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The synthesis of 2-hydroxycarbamazepine, a metabolite of carbamazepine in man, from 2-hydroxyiminostilbene or 2-hydroxyiminodibenzyl is described.

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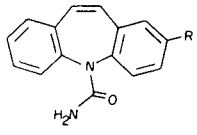
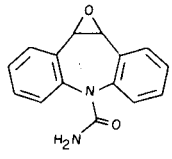
Carbamazepine (I), 5*H*-dibenz[*b*,*f*]azepine-5-carboxamide, is widely used for the treatment of convulsive disorders and the pain of trigeminal neuralgia (1). Since its pharmacological effects have aroused the interests of medicinal chemists, several derivatives have been synthesized. One of these compounds is compound II, 1a,10b-dihydro-6*H*-dibenz[*b*,*f*]oxireno[*d*]azepine-6-carboxamide. Compound II was also reported as a metabolite of carbamazepine and it showed more potent anticonvulsant actions in maximal electroshock and pentylenetetrazol tests when compared with carbamazepine (2). Recently, another metabolite of carbamazepine, 2-hydroxycarbamazepine (2-hydroxy-5*H*-dibenz[*b*,*f*]azepine-5-carboxamide, III) was found in patients' urine (3). Since the pharmacological properties of the metabolites are of interest in themselves, we wish to report a synthetic route to III from commercially available iminodibenzyl or iminostilbene.



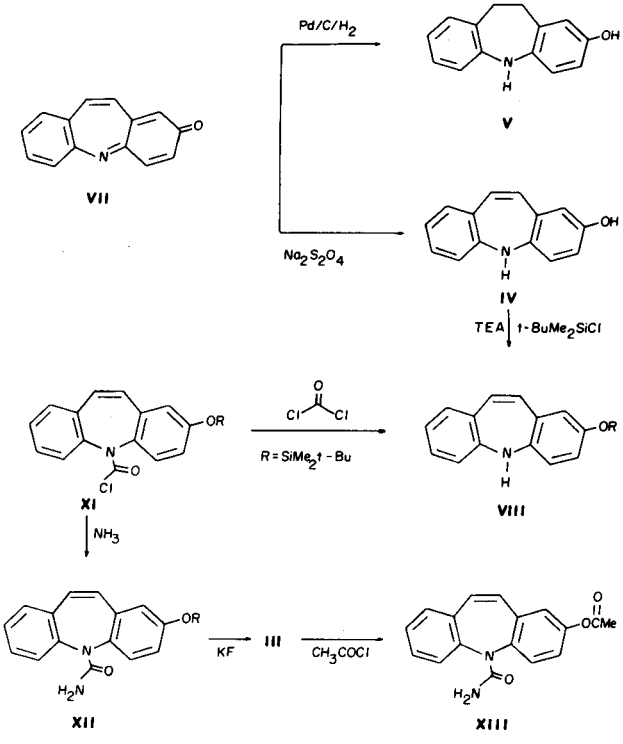
I, R = H
III, R = OH
XIV, R = CH_3



II

2-Hydroxy-5-dibenz[*b*,*f*]azepine (IV) and 2-hydroxy-10,11-dihydro-5-dibenz[*b*,*f*]azepine (V) (4) were employed as the starting materials in the synthetic strategy (Scheme 1 and 2). The reduction of 2-oxo-10,11-dihydro-2*H*-dibenz-[*b*,*f*]azepine (VI) by hydrogenation (5), with sodium borohydride (4) or sodium hydrosulfite (4) results in the formation of 2-hydroxyiminodibenzyl (V). However, the generation of 2-hydroxyiminostilbene (IV) has not yet been reported. Proctor *et al.* (6) has shown that 2-oxo-2*H*-dibenzo[*b*,*f*]azepine (VII), an analog of VI, undergoes hydrogenation to give V but not IV. The reduction reaction involved not only the iminoketone but the double bond as well. We find that compound IV can be obtained by treatment of VII with sodium hydrosulfite since sodium hydrosulfite reduces the iminoketone without affecting the double bond. The reduction product, 2-hydroxyiminostilbene (IV), is a stable yellow crystalline substance and converts back to the iminoketone, VII, in the presence of strong base and oxygen (air).

