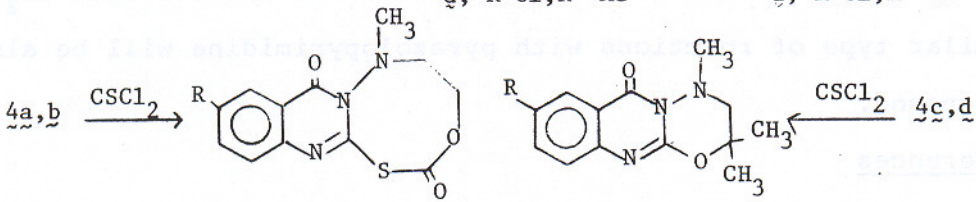


1a, R=H
b, R=Cl

2a, R^1=H
b, R^1=Me

3a, R=R^1=H
b, R=Cl, R^1=H
c, R=H, R^1=Me
d, R=Cl, R^1=Me

4a, R=R^1=H
b, R=Cl, R^1=H
c, R=H, R^1=Me
d, R=Cl, R^1=Me



5a, R=H
b, R=Cl

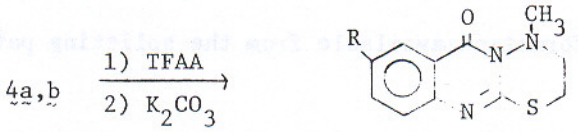
6a, R=H
b, R=Cl

methylhydrazino)-2-methyl-2-propanol (2b).

Compounds 4a and 4b afforded 5,6-dihydro-5-methyl-2-thioxo-4H,8H-[1,3,5;6]oxathiadiazocino[4,5-b]quinazolin-8-one (5a) and its 10-chloro analog 5b, respectively, upon treatment with thiophosgene. Compound 5a could also be prepared directly from 3a and thiophosgene. However, treatment of dimethyl compounds 4c and 4d with thiophosgene afforded 3,4-dihydro-2,2,4-trimethyl-2H,6H-[1,3,4]oxadiazino[2,3-b]quinazolin-6-one (6a) and its 8-chloro analog 6b, respectively.

Another mode of cyclization for compounds 4a and 4b was effected by treatment with trifluoroacetic anhydride (TFAA) followed by potassium carbonate. The resulting compounds were 3,4-dihydro-4-methyl-2H,6H-[1,3,4]-thiadiazino[2,3-b]quinazolin-6-one (7a) and its 8-chloro analog 7b, respectively.

The results of other cyclizations and attempted cyclizations of compounds 4a-d will be presented. The two different modes of thiophosgene-induced cyclization seen for compounds 4a-d will also be discussed.



7a, R=H
b, R=Cl