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A Convenient Synthesis of Ethyl (2-Amino-5,6-dichlorobenzyl)glycinate

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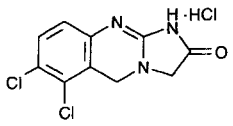
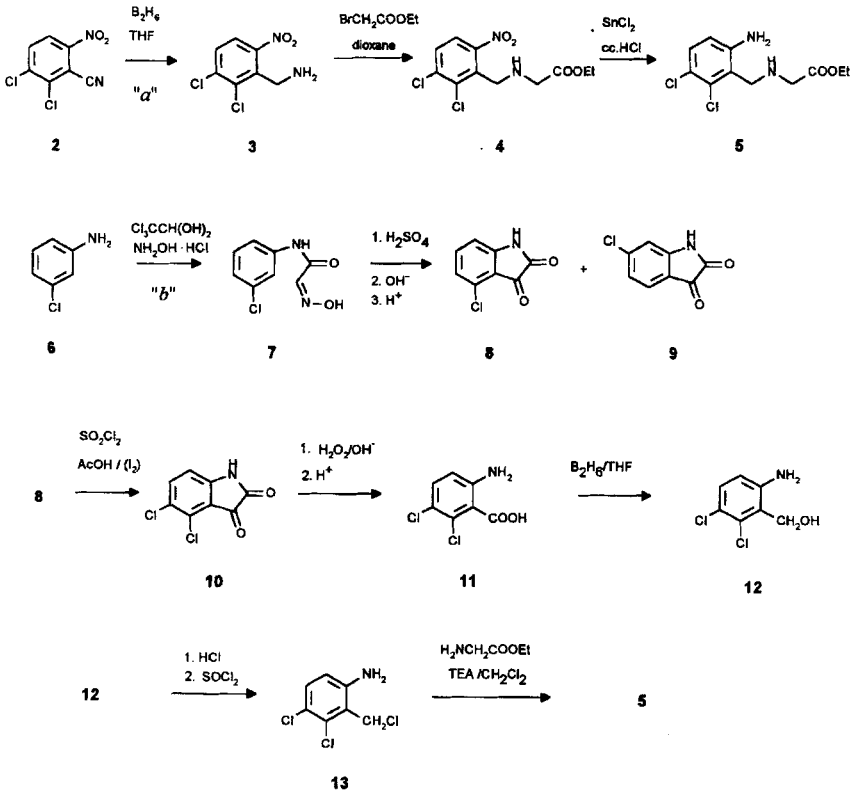
Anagrelide **1** [1–2] is in development as a new medicine to be used in essential thrombocythemia [3–4], heart disease and stroke [5] in America and Europe [6–7]. It has a strong blood platelet aggregation inhibitory activity without reducing the count of platelets [8] based on the selective blocking of c-AMP PDE and thus reducing the concentration of c-AMP in blood platelets [9–11].



1 Anagrelide

The ethyl (2-amino-5,6-dichlorobenzyl)glycinate (**5**) (Scheme 1) is one of the key intermediates of Anagrelide. It was synthesized first in 1979 by American authors [2] using two synthetical pathways. The first one (pathway "*a*", Scheme 1) starts from 2,3-dichloro-6-nitrobenzonitrile (**2**) [14] which is reduced selectively by diborane to 2,3-dichloro-6-nitrobenzylamine (**3**) that is alkylated with ethyl bromoacetate to the corresponding ethyl (2,3-dichloro-6-nitrobenzyl)glycinate (**4**), the nitro group of which is reduced with tin(II)chloride to yield **5**.

