# Angular Heterocycles: Studies in the Synthesis of Some Substituted 6-Anilino-5-alkoxy-12 H-benzo[a]phenothiazines

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6-Anilino-5-methoxy-12H-benzo[a]phenothiazines, 6-Anilino-5-isopropoxy-12H-benzo[a]-phenothiazines

6-Anilino-12H-benzo[a]phenothiazin-5-ol reacts with dimethyl sulphate or 2-bromopropane to give 6-anilino-5-alkoxy (methoxy/isopropoxy)-12H-benzo[a]phenothiazine. Synthesis of various 9,11-disubstituted analogues have been described. A common reaction path is suggested.

As a continuation of our studies in heterocyclic compounds [1-4] we investigated the reaction of halogeno-*p*-benzoquinones with substituted aromatic amines. Synthesis of benzophenothiazines [5, 6] is limited only to a few nuclear substituted derivatives, while these compounds are used as potential carcinogenic agents [7, 8]. This prompted our interest in this field.

It has been found that 2-anilino-3-chloro-1,4naphthoquinone (1) reacts with zinc mercaptide of substituted 2-amino thiophenol in presence of pyridine to give substituted 6-anilino-5H-benzo[a]phenothiazin-5-one (2). These substituted 6-anilino-5H-benzo[a]phenothiazin-5-ones (2) were reduced to substituted 6-anilino-12H-benzo[a]phenothiazin-5-ols (3) with sodium hydrosulphite in acetone. Substituted 6-anilino-12H-benzo[a]phenothiazin-5ols (3) were further converted into their 5-methoxy derivatives (4) by the reaction of dimethylsulphate in acetone. Analogues-5-isoproxy derivatives (5) have been obtained by the reaction of 2-bromopropane with 3 in acetone.

Attempts have also been made to convert 4 and 5 into their corresponding 7-oxides with  $H_2O_2$  (30%) in acetone-ethanol medium. Oxydative dealkylation occured in each case with the formation of substituted 6-anilino-5H-benzo[a]phenothiazin-5-ones (2) instead of the desired product 6 and 7. Similar conversion of 3-methoxy-phenothiazine to phenothiazin-3-one was reported previously [9].

## Experimental

IR spectra were recorded for KBr wafer with a Beckman IR-4-spectrophotometer. 2-Amino-5chloro-, 2-amino-5-bromo-, 2-amino-5-fluoro-, 2amino-5-methyl-, 2-amino-5-methoxy-, 2-amino-5ethoxy-, 2-amino-3-bromo-5-methyl-, 2-amino- and 2-amino-3,5-dimethyl benzenethiols were prepared by the methods reported earlier [1, 10, 11]. 2-Anilino-3-chloro-1,4-napthoquinone was prepared by the procedure described by van Allan *et al.* [12]. The purity of compounds was tested by t.l.c. on



Scheme 1.

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Silicagel G (Merk) in various non-aqueous solvent systems. Organic solutions were dried with anhydrous sodium sulphate and decolorized with Darco-G60. All melting points are uncorrected.

## Substituted 6-anilino-5H-benzo[a]phenothiazin-5-ones (2)

A mixture of zinc mercaptide of substituted 2-aminothiophenol (0.025 mole) and 2-anilino-3chloro-1,4-napthoquinone (0.05 mole) in dry pyridine (250 ml) was stirred and refluxed for 3 h. An equal volume of methanol was added and the solution was chilled, filtered, washed with ethanol and 4% HCl. Crystallization from benzene gave 2.

#### Substituted 6-anilino-12H-benzo[a]phenothiazin-5-ols (3)

A mixture of substituted 6-anilino-5H-benzo[a]phenothiazin-5-one (0.005 mole), sodiumhydrosulphite (2 g), water (5 ml) and acetone (50 ml) was refluxed for 80 min. The mixture which turned to colourless was poured in ice cold water (1 l) containing sodium hydrosulphite (5 g). The ppt was extracted with ether dried with Na<sub>2</sub>SO<sub>4</sub> and crystallized from benzene-pet-ether (60-80 °C) to obtain 3.

