#### NOTES

# THE SYNTHESIS OF 10-SUBSTITUTED PHENOXAZINES

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The recent publication by Muller, Buu Hoi, and Rips (1) describing the cyanoethylation of phenoxazine, and the issuing of a Belgian patent (2) describing the preparation of a series of 10-dialkylaminoalkyl phenoxazines, prompt us to report some work on the chemistry of phenoxazine, which has been in progress in these laboratories for some time. Dialkylaminoalkyl chlorides reacted with phenoxazine in the presence of freshly prepared sodamide to yield a series of 10-dialkylaminoalkyl phenoxazines which are listed in Table I. Some differences in the physical constants of these compounds from those reported by the Belgian workers are noted.

The addition of phenoxazine to acrylonitrile (1) and ethyl acrylate yielded 3-(10-phenoxazinyl)propionitrile (I) and ethyl 3-(10-phenoxazinyl)propionate (II) respectively and they were both hydrolyzed to 3-(10-phenoxazinyl)propionic acid (III). Lithium aluminum hydride reduction of II and III yielded 10-(3-hydroxypropyl)phenoxazine (IV). Attempts to prepare the corresponding chloride by treatment of IV with either thionyl chloride or phosphorus pentachloride only resulted in extensive polymerization. However, IV reacted smoothly with phosphorus tribromide to yield 10-(3-bromopropyl)phenoxazine (V). When V was allowed to react with 1-methylpiperazine, 10-(3-(3-methyl-1-piperazinyl)propyl)phenoxazine (VI) was formed.



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3-(10-Phenoxazinyl)propionic acid (III) underwent cyclization with phosphorus pentoxide to give a yellow ketone, assumed to be 2,3-dihydro-1H-pyrido(3,2,1-kl) phenoxazine-3-one (VII), m.p. 104–105°. Muller, Buu Hoi, and Rips have reported a melting point of 144° for this compound.



#### EXPERIMENTAL

#### 10-(3-Dimethylaminopropyl)phenoxazine

The procedure for the synthesis of 10-(3-dimethylaminopropyl)phenoxazine is a general one and has been followed for the synthesis of all 10-dialkylaminoalkyl phenoxazines listed in Table I.

A suspension of sodamide in 100 ml of xylene was prepared from 100 ml of liquid ammonia and 3.04 g of sodium according to the procedure of Hauser, Swamer, and Adams (3). To this stirred and refluxing mixture a solution of 22 g of phenoxazine in 150 ml of xylene was slowly added. During the addition the reaction mixture turned a greenish color. It was stirred and refluxed for another hour. To this mixture a solution of dimethylaminopropyl chloride (obtained from 19 g of the corresponding hydrochloride treated with 18 g of sodium hydroxide in 66 ml of H<sub>2</sub>O and extracted with 75 ml of xylene and dried over sodium sulphate) was added. The reaction mixture thus obtained was stirred and refluxed for 6 hours. After this mixture was cooled and filtered, the xylene was distilled under reduced pressure. The oily residue was distilled *in vacuo*. Twenty-six grams (80.5%) of a yellow oil was obtained distilling at 178°/2 mm.

### Addition of Phenoxazine to Ethyl Acrylate or Acrylonitrile

To a stirred and ice-cooled mixture of 20 g phenoxazine and 33 ml ethyl acrylate (or 50 ml acrylonitrile), 2 ml of 35% methanolic benzyltrimethylammonium hydroxide was added dropwise. After the addition was completed the reaction was heated overnight (or 1 hour) on the steam bath. The excess of ethyl acrylate (or acrylonitrile) was distilled under reduced pressure. The residual ethyl 3-(10-phenoxazinyl)propionate (II) was distilled *in vacuo* to yield 20.6 g (66.5%), b.p. 187°/1 mm.

The residual 3-(10-phenoxazinyl)propionitrile was recrystallized from aqueous ethanol to yield 19.5 g (72.9%), m.p. 121–122°.

#### 3-(10-Phenoxazinyl)propionic Acid (III)

(a) A mixture of 4 g of 3-(10-phenoxazinyl)propionitrile, 4 g sodium hydroxide, 12 ml of water, and 40 ml of methanol was refluxed for 15 hours. The hydrolysis product was poured into ice water, acidified with dilute hydrochloric acid, filtered, and recrystallized from aqueous ethanol. 2.3 g of III was obtained, m.p. 136–138°.

(b) Ethyl-3-(10-phenoxazinyl)propionate (14.15 g, 0.05 mole) was dissolved in 300 ml of 10% ethanolic potassium hydroxide and refluxed for 2 hours. To this mixture after being cooled, 300 ml of water was added. The alcohol (300 ml) was distilled and the

