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Mono-N-Alkylation Of Anthranilamides *via* Quinazolinones. An Efficient Synthesis of G5598, A Benzodiazepine Dione GpIIbIIIa Antagonist.

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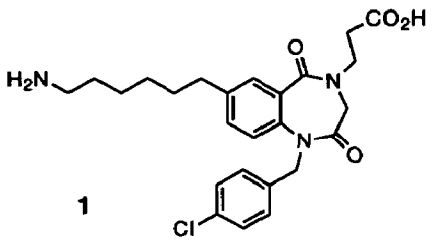
Summary. The mono-N-alkylation of an anthranilamide derivative via the reductive ring opening of a quinazolinone precursor, enables the synthesis of benzodiazepine dione derivative G5598, a potent inhibitor of the *in vitro* binding of GpIIbIIIa to fibrinogen.

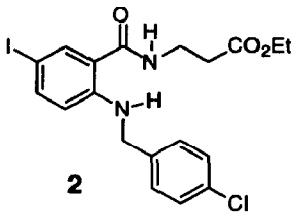
As part of a program aimed at developing an inhibitor of the interaction of Glycoprotein IIbIIIa (GpIIbIIIa) with fibrinogen (Fg), we recently required an efficient synthesis of benzodiazepine diones. Since the benzodiazepine dione derivative G5598 (**1**, below) had been shown to be a potent inhibitor of the binding of GpIIbIIIa to fibrinogen, and a potent inhibitor of platelet aggregation *in vitro*,[1] our goals were an efficient, large scale synthesis of **1** for further evaluation *in vivo*, and a general synthesis of substituted benzodiazepine diones of this type to provide for the rapid preparation and evaluation of analogs in this series.



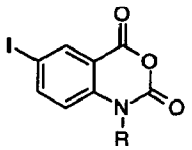
1

A cursory search of the literature indicated that the most likely approach to the synthesis of this compound would be from the appropriately substituted anthranilamide **2**. Opening of isatoic anhydride **4** with the appropriate amine (β-alanine ethyl ester) would give **2**,[2,3] and the subsequent annulation of **2** to the seven-membered ring, followed by installation of the alkylamine side chain via palladium-mediated coupling of the aryl iodide with an acetylene would complete the synthesis. Unfortunately, our attempts at alkylating 5-iodoisatoic anhydride **3** with *p*-chlorobenzyl chloride (NaH/DMF/rt, K_2CO_3/DMF/Δ)[4] to produce **4** returned 15-30% starting material (yields determined only after isolation, purification, and characterization of products).[5]

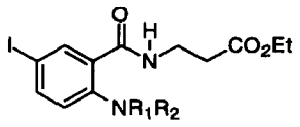
We next explored the possibility that the 5-iodo-anthranilamide **5** could be alkylated directly with *p*-chlorobenzyl chloride to give **2**. Anthranilamide **5** was efficiently produced from **3** by treatment with β-alanine ethyl ester in DMF/NEt_3. In this case, however, attempted direct alkylation gave a mixture of **5**, **2** and the corresponding di-N-alkylated material **6**. Both of these approaches necessitated tedious chromatographic separations to isolate the desired materials, rendering these procedures unsuitable for use in even modest scale up.



2

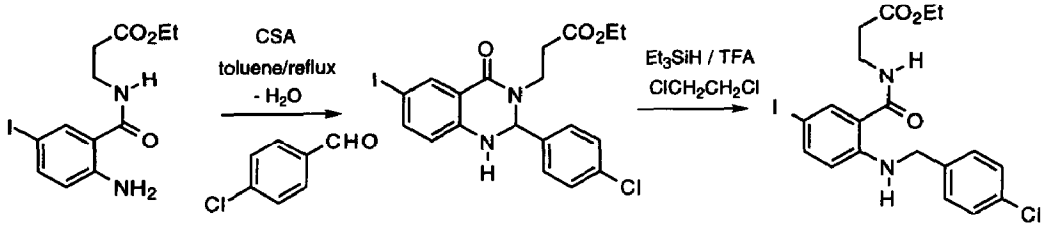


3 : R = H
4 : R = *p*-Cl-benzyl



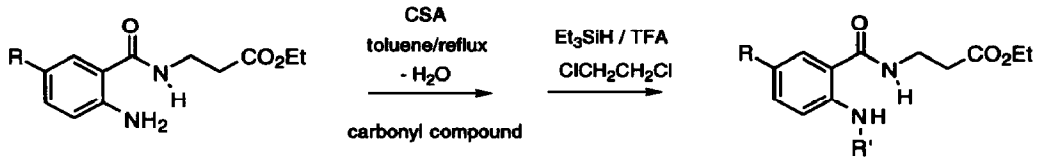
5 : R_1, R_2 = H
6 : R_1, R_2 = *p*-Cl-benzyl

