SYNTHSIS OF THIENO[3,4-b][1,4]DIAZEPIN-2-ONE

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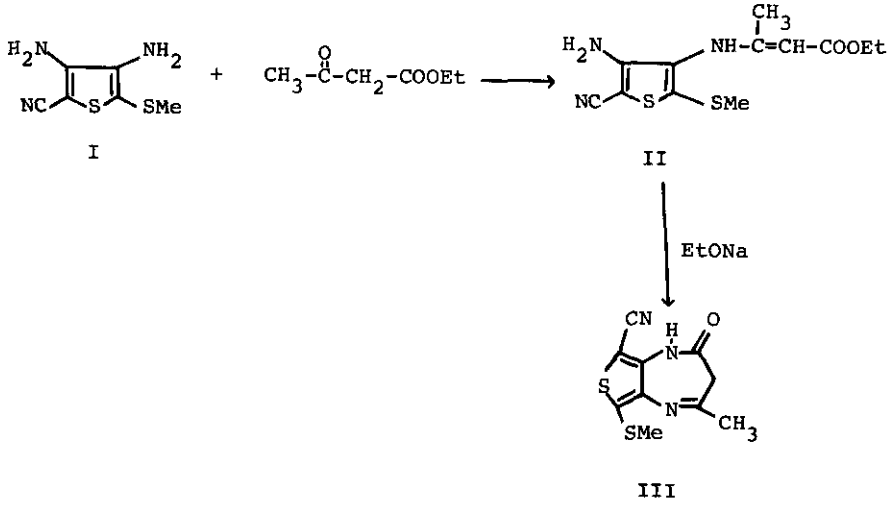
Abstract – Thieno[3,4-b][1,4]diazepin-2-ones were prepared by condensation of 3,4-diaminothiophenes with 1,3-dicarbonyl compounds (ethyl acetoacetate, diethyl acetonedicarboxylate, diketene, ethyl benzoylacetate) in a good yield.

Previously we reported a new synthesis of 3,4-diaminothiophenes, which were reacted with 1,2-dicarbonyl compounds giving thieno[3,4-b]pyrazines in a good yield.[1] In the present communication we wish to report the synthesis of thieno[3,4-b][1,4]-diazepin-2-ones by condensation of 3,4-diaminothiophene (I) with 1,3-dicarbonyl compounds because of pharmacological interest of 1,4-diazepine derivatives. Davoll reported that 1,3-dihydro-2H-1,5-benzodiazepin-2-one was obtained by cyclization of ethyl o-aminoanilinocrotonate with sodium ethoxide in boiling ethanol.[2] Initially, in an above similar Davoll's method, compound II, which was prepared by condensation of 3,4-diamino-5-cyano-2-methylthiothiophene (I) with a excess of ethyl acetoacetate at 100°, was treated with sodium ethoxide in refluxing ethanol for 2 hr. Evaporation and addition of acetic acid to a solution of the residue in water gave 6-cyano-2-methyl-8-methylthio-1,3-dihydro-2H-thieno[3,4-b][1,4]diazepin-2-one (III), colorless needles, mp 234°, in 87% yield. It is regarded that the condezation of 3-amino group of I with the carbonyl function of ethyl acetoacetate occurred since a nucleophilicity of 3-amino group for electron-donating of methylthio group is stronger than that of 4-amino group for electron-withdrawing of cyano group. Actually, the reaction of I with benzaldehyde gave 4-amino-3-(N-benzylideneamino)-5-cyano-2-methylthiothiophene in a good yield.[3]

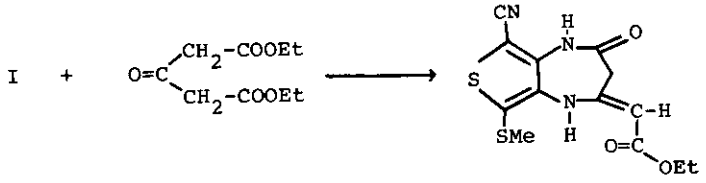
Muller reported that the reaction of o-phenylenediamine with diethyl acetonedicarboxylate gave 4-alkoxycarbonylmethylene-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-ones assigned the enamine structure from IR and NMR spectra data.[4] We also examined the

reaction of I with diethyl acetonedicarboxylate at 100° for 5 hr to give 8-cyano-4-ethoxycarbonylmethylene-6-methylthio-1,3,4,5-tetrahydro-2H-thieno[3,4-b][1,4]diazepin-2-one (IV), pale yellow needles, mp 175 - 177°, in 77% yield. Compound IV was assigned the enamine structure, with an exocyclic double bond, largely by interpretation of IR and NMR spectra, which indicated that they existed in hydrogen bonded form IV.