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TABLE I

zz 10-Substituted phenoxazines

|     |  |            |                                    |                | Car   | bon   | Hydı  | rogen | Nitr  | ogen  |
|-----|--|------------|------------------------------------|----------------|-------|-------|-------|-------|-------|-------|
| No. | R  | Yield $\%$ | B.p.                               | M.p.           | Calc. | Found | Calc. | Found | Calc. | Found |
| I   | $(H_3C)_2NCH_2CH_2$  | 60.2       | $168^{\circ}/2.5 \mathrm{mm}^{a}$  |                | 75.54 | 75.75 | 7.08  | 7.01  | 11.02 | 11.11 |
| 5   | (H <sub>3</sub> C) <sub>2</sub> NCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>             | 80.5       | 178°/2 mm                          |                | 76.07 | 75.80 | 7.46  | 7.75  | 10.44 | 10.59 |
| 3   | (H <sub>5</sub> C <sub>2</sub> ) <sub>2</sub> NCH <sub>2</sub> CH <sub>2</sub> hydrochloride | 54.8       |                                    | $241-242^{ob}$ | 67.79 | 67.72 | 7.24  | 6.88  | 8.81  | 8.88  |
| 4   | $(H_3C)_2N_C^{-1}HCH_2$  | 55.9       | 168°/2.5 mm                        |                | 76.07 | 75.47 | 7.46  | 7.69  | 10.44 | 11.03 |
|     | $\operatorname{CH}_3$  |            |                                    |                |       |       |       |       |       |       |
|     | 0=   |            |                                    |                |       |       |       |       |       |       |
| 5   | $H_bC_2OUC-CH_2CH_2$   | 66.5       | $187^{\circ}/1 \text{ mm}^{\circ}$ |                | 72.08 | 71.73 | 6.00  | 5.98  | 4.95  | 5.07  |
| 9   | HOOCCH2CH2   | 57         |                                    | $138^{od}$     | 70.59 | 70.45 | 5.09  | 5.27  | 5.49  | 4.93  |
| 2   | HOCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>  | 65.5       |                                    | 68°e           | 74.68 | 74.76 | 6.22  | 6.49  | 5.81  | 5.79  |
| 80  | BrCH2CH2CH2  | 48         |                                    | $55^{\circ}$   | 59.21 | 59.00 | 4.60  | 4.62  | 4.60  | 4.73  |
| 6   | H <sub>3</sub> C-N N-CH <sub>2</sub> CH <sub>2</sub>   |            |                                    |                |       |       |       |       |       |       |
|     | CH <sub>2</sub>  | 73.6       |                                    | °10–91°        | 74.30 | 74.08 | 7.73  | 7.96  | 13.16 | 12.98 |

NOTES

<sup>a</sup>The hydrochloride has been reported to melt at 241° (7). <sup>b</sup>Lit. value (2) 167–169°. <sup>c</sup>Lit. value (2) 210°/2 mm. <sup>d</sup>Lit. value (1) 138°. <sup>e</sup>Only a boiling point of 200°/0.8 mm is reported (2).

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remaining mixture was acidified with 6 N hydrochloric acid. 3-(10-Phenoxazinyl)propionic acid (III) precipitated and was recrystallized from aqueous ethanol; 7.3 g (57%) of the acid (III) was obtained melting at 137–138°.

## 10-(3-Hydroxypropyl)phenoxazine (IV)

A solution of 14 g of ethyl 3-(10-phenoxazinyl)propionate in 100 ml of ether was added slowly to a mixture of lithium aluminum hydride (2 g) in 100 ml of ether at such a rate as to maintain gentle refluxing. The reaction mixture was stirred and refluxed for 45 minutes. The excess hydride was destroyed with 2 ml of water. The reaction mixture was poured into ice water, acidified cautiously with 2 N sulphuric acid, and the ether layer was separated. The aqueous layer was saturated with ammonium sulphate and further extracted with ether. The combined ether extracts were washed with water and dried over sodium sulphate. The solvent was distilled and the residue recrystallized from a mixture of benzene ligroin. Eight grams (65.5%) of IV was obtained, m.p. 68°. 10-(3-Hydroxypropyl)phenoxazine was also obtained in a similar yield when 3-(10-phenoxazinyl)propionic acid (III) was reduced by lithium aluminum hydride in ether according to the procedure of Dahlbom (4) for the phenothiazine analogue.

#### 10-(3-Bromopropyl)phenoxazine (V)

Freshly redistilled phosphorus tribromide (4.2 nl) was added to 15 g of 10-(3-hydroxypropyl)phenoxazine with cooling. The reaction mixture was heated on the steam bath for 1 hour and then poured onto crushed ice. The bromide (V) separated as an oil which solidified on standing overnight. It was filtered, washed with water on the filter, and after recrystallization from ethanol melted at 55–56°. The yield was 9 g (48%).

# 10-(3-(4-Methyl-1-piperazinyl)propyl)phenoxazine (VI)

A mixture of 9 g of 10-(3-bromopropyl)phenoxazine and 18 ml of 1-methylpiperazine was heated on the steam bath for 4 hours. Eighty milliliters of 10% sodium hydroxide solution was added to the reaction mixture which was then thoroughly extracted with ether. The ether extracts were combined and dried over  $Na_2SO_4$ . The ether was distilled and the residue was recrystallized from ligroin. Seven grams (73.6%) of VI was obtained, m.p. 89–91°.

### 2,3-Dihydro-1H-pyrido(3,2,1-kl)phenoxazine-3-one

The procedure of Smith (5) and Buu Hoi (6) for the phenothiazine and phenoselenazine analogue was followed in principle.

Fifty grams of phosphorus pentoxide was suspended in 200 ml of benzene and 10 g of 3-(10-phenoxazinyl)propionic acid was added to the stirred and heated reaction mixture. The mixture was stirred and refluxed for 1 hour and then left at room temperature overnight. It was filtered and the material remaining on the filter was washed thoroughly with an additional quantity (100 ml) of benzene. The benzene was removed from the filtrate by distillation and the residue was recrystallized from a minimum amount of ethanol; 4.5 g (48.4%) of a yellow ketone was obtained, m.p. 104°. Anal. for  $C_{15}H_{11}NO_2$ . Calc.: C, 75.95; H, 4.64; N, 5.91%. Found: C, 75.50; H, 4.68; N, 5.90%.

The corresponding semicarbazone was prepared and melted at 232°. Anal. for  $C_{16}H_{14}N_4O_2$ . Calc.: C, 65.3; H, 4.76%. Found: C, 65.13; H; 4.92%.

2. BELG. PATENT No. 569,697 (January, 1959): Chem. Abstr. 54, 586 (1960).

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<sup>1.</sup> P. MULLER, N. P. BUU HOI, and R. RIPS. J. Org. Chem. 24, 1699 (1959).

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