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SYNTHETIC AMINO ACID-ANALOGS OF γ-AMINOBUTYRIC ACID

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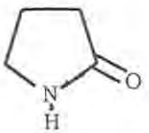
ABSTRACT. The syntheses of N-phenyl-N-tosyl alkyl amino acids are reported. A facile one-step synthesis of cyanoalkylanilines is described.

INTRODUCTION

γ-Aminobutyric acid (GABA) which is enzymatically derived from L-glutamic acid is found in the mammalian central nervous system (1,2). The roles of GABA in the etiology of a host of neurological and psychiatric disorders (3) such as Huntington's disease, parkinsonism, epilepsy, schizophrenia, senile dementia, etc. have been investigated (1,4,5,6).

The brain is known to contain up to 8-13 moles/g of L-glutamic acid (7,8), and in situations where low levels of GABA are encountered, difficulties have been faced to exogenously supply GABA. Attempts to supply GABA-lactam **1** have been futile because of its resistance to hydrolysis.

This paper reports the chemical synthesis of GABA derivatives with lipophilic substituents. The new compounds may be regarded as analogs of mescaline **2** and its more active derivative **3.**



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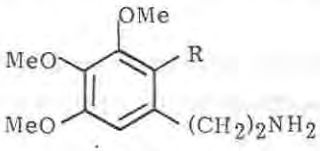

2 R = H
3 R = OMe

RESULTS AND DISCUSSION

Anilines undergo N-alkylation to give very high yields of N-dialkylated products. Monoalkylation (9,10) with bromocyanides (n = 3,4) resulted in low yields of N-monocyanolkylanilines (eq. 1). This result was not surprising because the

$$R\text{-}C_6H_4\text{-}NH_2 + Br\text{-}(CH_2)_nCN \xrightarrow{\Delta} NC(CH_2)_n\text{-}NHC_6H_4 + \text{Dialkylated Product} \quad \text{..... Eq. 1}$$

increased reactivity of the initially formed N-alkylaniline to a second cyanoalkyl halide. Alkylation of the N-tosylated (11) derivatives, (**4, 5**) however, lead to good yields of monoalkylated products, (**6-9**) Scheme 1. The tosylanilnes reacted smoothly with bromoalkylnitriles in hot DMF containing 1.25 equivalents of Na H (9). The N-cyanoalkyl-N-tosylanilines produced were readily converted to the corresponding acids (**10, 11**) upon hydrolysis with boiling 2 M aq. NaOH. The yields, physical and spectroscopic properties of the compounds synthesized are shown in Table 1.

Tabel 1. Physical properties, yields and spectroscopic data for products[a].

Compound	M.P., °C	Yield %	Rf	IR KBr cm^{-1}
N-Tosylaniline **4**	94 - 97	77.7	0.87[b]	3239,(-NH-) 3027, 2910 2837 ($-CH_2-$) 1337 (SO_2)
N-Tosyl-3,4,5-trimethoxy-aniline **5**	137 - 138	71.7	0.47[b]	
N-Phenyl-N-tosyl γ-aminobutryonitrile **6**	99 - 101	75.2	0.79[b]	3068, 2992, 2950, 2865 ($-CH_2-$) 2238 (-CN-)
N-Phenyl-N-tosyl)-d-nitrile **7**	69 - 70	72.9	0.93[b]	3034, 2964, 2872 ($-CH_2-$) 2245 (-CN-)
N-Tosyl-N-(3,4,5-trimeth-oxyphenyl) γ-amino-butyro nitrile **8**	119 - 120	83.2	0.76	2245(CN)
N-Tosyl-N-(3,4,5-trimethoxyphenyl)amino nitrile **9**	165 - 166	78.4	0.87[b]	2971, 2943, 2879, 2832 $-CH_2-$) 2245 (-CN-)
N-Tosyl-N-(3,4,5 γ-aminobutyric acid **10**	162 - 165	94.8	0.46[b]	2871, 2879, 2767, 3126 3055 ($-CH_2-$),1703 (C=0), 1337 ($-SO_2-$)
N-Tosyl-N-(3,4,5-trimethoxyphenyl)-γ-aminobutyric acid **11**	157 - 158	90.7	0.26[b]	3105, 3041, 2964, 2837 (-C=O) 1717 ($-CH_2-$) 1315 ($-SO_2-$)
N-(2-Cyanoethyl)-aniline **12**	44 - 46	35	0.43[b]	3112, 3084 (-NH-), 2984 2844 (CH_2-) 2252 (-CH)
N-(2-Cyanoethyl-3,4,5-trimethoxyaniline. **13**	88 - 90	40.8	0.28[b]	3344 (-NH-) 2245(-CN)
N-(3,4,5-trimethocyphenyl-tosyl)β-aminoprionic acid **15**	97 - 98	25.3	0.14[b]	3484(-OH acid) 2964 2879, 2844 ($-CH_2-$) 1745 (C=0) 1291 (SO_2-)

[a]Satisfactory elemental analysis data were obtained for all new compounds.

