Synthesis of A New Benzo[a]phenothiazine Amino Alcohol as a proposed Antimalarial

Prakash C. Taunk

Wyeth Laboratories, Inc., Chemical Development Division,
West Chester, PA 19382

Received February 4, 1985

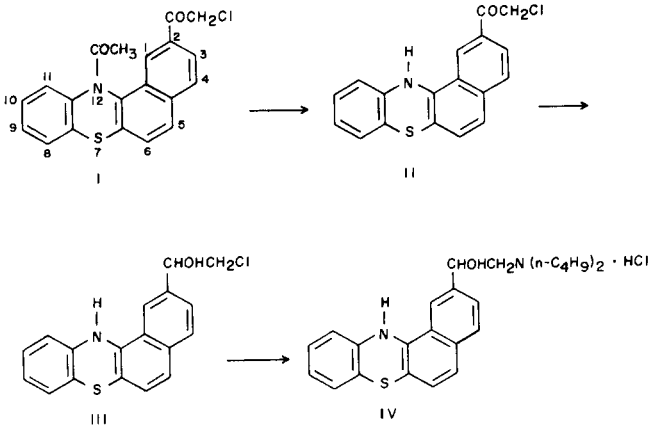
The synthesis of α-(di-*n*-butylaminomethyl)-2-benzo[*a*]phenothiazinyl methanol hydrochloride is described. The ir and nmr spectra are also included.

J. Heterocyclic Chem., **22**, 1219 (1985).

Since the discovery of methylene blue as an antimalarial by Ehrlich in 1891 [1] not much work has been done on phenothiazine antimalarials [2-5,6]. It is well known that introduction of amino alcohol side chains on various ring systems at proper positions enhances antimalarial activity [3,4]. Recently Nodiff *et al.* [6] have reported antimalarial phenothiazine amino alcohols. Among these was one which was almost twice as active as quinine.

Some of the compounds, which depend on intercalation with DNA for their activity benefit from increased planer area [7,8]. The mode of action of the phenothiazine amino alcohol antimalarials is uncertain. However, it may be possible to enhance the activity of phenothiazine amino alcohols by increasing their planer area *via* conversion to the corresponding benzo[*a*]phenothiazine amino alcohol in which a flat surface has been added to the phenothiazine. Keeping the planer concept in mind in order to evaluate the antimalarial activity, the target compound IV was synthesised as shown in Scheme 1. Synthesis of some benzo[*a*]phenothiazines have been reported in the literature [9-13].

Scheme I



I II III IV

The structures of these compounds were confirmed by their analytical, ir and nmr spectral data. Purity of these compounds was tested by tlc which showed single spots.

The α-(di-*n*-butylaminomethyl)-2-benzo[*a*]phenothiazinylmethanol hydrochloride IV was ineffective and was nontoxic over the entire dosage range [14].

EXPERIMENTAL

Melting points were determined in capillary tubes in an electrically heated Thiele-Dennis apparatus and are uncorrected. Elemental analyses were performed by Micro-Analysis, Inc, Wilmington, Delaware. Infrared spectra were taken as nujol mulls on a Perkin-Elmer Model 137B, infracord spectrophotometer. Thin layer chromatography was carried out on Eastman chromatogram sheets, type 6060, silica gel with fluorescent indicator. The ^{1}H-nmr spectra were determined on a Varian XL-100 MHz spectrometer in DMSO-d_6. Chemical shifts are given in δ units and TMS was used as an internal standard. The letters, b, s, d and m are used to indicate broad, singlet, doublet and multiplet, respectively.

2-Chloroacetyl-12*H*-benzo[*a*]phenothiazine (II).