The solution to this problem presented itself in an unusual manner. Reductive alkylation of anthranilamide **5** (via borohydride reduction of the imine) is not a viable strategy for the mono-alkylation of this type of compound, as anthranilamides are known to condense rapidly with aldehydes to give, instead, the quinazolinones (eg. **7**) shown below.[6] *However, we found that treatment of anthranilamide **5** with p-chlorobenzaldehyde according to this protocol, followed by treatment of the intermediate quinazolinone **7** with Et_3SiH in dichloroethane containing 20% by volume CF_3CO_2H (TFA) gave high yields of the product mono-alkylated anthranilamide **2**.*[6,7]



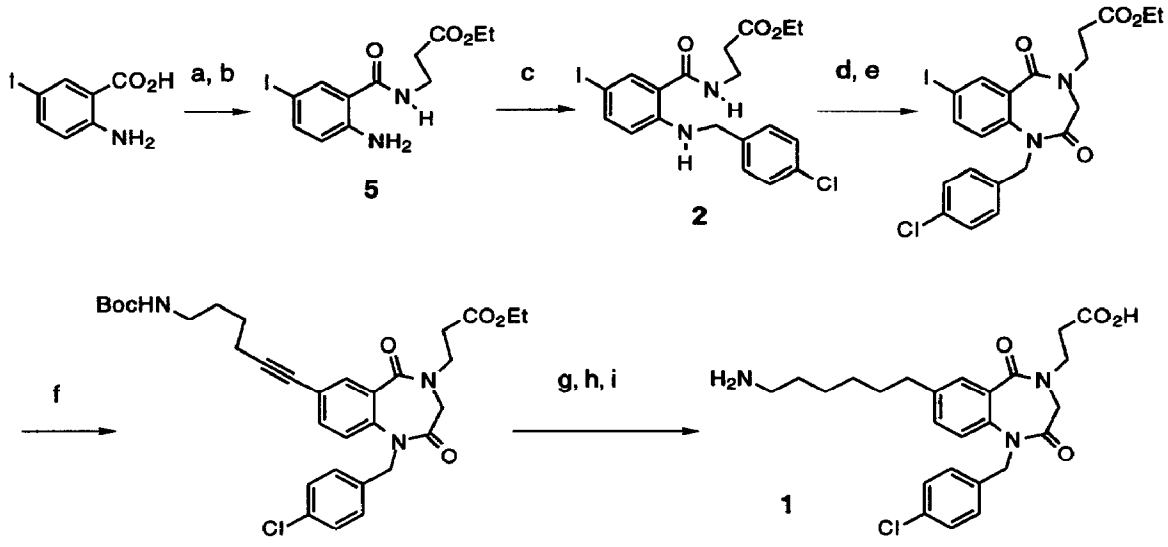
5 **7** **2**

We have not, to date, fully explored the generality of this alkylation procedure. However, all aldehydes used appeared to work well. Logistically, aldehydes containing electron-withdrawing groups worked best. Most notably, other compounds which could not be prepared via alkylation were easily prepared using this procedure. For example, the alkylation of anthranilamide **5** with 4-bromomethyl pyridine (K_2CO_3/DMF/Δ, (*i*-pr)$_2$NEt/DMF/120-150°C) gave dismal yields (<2%), whereas the above procedure, when employed with 4-pyridine carboxaldehyde, yielded 65% of the desired N-alkylated compound. Ketones in general did not work as well, i.e.. benzophenone and acetone, with the exception of cyclohexanone (see Table). Generally the procedure was performed in one pot, although the intermediate quinazolinones could be isolated.