[b]10 percent acetone/Chloroform (TLC plates were observed with UV light).

Scheme 1

$$R\text{-}C_6H_4\text{-}NH_2 \xrightarrow[Py,\ \Delta]{TsCl} R\text{-}C_6H_4NH\text{-}Ts \xrightarrow[NaH/DMF/\Delta]{Br(CH)_2{}_nCN} R\text{-}C_6H_4\text{-}NTs(CH_2)_nCN$$

4 R = H
5 R = 3,4,5-OMe

6 R = H, n = 3
7 R = H, n = 4
8 R = 3,4,5-OMe, n=3
9 R = 3,4,5-OMe, n=4

$$\xrightarrow[\Delta]{NaOH} R\text{-}C_6H_4NTs(CH_2)_nCO_2H$$

10 R = H, n =3
11 R = 3,4,5-OMe, n = 3

Scheme 2

$$R\text{-}C_6H_4NH_2 + CH_2 = CH\text{-}CN \xrightarrow[\Delta]{HOAc} R\text{-}C_6H_4NH(CH_2)_2CN$$

12 R = H
13 R = 3,4,5-OMe

$$\xrightarrow[\Delta]{NaOH} R\text{-}C_6H_4\text{-}NH\text{-}(CH_2)_2CO_2H \xrightarrow[Py,\ \Delta]{TSCl} R\text{-}C_6H_4\text{-}NTs(CH_2)_2CO_2H$$

14 R = 3,4,5-OMe

15 R = 3,4,5-OMe

N-cyanoethylanilines (**12**, **13**) were easily prepared (see Scheme II) but the isolation of the hydrolysis (12) products were difficult probably because of the water solubility of the zwitterionic forms. However, the product mixture was allowed to dry completely and was N-tosylated. The N-tosylated acids (**15**) were easily isolated following work up in ice-cooled water. In conclusion it is observed that N-tosylated anilines undergo acid catalysed nucleophilic substitution reaction to form high yields of N-monoalkylated products. The yield of N-2-cyanoethyl product was higher for 3,4,5-trimethoxyaniline than from aniline. This implied that electron-donating ring substitutents favor the formation of alkylation products. γ-Aminobutyric acids were produced in high yield by hydrolysis of the corresponding nitriles. The low yield of the β-aminopropionic acid, (**15**) could be accounted for by its zwitterionic nature thereby requiring a secondary reaction (N-tosylation) in order to convert it to an easily isolable acid.

EXPERIMENTAL

Materials and Methods. Melting points were obtained with a Mel-temp apparatus and are uncorrected. IR spectra were obtained on a Nicolet Model 700 FT-IR instrument. Atlantic Microlabs, Inc., Atlanta, Georgia supplied the elemental analyses. 3,4,5-Trimethoxyaniline, aniline, 4-chlorobutyronitrile, 5-chloro valeronitrile, p-toluenesulphonyl chloride, acrylonitrile were purchased from Aldrich.

N-Tosylaniline (4); N-Tosyl-3,4,5-trimethoxyaniline (5). These compounds were prepared by reacting the anilines (1 g, 0.01 mole for **4**); and 3,4,5-trimethoxyaniline (1 g, 0.005 mole for **5**) and p-toluenesulphonyl chloride (2.04 g, 0.001 mole for **4**: and 1 g 0.005 mole for **5**), in pyridine (6 ml) under heat. The progress of the reaction was followed either by TLC or by the colour change. At the end of the reaction, the mixture was poured into water contining ice with constant swirling. The solid prouct obtained was recystallized from hot ethanol to give 2.07 g for **4**; and 1.32 g for **5** after oven drying at 80°.