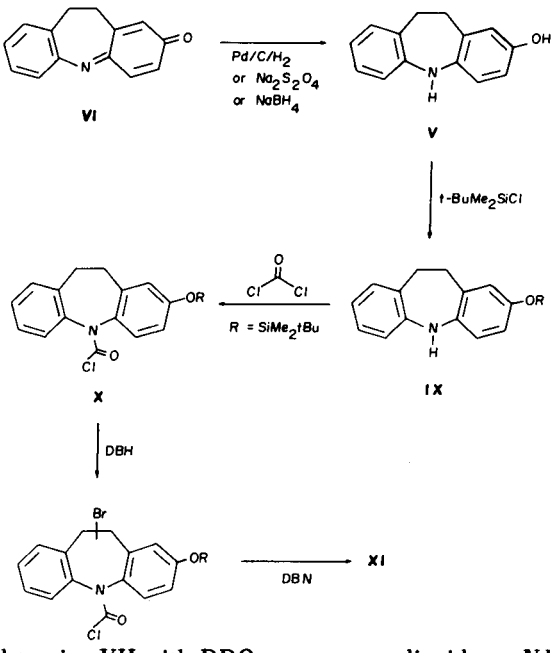
Scheme I



In order to introduce the carbamoyl functional group at the 5-position (nitrogen) of IV or V, it is necessary to block the hydroxyl group. Since the acetylation of IX with acetyl chloride gave the *N,O*-diacetyl derivative (5), *t*-butyldimethylchlorosilane was chosen to protect the hydroxyl functional group. The silylation reactions of IV or V were carried out in triethylamine/chloroform solution.

After the reaction was complete, chloroform and excess *t*-butyldimethylchlorosilane were removed *in vacuo*. The intermediates, chlorocarbonyl dibenzazepine derivative (X, XI) were prepared by passing phosgene through tetrachloromethane or toluene solutions of VIII and IX, respectively. The conversion of X to XI requires the introduction of a double bond at 10,11 position. When *O*-alkylated chlorocarbonyliminodibenzyls (analogs of X) were treated with 2,3-dichloro-5,6-dicyanoquinone (DDQ) or sulfur, formation of XII (R = alkyl) was not observed (7). It has been reported that quinoneimine, VI, could not be dehydrogen-

Scheme II



ated to give VII with DDQ, manganese dioxide or *N*-bromosuccinimide (NBS) (6b). Bromination of compound XI with 1,3-dibromo-5,5-dimethylhydantoin (DBH) in refluxing tetrachloromethane produced a mixture of two monobromo isomers. Without separation, these two isomers react with 1,5-diazabicyclo[3.4.0]non-5-ene (DBN) to yield compound XI. The amidation of XI is carried out by passing ammonia through refluxing ethanol. Removal of the *t*-butyldimethylsilyl group from XII by reacting with potassium fluoride produces the title compound III. Treatment of III with acetyl chloride generates 2-acetyloxycarbamazepine (XIII).

2-Methylcarbamazepine (XIV), another carbamazepine derivative, has been suggested as an internal standard for the analytical chromatographic method in carbamazepine assays (8). It is possible that XII and III derivatives both may exhibit a behavior similar to 2-methylcarbamazepine in the determination of carbamazepine concentration in plasma.

EXPERIMENTAL

General.

2-Hydroxyiminodibenzyl (4-6) and 2-oxo-2*H*-dibenzo[*b*,*f*]azepine (6) were prepared according to the literature methods.

Proton nmr spectra were recorded on a Varian T-60A spectrophotometer [internal TMS as a reference, δ (ppm)]. Mass spectral data were collected at 70 eV on a Hewlett-Packard 5985A GC/MS system. Melting points were taken in open capillary tubes and are not corrected. The ir spectra were recorded as potassium chloride disks on a Perkin-Elmer Model 237 spectrometer. Elemental analyses were determined by Analytical Services, Chemistry Department, Miles Laboratories, Inc., Elkhart, IN.

