NOVEL CONVENIENT SYNTHESIS OF 1,4-DIAZEPINES; 6-ALKOXY-5,6-DIHYDRO -4H-PYRROLO [1,2-a] THIENO [3,2-f] -1,4-DIAZEPINE-4-ONES

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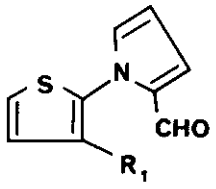
Abstract - Cyclisation of N-(3-cyano-2-thienyl)-2-formyl pyrrole with alcohols in sodium hydroxide solution resulted in the formation of the corresponding 6-alkoxy-5,6-dihydro-4H-pyrrolo [1,2-a] thieno [3,2-f] -1,4-diazepine-4-ones.

In view of antibiotic and antitumor activity of anthramycin [1] and related compounds, considerable interest has been recently directed to the synthesis of tricyclic diazepines. As part of our project for the synthesis of pyrrolothieno diazepines [2,3], we recently reported that N- [2-(3-cyanothienyl)] -2-formyl pyrrole could be used for intramolecular cyclisation to give the 5,6-dihydro -4H-pyrrolo [1,2-a] thieno [3,2-f] -1,4-diazepine by catalytic hydrogenation [4] or 6-acyl-5,6-dihydro-4H-pyrrolo [1,2-a] thieno [3,2-f] -1,4-diazepine-4-ones by reaction with methyl ketones in alkaline hydrogen peroxide solution. [5,6] We wish to report herein an interesting synthesis of 6-alkoxy-5,6-dihydro-4H-pyrrolo [1,2-a] thieno [3,2-f] -1,4-diazepine-4-ones (III) via the interaction between compound (I) and some aliphatic alcohols. This cyclisation of diazepine ring presumably involved base catalysed hydrolysis of the nitrile to an amido function and interaction of the solvent and the amido group with the formyl function.

Table. M.p. and ^{1}H N.M.R. spectroscopic data of diazepines III, IV, VI and VIII

Compd.	M.p.	N.M.R. (DMSO-d_6 δ/p.p.m.)					
N°	(°C)	H2	H3	H7	H8	H9	other protons
IIIa	158	7,33	7,15	6,2	6,2	7,10	5,61(H6);6,2(NH);3,75(CH3).
IIIb	140	7,31	7,14	6,2	6,2	7,11	5,60(H6);6,2(NH);4,16(CH2);1,10(CH3).
IIIc	115	7,31	7,15	6,3	6,3	7,10	5,66(H6);6,3(NH);4,08;1,63(CH2);0,95(CH3).
IIId	138	7,33	7,13	6,3	6,3	7,08	5,63(H6);6,3(NH);4,13;3,5(CH2);1,11(CH3).
IIIe	81	7,35	7,11	6,3	6,3	7,08	5,63(H6);6,3(NH);4,2;3,5;1,0(CH2,CH3).
IIIf	116	7,33	7,16	6,2	6,2	7,10	5,63(H6);6,2(NH);5,93(CH);5,21;4,63(CH2).
IVa	114	7,43	7,30	7,08	6,33	7,70	3,93(CH3).
VI	102	7,31	7,16	7,08	6,28	6,13	4,33(CH2);3,71(CH3);4,3(CH)
VIII	232	7,41	7,28	6,55	7,35	7,75	3,5(NH).

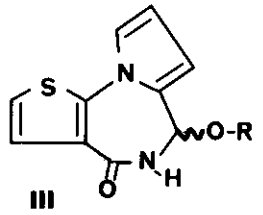
All compounds are crystallised from ether (except IIIa-b and VIII from acetone). Satisfactory analytical and I.R. spectral data were obtained for all products. J H6/NH=5,8 Hz.



I R_1: CN

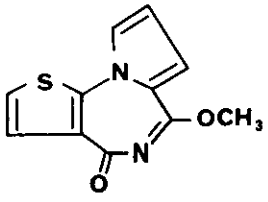
II R_1: $CONH_2$

V R_1: COOH

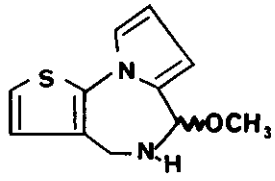


III

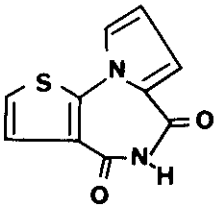
a; R : Me
b; R : Et
c; R : Pr-n
d; R : $(CH_2)_2$ OEt
e; R : $(CH_2)_2$ OBu-n
f; R : Allyl



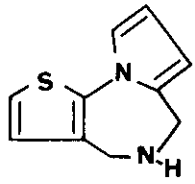
IV



VI



VIII



VII

A typical experiment is as follows. A mixture of aqueous sodium hydroxide solution (20%, 50 ml) methanol (80 ml) and compound (I) (2 g) was heated gradually so that the temperature reached 50° in 2 hr. Water was added to the reaction mixture from which compound (IIIa) was precipitated (1,9 g). This reaction seems to be quite general with all alcohols sufficiently miscible with aqueous sodium hydroxide solution and can be applied to give numerous diazepine derivatives of the type (III). On the other hand when the reaction was carried out in immiscible alcohols under these conditions, or using co-solvents, the starting materials were recovered unreacted. However, in all cases, the reaction afforded the thiophene carboxylic acid (V) when it was conducted at a higher temperature than 60°. The carbamoylthiophene (II) which is a presumable intermediate product of the pyrrolothienodiazepines could not be isolated. The ready oxidation of dihydro compound (IIIa) using potassium permanganate in acetone at room temperature gave the expected diazepine (IV).

Catalytic hydrogenation in ethanol of compound (IIIa) under pressure (80 atm) over Raney nickel in a steel bomb gave the diazepine (VI). The reduction of (IIIa) with lithium aluminium hydride in ether afforded compound (VII) which was identical with the sample prepared in our previous paper [4]. This reaction confirmed the structure of compounds (III). The diazepine-4,6-dione (VIII) was obtained by treatment of compound (IV) with hydrochloric acid in aqueous methanolic solution.

Further studies concerning these reactions, and biological screening are under investigations.

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