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SYNTHESIS OF 2-ARYL-6,7-BENZO-2-AZABICYCLO[4.2.0]OCTAN-3,8-DIONE: A NEW HETEROCYCLIC SYSTEM

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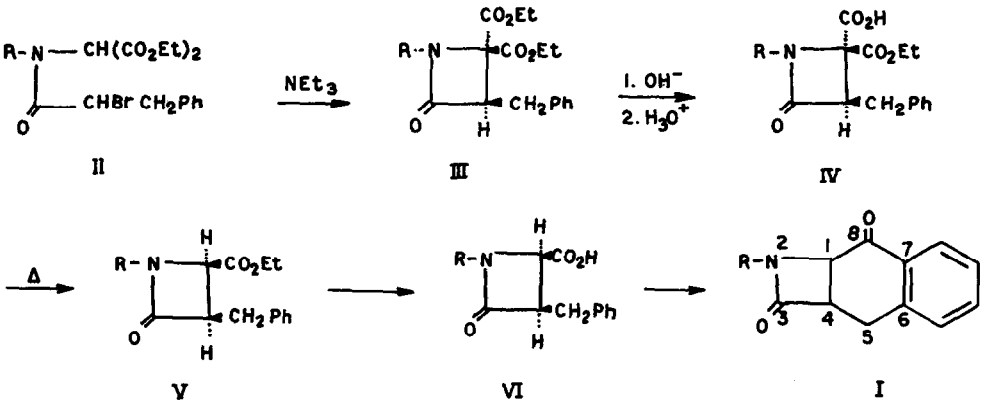
As 2-azetidinone is the key feature of the penicillin and cephalosporin antibiotics, much interest has been directed towards the synthesis of a variety of polycyclic systems containing the fused 2-azetidinone ring[1]. Due to the lability of the β-lactam ring synthetic approaches to such compounds have been generally based upon the construction of this moiety at the final step. Another possible approach to the synthesis of these polycyclic compounds by way of conventional Friedel-Crafts cycloacylation of appropriate 2-azetidinone derivatives has not drawn attention probably because of the susceptibility of the 2-azetidinones to molecular rearrangement[2] in the presence of Friedel-Crafts catalysts.

Based upon the latter approach, the synthesis of a novel heterocyclic system, 2-aryl-6,7-benzo-2-azabicyclo[4.2.0]octan-3,8-dione (I) is reported as a model compound.

The amides (II)[3] were prepared in 65-70% yield from substituted anilinomalonates and 2-bromo-3-phenylpropionic acid in presence of PCl_3. On treatment of (II) with triethylamine, the β-lactam diesters (III) were obtained (100% elimination of HBr)[4]. Partial saponification of (III) with alcoholic KOH afforded β-lactam ester acid (IV). The NMR spectra of (IV) show an AA'B pattern [τ 1.08 (s, 1H), 2.76 (m, 10H), 5.75 (q, 2H), 5.84 (t, 1H), 6.91 (q, 2H), 8.91 (t, 3H)]. The base preferentially attacks the C_3-ester trans to C_4-benzyl group and hence subsequent decarboxylation in presence of pyridine at 125-30° afforded cis β-lactam (V) exclusively[5] in 30% overall yield. The NMR spectra of (V) displayed following pattern [τ 2.75 (m, 10H), 5.31 (d, 1H), J = 5.8 Hz), 5.9 (q, 2H), 6.1 (m, 1H), 6.91 (q, 2H), 8.8 (t, 3H)]. Attempts to hydrolyse the ester group of (V) with alcoholic KOH led to the cleavage of the 2-azetidinone ring. However, on refluxing with anhydrous LiI in pyridine[6] under nitrogen for 48 hrs, (V) could be converted into the β-lactam acid (VI) in 23% yield. A better yield of (VI) (53%) was obtained by refluxing (V) in acetone with 0.1N sodium



II III IV

V VI I

I a, R = Ph; b, R = C_6H_4-CH_3-p

hydroxide[7] for 1/2 hr. (VIa, m.p 162°; VIb, m.p 188°). Compounds (VIa) and (VIb) were converted into the corresponding acid chlorides with thionyl chloride. A highly diluted solution of acid chloride in carbon disulphide was treated with anhydrous aluminium chloride at 0°C. The crude products obtained were chromatographed to afford (I) in 53-55% yield. [Ia, m.p 140-1°; ν_{max} (nujol), 1754, 1690 cm^{-1}; τ 2.38 (d, 1H), 2.75 (m, 8H); 5.34 (d, 1H, J = 2.5 Hz), 5.94 (m, 1H), 6.74 (m, 2H); m/e 263 (M^+), 235 (M-28), 144 (M-119); Ib, m.p 148°; ν_{max} (Nujol), 1758, 1690 cm^{-1}; τ 2.36 (d, 1H), 2.9 (m, 7H), 5.43 (d, 1H, J = 2.5 Hz), 6.03 (m, 1H), 6.75 (m, 2H); m/e 277 (M^+), 249 (M-28), 144 (M-133)].

Attempts to cyclise the acid (IV) with polyphosphoric acid or the derived acid chloride with aluminium chloride did not succeed. Apparently the cis stereochemistry between C_4-carboxy and C_3-benzyl groups is prerequisite for the cycloacylation reaction to occur. The method described here is thus applicable to the synthesis of polycyclic azetidinones containing an aromatic ring.

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