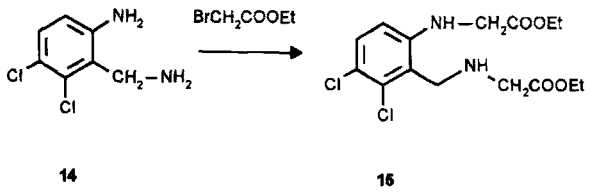
The second route (pathway "*b*"), (Scheme 1) starts from *m*-chloroaniline (**6**) which is converted with chloral hydrate



Scheme 1

and hydroxylamine to the corresponding isonitroso derivative (**7**). This is ring closed with sulfuric acid to the mixture of the 4-chloro and 6-chloroisatine derivatives **8** and **9** that have to be separated. The 4-chloro isomer (**8**) is chlorinated with sulfuryl chloride to the corresponding 4,5-dichloroisatine derivative **10** which is oxidized with hydrogen peroxide to 2-amino-5,6-dichloroanthranilic acid (**11**). The carboxylic group of **11** is reduced with diborane to yield the corresponding benzyl alcohol derivative **12** that is converted with thionyl chloride to the corresponding benzylchloride derivative **13**. The reaction of **13** with ethyl glycinate affords the expected **5**.

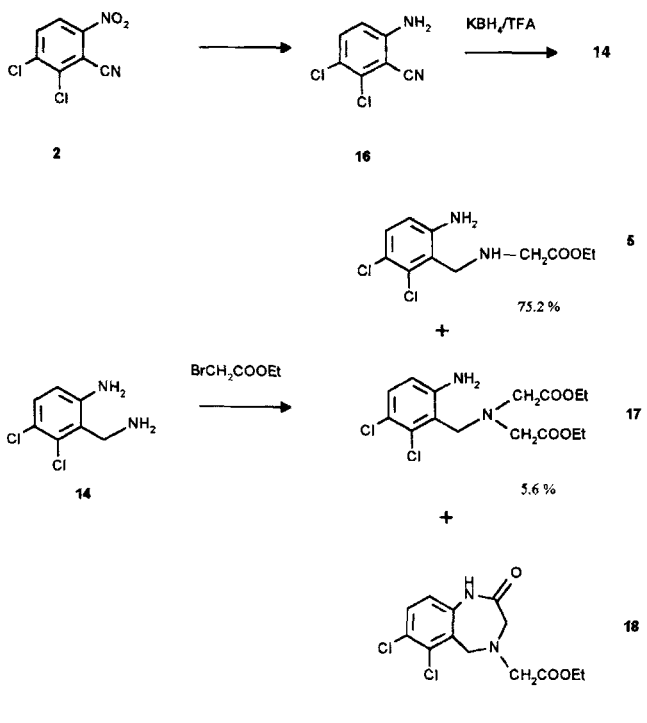
Route "*b*" is too long for industrial use, while route "*a*" requires the selective reduction of the nitrile group of **2** in the presence of the more reactive nitro group (Scheme 1). However, when planning the reaction sequence of route "*a*", authors apparently feared the possibility of double alkylation of the corresponding, more easily obtainable diamino derivative (**14**) with ethyl bromoacetate to yield also instead of the expected



Scheme 2

5, the unwanted derivative **15** (Scheme 2).

Our synthetic strategy (Scheme 3) was based on the idea that the two amino groups of **14** had to possess different behaviour, as one is a benzylic amino group and the other contains an "anilino" nitrogen. Thus we decided to reduce first the more easily reducible nitro group of **2** to yield 2-amino-5,6-dichlorobenzonitrile (**16**) that could be easily reduced to 2-amino-5,6-dichlorobenzylamine (**14**). As expected, the alkylation of **14** with ethyl bromoacetate in dioxane led in good yield to **5** (Scheme 3) besides a small amount of **17** and **18** (formed most probably by ring closure of **17**) that could be easily separated from **5** enabling a simple, straightforward synthesis of ethyl (2-amino-5,6-dichloro-benzyl)glycinate (**5**). This method can be used also in industrial scale. This new synthetical method was patented recently [12].



Scheme 3

Authors thank is due to Mrs. Éva Szabó for performing the MS and GC-MS measurements and Mr. Tibor Merczel and Mr. Ádám Sárosi for technical help.

