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SYNTHESIS OF DIHYDROFURANS FROM DIAZOMETHANE AND PHENOLIC MANNICH METHIODIDES
PREPARATION OF 3-DEMETHOXY-4',5'-DIHYDROFURO[2',3':3,4]THIOCOLCHICINE

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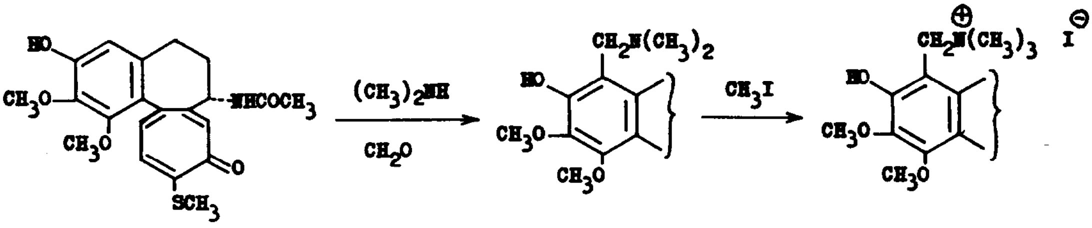
In view of recent publications concerning some reactions of carbenes (2) and ylides (3,4,5,6) which have been applied to the synthesis of five-membered heterocyclics we would like to report an example of what seems to be a new reaction of diazomethane leading to formation of dihydrofurans. We feel that this reaction, which we here describe as applied to the Mannich methiodide of 3-demethylthiocolchicine, might constitute a general method for the synthesis of dihydrofurans based on the reaction of diazomethane with phenolic Mannich bases or their methiodides.

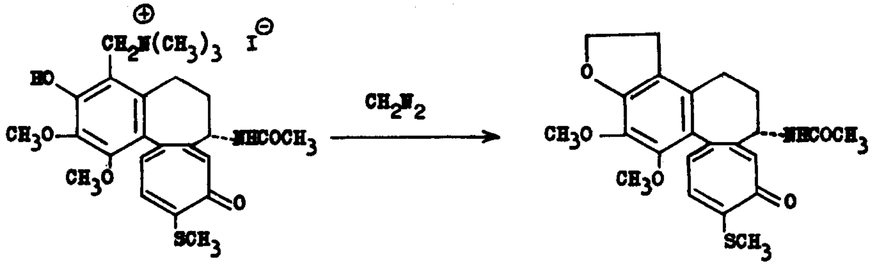
Reaction of 3-demethylthiocolchicine (I) (7) with an excess of aqueous dimethylamine and formaldehyde in boiling ethanol for 7 hours, followed by recrystallisation of the crude product from ethyl acetate, gave a 80% yield of 3-demethyl-4-dimethylaminomethylthiocolchicine (II), m.p. about 190° (8). Anal. Calcd for $C_{24}H_{30}O_5N_2S$: C, 62.75 ; H, 6.58 ; N, 6.12 ; S, 6.98. Found : C, 63.0 ; H, 6.6 ; N, 5.7 ; S, 6.8 . $[\alpha]_D$ – 188° (*c* 0.5 $CHCl_3$) .



I II III

Treatment of Mannich base II with methyl iodide in benzene-methanol solution afforded the corresponding methiodide III in excellent yield. On reaction with a large excess

of diazomethane in methylene chloride-methanol solution for 48 hours at 5°, compound III gave the crude dihydrofuran derivative IV in 67% yield. Recrystallisation from ethyl acetate afforded a 12% yield of pure 3-demethoxy-4′,5′-dihydrofuro[2′,3′:3,4]thiocolchicine (IV), m.p. about 194°. Anal. Calcd for $C_{23}H_{25}O_5NS$: C, 64.65 ; H, 5.89 ; N, 3.27 ; S, 7.50 ; CH_3O, 14.5 . Found : C, 64.3 ; H, 6.2 ; S, 7.8 ; CH_3O, 14.6 . $[\alpha]_D$ - 199° (c 0.5 $CHCl_3$) .