R	R'	Yield	R	R'	Yield
H	ethyl	100%	H	*i*-butyl	60%
H	valeryl	83%	H	*p*-chlorobenzyl	80%
Iodo (**5**)	*p*-chlorobenzyl	97%	Iodo	*p*-nitrobenzyl	79%
Iodo	*p*-MeO-phCH$_2$	37%	Iodo	*p*-CH$_2$-pyridyl	80%
Iodo	cyclohexyl	59%	Iodo	*p*-phO-phCH$_2$	23%
Iodo	1-naphthyl	51%	*p*-CNphCONH	*p*-chlorobenzyl	79%

The preparation of anthranilamide **5** using this procedure enabled the large scale synthesis of G5598 shown below. The high yield, and the single crystalline product obtained in this key step allowed us to prepare compound **1** in nine (9) steps in 50% overall yield from 5-iodoanthranilic acid,[8] since all the other intermediates in the route were crystalline and no chromatography was required. G5598 itself was isolated by neutralization in the ester cleavage step to pH 5.5, at which point the product amino acid (G5598) precipitated, and could be easily recrystallized from water.



a: phosgene (20% in toluene), 2N Na_2CO_3, 0°C; b: β-alanine ethyl ester, NEt_3, DMF, DMAP, 0°C; c: *p*-chlorobenzaldehyde, toluene/reflux, camphorsulfonic acid, -H_2O; Et_3SiH, 20% TFA/$ClCH_2CH_2Cl$, room temperature; d: bromoacetyl bromide, H_2O/CH_2Cl_2, 0°C;[9] e: Cs_2CO_3/DMF, room temperature; f: $Pd^{(II)}$ (1 mol %), $Cu^{(I)}$, N-boc-1-amino-5-hexyne, NEt_3/reflux;[10] g: H_2, PtO_2, EtOH; h: TFA/CH_2Cl_2; i: 50% KOH, THF-MeOH-H_2O (3:2:1).

Mechanistically, the above result suggests that the reaction proceeds via acid-catalyzed ring opening of the quinazolinone to form an iminium ion intermediate, which is then reduced with Et_3SiH.[11]

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7. 3-(2-N-((*p*-Chloro)benzyl)amino-5-iodo)benzamidopropionic Acid Ethyl Ester **2**; Representative Procedure For Reductive Alkylation Of Anthranilamides.

A solution of 3-(2-amino-5-iodo)benzamidopropionic acid ethyl ester (100g, 0.27 mol) in toluene (400 mL) was treated with *p*-chlorobenzaldehyde (40g, 0.27 mol) and camphor-sulfonic acid (0.1 g) and the resulting mixture was heated to reflux with removal of water (Dean-Stark trap). After 1/2 h, TLC (25% EtOAc/hexanes) indicated the absence of the starting anthranilamide and presence of the intermediate quinazolinone. The solution was cooled and evaporated to dryness, and the dark yellow solid remaining was dissolved in dichloroethane (500 mL), cooled to 0°C (ice bath), and triethylsilane (66 mL, 0.41 mol) followed by trifluoroacetic acid (130 mL) were added slowly dropwise over 1/2 h. The solution was allowed to warm to room temperature, and stirred for 24 h. TLC (25% EtOAc/hexanes) indicated the absence of the quinazolinone, and the presence of the product anthranilamide **2**. The solution was evaporated to dryness, and the solid remaining was recrystallized from EtOAc-hexanes to yield 129g (97%) of **2** as colorless crystals: mp. 144-146°C; ^{1}H NMR ($CDCl_3$) δ7.58(d, J=3Hz, 1H, ArH), 7.44(d, J=6Hz, 1H, ArH), 7.26(brs, 4H, ArH), 6.69(brs, 1H, NH), 6.36(d, J=6Hz, 1H, ArH), 4.35(s, 2H, $ArCH_2$), 4.18(q, J=6Hz, 2H, OCH_2CH_3), 3.67(q, J=6Hz, 2H, $CONCH_2$), 2.63(q, J=6Hz, 2H, CH_2CO_2Et), 1.30(t, J=6Hz, 3H, OCH_2CH_3);^{13}C NMR ($CDCl_3$) δ172.68(CO_2Et), 168.32(NCO), 148.19(Ar), 141.61(Ar), 136.67(Ar), 135.70(Ar), 135.67(Ar), 132.94(Ar), 128.81(Ar), 128.38(Ar), 117.83(Ar), 114.80(Ar), 61.01(OCH_2), 46.60 (NCH_2Ar), 35.22 ($CONCH_2$), 33.87(CH_2CO_2Et), 14.20(OCH_2CH_3); MS(FAB) *m/z* 487.1(M+H)$^+$; Analysis ($C_{19}H_{20}N_2O_3ICl$) C, H, N, Cl.

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