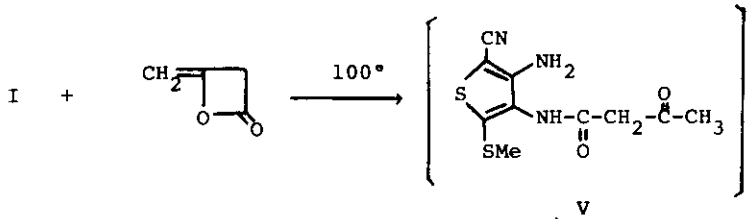
Next, the reaction of I with diketene under heating at 100° afforded a diazepin derivative, 6-cyano-1,3-dihydro-4-methyl-8-methylthio-2H-thieno[3,4-b][1,4]diazepin-2-one (VI) as colorless needles, mp 174°, in 85% yield. Compound VI was obtained via intermediate V and differed from compound II at melting point and IR, UV, and NMR spectral data. On the other hand, the reaction of I with ethyl benzoylacetate gave N-(4-amino-5-cyano-2-methylthio-3-thienyl)-3-phenyl-3-oxopropinamide as colorless needles, mp 168°, in 67% yield, which was heated at 150° for 2 hr to yield diazepine derivative, 6-cyano-1,3-dihydro-8-methylthio-4-phenyl-2H-thieno-[3,4-b][1,4]diazepin-2-one (VIII), colorless needles, mp 261°, in 97% yield. Ried reported that reaction of o-phenylenediamine with diketene or also ethyl benzoylacetate has been used to prepare the benzodiazepinones.[5] In a similar method, 2-phenyl-6,8-dimethyl-3H-pyrimido[4,5-b][1,4]diazepine-4,7,9(5H,6H,8H)-triones were synthesized by Fukushima et al..[6]



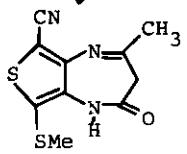
I II III



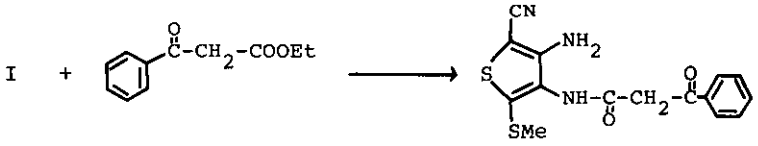
IV



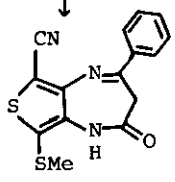
V



VI



VII



VIII

Spectral Data of Thieno[3,4-b][1,4]diazepin-2-ones

III: IRν_{max}^{KBr} cm^{-1}: 3180(NH), 2180(CN), 1690(CO). UVλ_{max}^{EtOH} nm(log ε): 253(4.11), 280(4.17), 338(4.01). NMR(in DMSO-D_6)δ: 2.23(3H, s, SMe), 2.58(3H, s, 4-Me), 3.28(2H, s, $-CH_2-$), 11.00(1H, bs, NH).

IV: IRν_{max}^{KBr} cm^{-1}: 3220(NH), 2180(CN), 1700, 1640(CO). UVλ_{max}^{EtOH} nm(log ε): 230(4.14), 294(4.44), 350(4.15). NMR(in $CDCl_3$)δ: 1.23(3H, t, OCH_2CH_3), 2.43(3H, s, SMe), 3.23(2H, s, $-CH_2-$), 4.11(2H, q, OCH_2CH_3), 4.83(1H, s, =CH-), 8.80(1H, bs, NH), 10.90(1H, bs, NH).

VI: IRν_{max}^{KBr} cm^{-1}: 3150(NH), 2200(CN), 1670(CO). UVλ_{max}^{EtOH} nm(log ε): 230(4.19), 312(4.05). NMR(in $CDCl_3$)δ : 2.40(3H, s, SMe), 2.46(3h, s, 4-Me), 3.25 (2H, s, $-CH_2-$), 8.32(1H, bs, NH).

VIII: IRν_{max}^{KBr} cm^{-1}: 3140(NH), 2200(CN), 1670(CO). UVλ_{max}^{EtOH} nm(log ε): 224(4.30), 275(4.35), 338(4.25). NMR(in DMSO-D_6)δ : 2.60(3H, s, SMe), 3.74(2H, s, $-CH_2-$), 7.46-7.64(3H, m, phenyl proton), 8.06-8.18(2H, m, phenyl proton), 10.47 (1H, bs, NH).

References

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