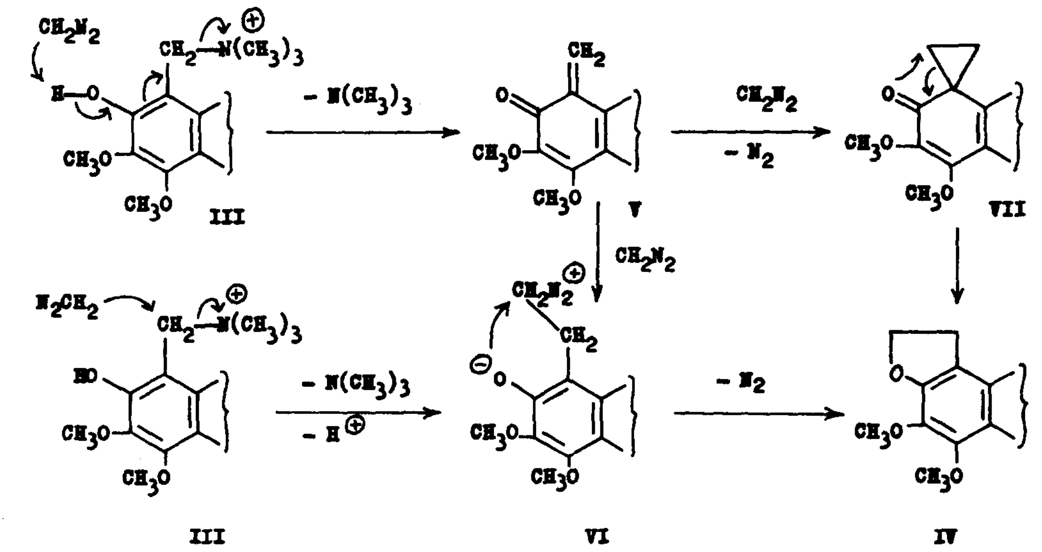


III IV

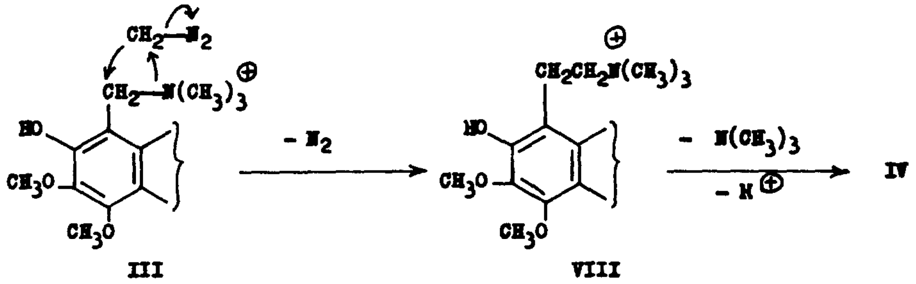
The NMR-spectrum of IV in $CDCl_3$ was in agreement with the adopted structure. In addition to peaks corresponding to the acetylamino (τ 7.90, HN-CO$C\underline{H}_3$; τ 2.02, $\underline{H}$N-COCH$_3$), the thiomethyl (τ 7.54) and the two methoxy groups (τ 6.36 , 5.98), the vicinal aromatic protons of ring C (τ 2.92 , 2.70) and the isolated proton of the same ring (τ 2.49) the spectrum contained an A_2X_2 system with a triplet centered at τ 5.27 (J = 9 cps ,-O-C$\underline{H}_2$-CH$_2$) and another centered at τ 6.84 (-O-CH$_2$-C$\underline{H}_2$-).