Experimental

Melting points were determined on a Kofler-Boëtius apparatus and are not further corrected. The infrared spectra were obtained using potassium bromide pellets using Bruker IFS-113 spectrophotometer. The ^1H NMR and ^{13}C NMR measurements were performed using Bruker WM-250 instrument at 250 MHz (^1H) and 62.89 MHz (^{13}C), respectively, in DMSO-d_6 solution using TMS and DDS, respectively, as internal standards. The MS spectra were taken with a KRATOS MS 25 RFA double focusing instrument, ionisation energy 70 eV, speeding voltage 4 kV in EI and CI (isobutane) mode.The GC determinations were performed with a Shimadzu GC-9A apparatus using a Chrompack, CP-SIL-PCB, 25 m long half capillary column. The peaks were determined by GC-MS with the above GC instrument attached to a Carlo Erba/HRGC/MS apparatus. The HPLC determinations were performed using a KNAUER apparatus (KNAUER HPLC PUMP 64, KNAUER MODEL detector UV-1, EUROSPHER column 100-C8, 25 × 4 mm ID, 5 µm; EUROCHROM-2000 software, loop 20 µl), as eluent a 4 : 6 mixture of acetonitrile and 0.1 M ammonium acetate buffer (pH = 4.4) was used. The LC-MS determinations were performed with a VQ QUATRO apparatus (electronspray) connected to a HPLC (Spectra Physics P-200 pump, UV-100 detector, HPMOS 2,1×100 mm (C-8) column, eluent a 1 : 1 mixture of formic acid and water, software MASSLYNX). The reactions were followed by GC, TLC and HPLC respectively. All TLC determinations were performed on DC-Alufolien Kieselgel 60 F_{254} (Merck 5562). The spots were detected by UV at 254 and 366 nm, iodine vapours, 0.1 $KMnO_4$ and 0.1% ethanolic Bromocresol Green solution.The dry column flash chromatographies [13] were performed using Kieselgel 60H (Merck 7736) absorbent. As eluents different mixtures of cyclohexane and ethyl acetate of increasing polarities were used.

6-Amino-2,3-dichlorobenzonitrile (**16**)

Method 1 ($SnCl_2$)

Tin(II)chloride (2.4 kg, 12 mol, purity 94%) was added to conc. hydrochloric acid (2400 ml), and the mixture was heated to 50 °C. At this temperature 2,3-dichloro-6-nitrobenzonitirile (**2** [14], 445.1 g, 2 mol) was added to the reaction mixture at a

rate as to keep the temperature between 75–81°C. After the addition was completed the reaction mixture was left to cool to room temperature, the crystals that precipitated were filtered off, and washed with conc. hydrochloric acid (100 ml), water (300 ml) and 2-propanol (100 ml) to yield **16** (340 g, 91%), *m.p.* 145–146 °C (purity measured with HPLC, 98.2 %).

Method 2 (catalytic hydrogenation)

To a solution of 2,3-dichloro-6-nitrobenzonitirile (**2** [14], 109.0 g, 0.5 mol) in tetrahydrofurane (800 ml) conc. hydrochloric acid (90 ml) and 10% Pd/C catalyst (12.0 g) were added and the mixture was hydrogenated at room temperature under 3–5 atm. hydrogen pressure for 3 hours (the consumption of hydrogen gas was 12.5 litres corresponding to 100% conversion). The catalysator was filtered off, the filtrate was made alkaline with conc. ammonium hydroxide (pH = 8) and the organic solvents were evaporated *in vacuo*. The crystals that precipitated from the remaining water solution were filtered off, washed with water (300 ml) and recrystallised from 2-propanol (400 ml; charcoal) to yield **16** (80.0 g, 86.1%), *m.p.* 141–145 °C (purity measured with HPLC 97.6%)

6-Amino-2,3-dichlorobenzylamine hydrochloride (**14**· HCl)

