Attempted Synthesis of the 2,4-Benzodiazepine Isomer of Alprazolam

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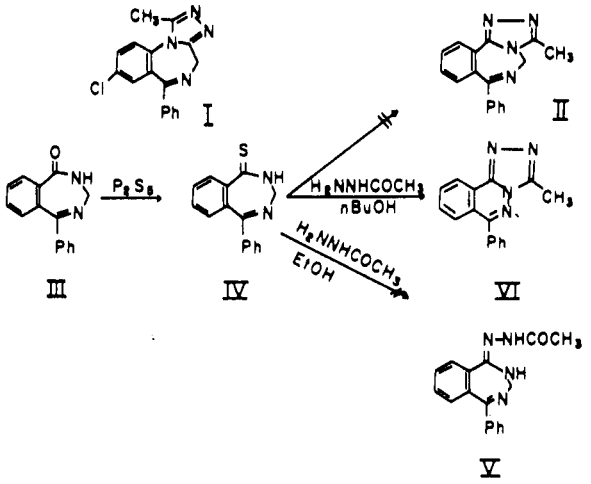
The impressive physiological activity of 1,4-benzodiazepinone derivatives upon the C.N.S. have greatly stimulated synthetic work in this series of heterocyclic compounds (1). It has recently been reported (2) that by fusing an additional heterocyclic ring on the 1-2 bond of their seven-membered moiety very potent drugs, as for instance, alprazolam (I) (3) are being obtained. Since it has been shown (4,5) that some 2,4-benzodiazepinone derivatives (III) do possess C.N.S. activity of an order similar to the one shown by the well known 1,4-isomer, the synthesis of 2,4-benzodiazepinone containing a fused heterocyclic ring at position 1-2 (II) seemed indicated.

The synthetic route which led to the formation of



alprazolam (I) (3) offered itself as a first choice. Reaction of 2,4-benzodiazepin-1-one (III) with phosphorus pentasulfide in refluxing pyridine afforded the thione (IV) in 38% yield. Treatment of the thione IV with acethyrazide in refluxing ethanol did not, however, yield the expected product V which was meant to serve as an intermediate for cyclization to II; the starting material (IV) was recovered instead. When the same reaction was carried out in refluxing 1-butanol in order to obtain the desired compound II, two products were isolated from the reaction mixture by means of chromatography; the major one was identified as VI while the minor one showed only aromatic hydrogens in the H^1-nmr spectra and was therefore disregarded.

The synthetic difficulties which are involved in the preparation of 2,4-benzodiazepinones (5,6) are revealed here as well.

EXPERIMENTAL

Melting points are uncorrected. H^1-nmr were recorded on a Varian A-60 instrument, using TMS as the internal standard. Chemical shifts are given in δ (ppm) and J in Hz. Silica gel HF_{254} was used for chromatography.

5-Phenyl-2,3-dihydro-1*H*-2,4-benzodiazepine-1-thione (IV).

A stirred mixture of III (5) (1 g., 4.2 mmoles), phosphorus pentasulfide (6 g.) in dry pyridine (60 ml.) was refluxed under Argon for 75 minutes, cooled and concentrated *in vacuo*. The residue was treated with chloroform and water and the organic layer was dried and evaporated. The residue was chromatographed on a silica gel column (50 g.) using chloroform as the eluant. The product IV was collected in fractions 2-7 (50 ml. per fraction). Evaporation of the solvent yielded a solid (0.4 g., 38%) m.p. 203° (it was not possible to recrystallize it because of decomposition); H^1-nmr (deuteriochloroform): δ = 9.9-9.45 (broad s, 1H -NH- disappears with deuterium oxide)), 8.52-8.30 (m, 1H aromatic), 7.82-7.27 (m, 8H aromatic), 5.2-4.82 (broad m, 1H $-CH_2-$), 4.5-4.08 (broad m, 1H, $-CH_2-$), when treated with deuterium oxide the $-CH_2-$ changes to a broad AB pattern at 4.65 J = 11.5. The H^1-nmr spectra is similar to III (5); mass: m/e 252 (M^+).

3-Methyl-6-phenyl-*s*-triazolo[3,4-*a*]phthalazine (VI).

A stirred mixture of IV (0.4 g., 1.5 mmoles), acethydrazide (0.6 g.) in 1-butanol (10 ml.) was refluxed under Argon for 20 hours, cooled and concentrated *in vacuo*. The residue was chromatographed on a silica gel column (40 g.) using chloroform as eluant. Fraction 3 (0.05 g.) (50 ml. per fraction), m.p. 205/206° (from benzene) which showed only aromatic hydrogens in H^1-nmr spectra was neglected. The product VI was collected in fractions 4-6, it was recrystallized twice form methylcyclohexane and benzene to yield 0.25 g. (60%) m.p. 203°; H^1-nmr (deuteriochloroform): δ = 8.90-8.42 (m, 1H aromatic), 8.15-7.50 (m, 8H aromatic), 2.82 (s, 3H $-CH_3$); mass m/e 260 (M^+).

Anal. Calcd. for $C_{16}H_{12}N_4$: C, 73.83; H, 4.65; N, 21.53. Found: C, 73.29; H, 4.76; N, 21.53.

REFERENCES AND NOTES

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