2-Hydroxy-5-dibenz[*b*,*f*]azepine (IV).

A solution of 3.0 g (0.015 mole) of 2-oxo-2*H*-dibenz[*b*,*f*]azepine in chloroform was extracted with freshly prepared sodium hydrosulfite solution (excess) until the organic layer changed from red to yellow. The organic phase was separated, dried over sodium sulfate and the solvent removed *in vacuo*. The residual solid was recrystallized from chloroform to give 2.8 g (95%) of IV as a yellow solid, mp 225-226°; pmr (deuteriochloroform/DMSO-d_6): 8.27 (s, 1H, -O*H*), 7.5-6.2 (m, 9mH, aromatic and olefin), 5.41 (s, broad, 1H, -N-H); ms: m/e 209 (M^+).

Anal. Calcd. for $C_{14}H_{11}NO$: C: 80.38; H, 5.36; N, 6.76. Found: C, 80.52; H, 5.35; N, 6.39.

2-Hydroxy-5*H*-dibenz[*b*,*f*]azepine-5-carboxamide (2-Hydroxycarbamazepine), III, from IV.

A mixture of 1.4 g (0.0067 mole) of 2-hydroxy-5-dibenz[*b*,*f*]azepine (IV), 2.5 g (0.019 mole) *t*-butyldimethylchlorosilane and 1 ml triethylamine in 80 ml chloroform were stirred at room temperature for 36 hours. The solvent and excess silane were evaporated under reduced pressure. After 50 ml of tetrachloromethane and 1 ml of triethylamine were added to the residue, phosgene was bubbled through the solution for 2 hours. The precipitated solid was removed by filtration and the filtrate was concentrated. The residue was dissolved in ethanol and the amidation was carried out by passing ammonia through the refluxing solution for 2 hours. The solvent was replaced by acetonitrile with a few drops of water and 1 g of potassium fluoride was added. The mixture was refluxed for 2.5 hours and the solvent removed *in vacuo*. The crude insoluble product was collected by filtration after *ca.* 100 ml water was added to the residual solid. It was recrystallized from ethanol and dried in an Abderhalden drier (toluene) for 24 hours to give 0.78 g (65%) desired product, mp 239-242°; pmr (DMSO-d_6): 8.25 (s, 1H, -O*H*), 7.5-6.6 (m, 9H, aromatic and olefin), 5.45 (s, 2H, -CON*H*); ir: max 1655 (C=O) cm^{-1}; ms: m/e 252 (M^+); 209 (M^+) -HNCO.

Anal. Calcd. for $C_{15}H_{12}N_2O_2 \cdot H_2O$: C, 66.67; H, 5.19; N, 10.37. Found: C, 66.32; H, 5.36; N, 10.14.

2-Acetoxy-5*H*-dibenz[*b*,*f*]azepine-5-carboxamide (XIII) froM III.

To a solution of 20 ml of ethyl acetate, 2 ml of triethylamine and 0.15 g (0.59 mmole) of 2-hydroxycarbamazepine (III), one ml of acetyl chloride was slowly added. The mixture was stirred at room temperature for 15 hours. After filtration, the filtrate was concentrated to give a solid residue which was recrystallized from ethyl acetate to yield the desired product 0.16 g (90%), mp 179-180°; pmr (perdeuteriomethanol): 7.7-6.9 (m, 9H, aromatic and olefin), 2.3 (s, 3H, $-CH_3$); ir: max 1750 ($-COCH_3$), 1670 ($-CONH_2$) cm^{-1}; ms: m/e 294 (M^+).

Anal. Calcd. for $C_{17}H_{14}N_2O_3$: C, 69.39; H, 4.76; N, 9.52. Found: C, 69.09; H, 4.92; N, 9.12.

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