To a mixture of potassium borohydride (165 g, 3 mol) and tetrahydrofurane (1500 ml) a solution of trifluoroacetic acid (350 g, 3.0 mol) in tetrahydrofurane (300 ml) was added dropwise at a rate as to keep the reaction temperature between 15–20 °C. To the reduction mixture thus obtained a solution of 6-amino-2,3-dichlorobenzonitrile (**16**) (190.5 g, 1 mol) in tetrahydrofurane (450 ml) was added at a rate as to keep the reaction temperature between 25–30 °C. The reaction mixture thus obtained was stirred for further 6 hours at room temperature, then water (500 ml) was added and the mixture was left to crystallise. The inorganic crystals that precipitated were filtered off, the filtrate was freed of organic solvents by evaporation *in vacuo* and the residual water solution was extracted with dichloromethane (3 × 300 ml). The combined organic layers were dried ($MgSO_4$), filtered, and saturated with gaseous hydrogen chloride (2 moles). The crystals that precipitated were filtered off washed with dichloromethane (100 ml) and ether (100 ml) to yield **14**·HCl (175.6 g, 77.2%), *m.p.* 237–240 °C (dec.) HPLC purity 97%. – ^{1}H NMR: δ 4.1 (br, 2H, CH_2), 6.2 (br, 2H, 6-NH_2), 6.5 (br, 3H, CH_2-NH_3^+), 6.72 [d (J = 8.7 Hz), 1H, Ph-5], 7.20 [d (J = 8.7 Hz), 1H, Ph-4) ppm. – ^{13}C NMR: δ 36.3 (CH_2), 119.7 (PhC-5), 121.7 (PhC-3), 125.0 (PhC-2), 131.8 (PhC-4), 134.1 (PhC-1), 142.1 (PhC-6) ppm. – MS (EI): $M^{+\cdot}$ = 190, (CI) : $(M+H)^{+\cdot}$ = 191.

6-Amino-2,3-dichlorobenzylamine (**14**)

To a solution of 6-amino-2,3-dichlorobenzylamine hydrochloride (**14**·HCl) (21.5 g. 0.1mol), as obtained above in methanol (120 ml), sodium methylate (5.4 g, 0.1 mol) was added with stirring. The sodium chloride that precipitated was filtered off and the filtrate was evaporated *in vacuo* to dryness to yield **14** (18.8 g, 98%) as an oily product, that upon long standing at room temperature formed with the atmospheric carbon dioxide a crystalline adduct **14**·CO_2 (23 g) , *m.p.* 76–80 °C. – ^{1}H NMR: δ 3.85 (s, 2H, CH_2), 4.3 (br, 2H, 1-NH_2), 5.6 (br, 2H, 6-NH_2), 6.63 [d (J = 8.7 Hz), 1H, PhH-5], 7.14 [d (J = 8.7 Hz), 1H, PhH-4] ppm. – ^{13}C NMR: δ41.0 (CH_2), 114.9 (PhC-5), 117.7 (PhC-3), 124.5 (PhC-1), 128.8 (PhC-4), 131.3 (PhC-2), 147.9 (PhC-6), 161.0 (CO_2) ppm; MS (EI): $M^{+\cdot}$ = 190(60), $(M\text{-}NH_2)^{+\cdot}$ = 176(100), $(CO_2)^{+\cdot}$ = 44(40).

Ethyl N-(6-amino-2,3-dichlorobenzyl)glycinate (5), Ethyl N-(6-amino-2,3-dichlorobenzyl)-N-(ethoxycarbonyl-methylene)glycinate (**17**), and *6,7-Dichloro-4-(ethoxycarbonylmethylene)-1,2,3,4-tetrahydro-5H-1,4-benzodiazepin-2-one* (**18**)