A mixture of 8.0 g (0.021 mole) of 2-chloroacetyl-12*H*-acetylbenzo[*a*]-phenothiazine (I) [13], 60 ml of glacial acetic acid and 40 ml of 50% aqueous hydrochloric acid was heated under reflux under a nitrogen atmosphere for 30 minutes to give a dark brown mixture. The mixture was allowed to cool to room temperature and filtered to give 6.5 g of crude II, mp 175-180° dec. This material was dissolved in boiling acetone and filtered to remove insoluble by-products. The filtrate was treated twice with carbon and concentrated under reduced pressure. The resulting slurry was diluted with anhydrous ether to give 4.5 g (66%) of II as an orange-red solid, mp 179-180° dec, tlc, single spot using acetone as the spotting solvent and anhydrous ether as the developing solvent; ir (nujol): cm^{-1} 3425 (-NH), 1725 (-C=O), 1150 (C-Cl); ^{1}H-nmr (DMSO-d_6): 5.35 (s, CH_2-C=O), 6.9-7.2 (m, 5, Ar-H_6 to H_{11}), 7.59 (d, 1, Ar-H_5), 7.97 (d, 1, Ar-H_4), 8.45 (d, 1, Ar-H_3), 8.58 (s, 1, Ar-H_1), and 8.7 (s, 1, -NH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{18}H_{12}ClNOS$: C, 66.35; H, 3.68; N, 4.30. Found: C, 66.61; H, 3.66; N, 4.21.

2-(1-Hydroxy-2-chloroethyl)-12*H*-benzo[*a*]phenothiazine (III).

Reduction of 1.63 g (0.005 mole) of 2-chloroacetyl-12*H*-benzo[*a*]phenothiazine (II) with aluminum isopropoxide as described by Hromatka *et al.* [16] gave 1.7 g of crude III, mp 169-170° dec. An additional crystallization from 2-propanol (100 ml) (carbon) gave the analytical sample (1.5 g, 92%) of orange-yellow color, mp 174-175° dec, tlc, single spot, using acetone as the spotting solvent and 2-propanol as the developing solvent; ir (nujol): cm^{-1} 3425 (-NH), 1075 (C-OH), 1150 (C-Cl); ^{1}H-nmr (DMSO-d_6): 3.45 (b, s, OH, deuterium oxide exchangeable), 3.84 (d, 2, CH_2Cl), 4.95 (t, 1, CH), 6.8-7.2 (m, 5, ArH_6, to H_{11}) 7.45 (d, 1, Ar-H_5), 7.6 (d, 1, Ar-H_4), 7.85 (s, 1, Ar-H_1), 8.4 (d, 1, Ar-H_3) and 8.65 (s, 1, -NH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{18}H_{14}ClNOS$: C, 65.95; H, 4.27; N, 4.27. Found: C, 66.24; H, 4.23; N, 4.19.

α-(Di-*n*-butylaminomethyl)-2-benzo[*a*]phenothiazinylmethanol Hydrochloride (IV).

A mixture of 2.4 g (0.0075 mole) of III, 4.0 g (0.0375 mole) of *n*-dibutylamine and 25 ml of *p*-dioxane was heated under reflux under a nitrogen atmosphere for 24 hours, allowed to cool and concentrated *in vacuo* to give brown viscous oil. It was extracted with (4 × 100 ml) of ether and the yellow colored extract was washed with (2 × 100 ml) of water, dried (magnesium sulfate), cooled and adjusted to *p*H 4 with ethereal hydrogen chloride. Crystalization of the resulting solid from chloroform-ethyl acetate gave 600 mg (18%) of IV as a bright yellow solid, mp 216-218° dec, tlc, single spot using acetone as the spotting as well as the developing solvent; ir (nujol): cm^{-1} 3350 (-NH), 2650 (-N-(n-C_4H_9)$_2$·HCl); ^{1}H-nmr (DMSO-d_6): 0.92 (m, 6, CH_3), 1.2-1.8 (m, 8, CH_2CH_2), 2.85 (b, s, 1, OH, deuterium oxide exchangeable), 3.3 (b, 6, -CH_2N (CH_2)$_2$), 5.38 (t, 1, CH), 6.8-7.15 (m, 5, Ar-H_6 to H_{11}), 7.3 (d, 1, Ar-H_5), 7.55 (d, 1, Ar-H_4), 7.9 (s, 1, Ar-H_1), 8.55 (d, 1, Ar-H_3), 8.85 (s, 1, -NH, deuterium oxide exchangeable) and 10.76 (b, 1, salt NH^+, deuterium oxide exchangeable).

Anal. Calcd. for $C_{26}H_{33}ClN_2OS$: C, 68.34; H, 7.22; Cl, 7.77; N, 6.13. Found: C, 68.21; H, 7.17; Cl, 7.62; N, 6.15.

Acknowledgement.

The author is grateful to Dr. E. A. Steck, Walter Reed Army Institute of Research for antimalarial screening data and also to Dr. E. A. Nodiff, Franklin Research Center, Philadelphia, PA for providing laboratory facilities.

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