To rationalize the formation of the five-membered ring several pathways may be considered. First of all , starting from III , two independent initial steps are possible which will lead to a common intermediate. As diazomethane approaches the positive centers of the methiodide III, that is, the phenolic hydrogen and the trimethylammoniummethylene group, it may either abstract the acidic proton initiating the formation of an o-quinone methide (V) or attack the methylene carbon with departure of trimethylamine. This latter nucleophilic displacement would thus give the same intermediate VI arising from reaction of V with diazomethane. From that common intermediate attack of the near phenolic oxygen on the carbon bearing the diazo group will then achieve cyclization with simultaneous departure of nitrogen.

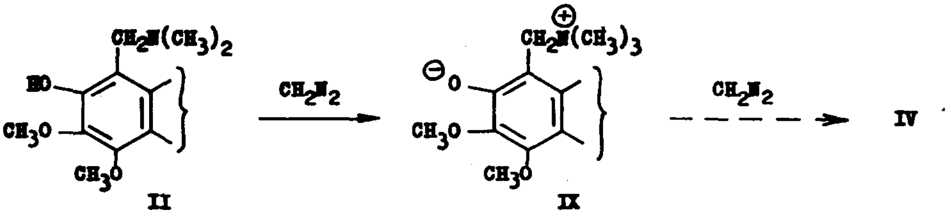
The unsaturated spiroketone VII might also be proposed as an intermediate in the reaction (6). It could lead to dihydrofuran IV by a rearrangement of the same type described for the thermal isomerisation of cyclopropane carboxaldehyde to dihydrofuran (6,9).



Finally one may consider a pathway starting with a C-N insertion of carbene on methiodide III similar to that reported for the reaction of phenyldiazomethane and 9-dimethylaminofluorene (10). The intermediate VIII thus formed could then easily undergo ring closure to IV.



When Mannich base II was treated directly with diazomethane the dihydrofuran IV was also obtained but the reaction proceeded very sluggishly. Probably a slow N-methylation reaction constitutes the first and rate-determining step of the sequence leading to IV



Methylation of tertiary amines by diazomethane is not a frequent reaction but formation of betaine IX may be considered analogous to the preparation of glycine betaine from diazomethane and glycine (11) and to the reaction of diazomethane with 8-hydroxyquinoline which affords 8-hydroxy-1-methylquinolinium betaine besides the normal O-methylation product (12).

Starting with 3-demethylcolchicine similar reactions as described for 3-demethylthiocolchicine were carried out and gave the corresponding dihydrofuran compound but we were unable to obtain the product in pure crystallised form .

The present paper represents the third of a series of publications concerning the synthesis of new 4-substituted derivatives of colchicine and thiocolchicine (13,14).

REFERENCES

1. Present address : Laboratorios Frumtost-Prem, Suiza-9 , Barcelona, Spain .
2. P. Hodge, J. P. Edwards and J. P. Fried, Tetrahedron Letters , 5175 (1966) .
3. G. Gaudiano, A. Umani-Ronchi, P. Bravo and M. Acampora, ibid. , 107 (1967) .
4. H.-G. Lehman, ibid. , 607 (1968) .
5. N. N. Sullivan, D. Ullman and H. Shechter, ibid., 456 (1969) .
6. E. Breuer and D. Melumad, ibid. , 1875 (1969) .
7. L. Velluz and G. Muller, Bull. soc. chim. France , 755 (1954) .
8. Melting points were determined on a Kofler hot bench. As it frequently occurs with colchicine derivatives melting points were not sharp due to heavy solvation by the recrystallization solvent.
9. C. B. Wilson , J. Am. Chem. Soc. , 69 , 3002 (1947) .
10. W. R. Bamford and T. S. Stevens, J. Chem. Soc. , 4675 (1952) .
11. H. Biltz and H. Paetzold, Chem. Ber. , 55 , 1066 (1922) .
12. J. P. Phillips and R. W. Keown, J. Am. Chem. Soc. , 73 , 5483 (1951) .
13. G. Muller and D. Branceni, C. R. , 255 (1962) , 2983 .
14. G. Muller, A. Bladé-Font and R. Bardoneschi, Ann. , 662 , 105 (1963) .