#### Substituted 6-anilino-5-methoxy-12H-benzo[a]phenothiazines (4)

A mixture of 3 (0.01 mole), sodium hydrosulphite (0.5 g) and 15 ml of 10% ethanolic Potassium

hydroxide solution was refluxed for 15 min. Then dimethyl sulphate (0.014 mole) was added to the above mixture and again refluxed for 6 h. Resulting suspension was poured into cold water 1 l. The ppt was extracted with ether, washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>) and crystallized from benzene-pet-ether (60-80 °C) to give 4 in quantitative yields (Table I).

## Substituted 6-anilino-5-isopropoxy-12H-benzo[a]phenothiazines (5)

Prepared similarly as 4 by using 3 (0.01 mole), sodium hydrosulphite (0.5 g), 15 ml of 10% ethanolic potassium hydroxide and 2-bromopropane (0.014 mole) to give 5 as nearly golden yellow crystals from benzeneligroin in quantitative yields (Table I).

### Oxydative dealkylation of substituted 6-anilino-5-alkoxy-12H-benzo[a]phenothiazines

A mixture of 4 or 5 (0.004 mole), ethanol (15 ml), acetone (30 ml) and 30% H<sub>2</sub>O<sub>2</sub> (2.6 ml) was heated under reflux for 3 h, concentrated, cooled and poured into cold water to give in each instance a quantitative yield of substituted 6-anilino-5H-benzo[a]phenothiazin-5-one (2) instead of the desired products 6 and 7. These phenothiazones were identical in each respect with the authentic samples.

$\mathbf{R_1}$	$\mathbf{R_2}$	m.p. [°C] 5-methoxy	Mol. formula 5-methoxy	m.p. [°C] 5-isopropoxy	Mol. formula 5-isopropoxy
н	н	240	$C_{23}H_{18}N_2OS$	235	$C_{25}H_{22}N_2OS$
H	Cl	210	$C_{23}H_{17}ClN_2OS$	201	$C_{25}H_{21}ClN_2OS$
H	$\mathbf{Br}$	223	$C_{23}H_{17}BrN_2OS$	214	$C_{25}H_{21}BrN_2OS$
H	F	175	$C_{23}H_{17}FN_2OS$	171	$C_{25}H_{21}FN_2OS$
$\mathbf{H}$	$CH_3$	203	$C_{24}H_{20}N_2OS$	194	$C_{26}H_{24}N_2OS$
$\mathbf{H}$	OCH <sub>3</sub>	217	$C_{24}H_{20}N_2O_2S$	211	$C_{26}H_{24}N_2O_2S$
H	$OC_2H_5$	207	$C_{25}H_{22}N_2O_2S$	197	$C_{27}H_{26}N_2O_2S$
Br	CH <sub>3</sub>	216	C24H19BrN2OS	209	C <sub>26</sub> H <sub>23</sub> BrN <sub>2</sub> OS
$CH_3$	$CH_3$	219	$C_{25}H_{22}N_2O\bar{S}$	213	$C_{27}H_{26}N_2OS$

Satisfactory C, H, N and S analysis have been performed in all the cases.

- [1] R. L. Mital and S. K. Jain, J. Chem. Soc. C 1969, 2148.
- [2] R. L. Mital and S. K. Jain, J. Chem. Soc. C 1971, 1875.
- [3] P. C. Taunk, R. R. Gupta, and R. L. Mital, Ann. Soc. Sci. Bruxelles 85, 291 (1971).
- [4] P. Truitt, M. F. Wood, and L. R. Hall, J. Org. Chem. 25, 1460 (1960).
- [5] E. Knoevenagel, J. Prakt. Chem. 89, 14 (1913).
  [6] F. Kehrmann and H. Dardel, Ber. 55B, 2346 (1922).
- [7] D. A. Shirley, J. C. Gilmer, and W. D. Waters, J. Chem. Soc. 1964, 5260.

- [8] D. A. Shirley, K. Sen, and J. C. Gilmer, J. Org. Chem. 26, 3587 (1961).
- [9] C. Bodea and M. Raileanu, Acad. Rep. Populare-Romine, Filiali Cluji, Studii Cercetari Chim. 11, 325 (1960); C. A. 58, 3420b (1963).
- [10] R. L. Mital and P. C. Taunk, Monatsh. Chem. 102, 760 (1971).
   [11] P. C. Taunk, Ph. D. thesis, Rajasthan University,
- [11] P. C. Taunk, Ph. D. thesis, Rajasthan University, 1972.
- [12] G. A. Reynolds, R. E. Adel, and J. A. van Allan, J. Org. Chem. 28, 2683 (1963).