N-Pheny-N-tosyl-γ-aminobutyronitrile (6); N-Phenyl-N-tosyl-aminovaleronitrile (7); N-Tosy-N-(3,4,5-trimethoxyphenyl)δ-aminovaleronitrile (9). The N-tosyl anilines (1 g, 0.004 mole for **6**: 0.28 g, 0.001 mole for **7**; 0.6 g, 0.002 mole for the case of **9**) were separately reacted with bromoalkylnitriles: 4-bromo butryronitrile, 1.19 g, 0.8 ml, 0.008 mole for **6**; 5-bromovaleronitrile, 0.22 ml, 0.02 mole for **7**: and 0.44 ml, 0.004 mole for **9**; in presence of prewashed sodium hydride: 0.24 g, 0.005 mole for **6**: 0.068 g, 0.001 mole for **7**, and 0.11 g, 0.005 mole for **9**; contained in dimethylformamide (DMF) under heat (70-80°). The solid products which precipitated were filtered and recrystallized from hot ethanol to give 0.95 g of **6**; 0.27 of **7** and 0.58 g of **9**.

N-Tosyl-N-(3,4,5-trimethoxyphenyl)-γ-amino butyronitrile 8 This compound was prepared in the same fashion as **6**, **7** and **9** above. The starting N-tosylaniline (1 g, 0.003 mole) was treated with 4-bromobutyronitrile (0.3 ml, 0.03 mole) in DMF containing 0.09 g (0.004 moles) of sodium hydride (50% oil suspension) prewashed with benzene. The precipitate was recrystallised from hot ethanol to give 0.99 g of product.

N-Phenyl-N-tosyl-γ-aminobutyric acid 10; N-Tosyl-N-(3,4,5-trimethoxyphenyl)-γ-aminobutyric acid 11. These were prepared by hydrolysis in 10% NaOH (of the nitriles) at 170-200° (oil bath temp.) overnight. N-Phenyl-N-tosyl-γ-amino butyronitrile (0.8 g, 0.002 mole) was used with 5 ml of NaOH for (**10**). N-Tosyl trimethoxyphenyl)-γ-aminobutyronitrile (0.4 g, 0.009 mole) was used with 4 ml of NaOH for **11**. The reaction mixture was worked up by acidifying it with conc. HCl and the white precipitate obtained was further purified by recrystallisation

from hot ethanol. The following weights were obtained 0.8 g for **10** and 0.38 g for **11**.

N-(2-cyanoethyl)aniline ***12.*** Aniline (2 g, 1.96 ml, 0.02 mole) was added to a reaction flask (25 ml) containing acrylonitrile (1.14 g, 1.41 ml, 0.02 mole) and glacial acetic acid at room temperature and refluxed overnight. TLC (10% acetone/chloroform) of the reaction mixture indicated 2 spots far apart from each other. The acid was quenched with 10% $NaHCO_3$ and the mixture was extracted with chloroform (3 x 10 ml). The organic solvent was evaporated and the oily residue was subjected to Kugel-rohr distillation, which led to the isolation of one product. The residue was recrystallized from a mixture of water and acetone (2:1).

N-(2-Cyanoethyl-3,4,5-trimethoxy) aniline ***13.*** 3,4,5-Trimethoxy aniline (3.95 g, 0.018 mole), acrylonitrile (35 ml) and 2 ml glacial acetic acid were refluxed for 2 days and worked up in the same fashion as for N-(2-cyanoethyl)aniline **12.** The solid product was recrystallized from hot ethanol to give 1.79 g of product.

N-(3,4,5-trimethoxyphenyl)-β-amino propionic acid ***14.*** N-(2-cyanoethyl-3,4,5 trimethoxyaniline, **13**, 1.4 g, 0.004 mole was dissolved in 10% NaOH (14 ml) and heated (130-140°) overnight. The hydrolysis product was worked up by quenching the base with conc. HCl to pH 4. The reaction mixture was left to dry up completely to form the solid sodium salt of the acid.

N-Tosyl-N-(3,4,5-trimethoxyphenyl)-β-amino propionic acid ***15.*** N-(3,4,5-Trimethoxyphenyl)-β-aminopropionic acid (sodium salt, 1 g) was reacted with p-toluenesulphonyl chloride (1 g, 0.006 mole) in pyridine (6 ml) under heat. This reaction was conducted in the same fashion as for **4** and **5.** The pH was adjusted to 2 with conc. HCl and poured into cold water. The solid obtained was recrystallized from hot ethanol, 0.25 g after oven drying at 50°.

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