To a suspension of 6-amino-2,3-dichloro-benzylamine hydrochloride (**14**· HCl) (46.0 g, 0.2 mol) and dioxane (300 ml), preheated to 100 °C triethylamine (60 ml, 0.43 mol) was added followed by dropwise addition of a solution of ethylbromoacetate (35.7g, 0.2 mole) in dioxane (200 ml) within 2 hours. The mixture was refluxed under stirring for 1 hour (within this time the reaction was completed, GC), filtered, and the filtrate was evaporated to dryness *in vacuo*. To the residual oily product an ethanolic solution of hydrogen chloride (60 ml, corresponding to 0.3 mol of hydrogen chloride) was added at 0 °C and stirred at this temperature for 2 hours. The crystals of **5**· HCl that precipitated were filtered off, dissolved in water (150 ml), and the solution made alkaline with potassium carbonate (pH = 9). The crystals that precipitated were filtered off and washed with 2-propanol (20 ml) to yield **5** (37.8 g, 68.3%), *m.p.* 57–58 °C (Lit [2] *m.p.* 56–60 °C). – ^{1}H NMR: δ 1.21[t (J = 7.0 Hz), 3H, CH_3), 3.35 (s, 2H, CH_2COOEt), 3.86 (s, 2H, $PhCH_2$), 4.12 [q (J = 7.0 Hz), 2H, OCH_2], 5.5 (b, 1H, NH), 5.7 (b, 2H, NH_2), 6.66 [d (J = 8.7 Hz), 1H, PhH-5], 7.18 [d (J = 8.7 Hz), 1H, PhH-4] ppm. – ^{13}C NMR: δ 13.9 (CH_3), 46.0 (CH_2COOEt), 48.4 ($PhCH_2$), 60.4 (OCH_2), 115.0 (PhC-5), 117.8 (PhC-3), 119.4 (PhC-1), 129.5 (PhC-4), 132.0 (PhC-2), 148.4 (PhC-6) ppm (the ^{13}C NMR and ^{1}H assignments were checked by 2D and INEPT). – MS (EI): $(M)^{+\cdot}$ = 276; (CI): $(M+H)^{+\cdot}$= 277.

In order to isolate the by-products of the reaction, the acidic ethanolic filtrate of **5**· HCl was made alkaline with triethylamine (pH = 8) and evaporated *in vacuo* to dryness. The oily residue was dissolved in chloroform (100 ml), extracted with water (2 × 50 ml), dried ($MgSO_4$) and evaporated *in vacuo* to dryness. The residual oily product was dry column flash chromatographed to yield successively:

Compound **17** (4.1 g, 5.6%), *m.p.* 99–101 °C; ν_{max} 1736 and 1723 cm^{-1} (CO). – ^{1}H NMR: δ 1.19 [t (J = 7.1 Hz), 6H, CH_3), 3.32* (s, 2H, CH_2COOEt), 3.48* (s, 2H, CH_2COOEt), 3.92 (s, 2H, $PhCH_2$), 4.12 [q (J = 7.1 Hz), 4H, OCH_2], 6.1 (b, 2H, NH_2), 6.62 [d (J = 8.8 Hz), 1H, PhH-5], 7.20 [d (J = 8.8 Hz), 1H, PhH-4] ppm. – ^{13}C NMR: δ 14.1(CH_3), 51.6 ($PhCH_2$), 53.7 (CH_2COO-Et), 60.2 (OCH_2), 114.4 (PhC-5), 116.8 (PhC-3), 118.7 (PhC-1), 129.7 (PhC-4), 132.4 (PhC-2), 149.0 (PhC-6), 172.0 (COOEt) ppm. – MS (EI): $M^{+\cdot}$ = 362, (CI): $(M+H)^{+\cdot}$= 363;

Compound **5** (3.8 g, 6.9%), *m.p.* 57–58 °C, that was identical (mixed *m.p.*, HPLC) with that of obtained above;

Compound **18** (3.5 g, 1.6%), *m.p.* 124–126 °C. ν_{max} 1740 and 1690 cm^{-1} (CO). – ^{1}H NMR: δ 1.20 [t (J = 7.1 Hz), 3H, CH_3), 3.33 (s, 2H, 4-NCH_2), 3.46 (s, 2H, 3-CH_2), 4.06 (s, 2H, 5-CH_2), 4.11[q (J = 7.1 Hz), 2H, OCH_2], 7.06 [d (J = 8.7 Hz), 1H, PhH-9], 7,55 [d (J = 8.7 Hz), 1H, PhH-8], 10.3 (b, 1H, NH) ppm. – ^{13}C NMR: δ14.1 (CH_3), 52.8 (5-CH_2), 56.2* (4-NCH_2), 57.5* (3-CH_2), 60.3 (OCH_2), 120.7 (PhC-9), 127.0 (PhC-5a), 128.3 (PhC-7), 129.9 (PhC-8), 131.9 (PhC-6), 139.5

(PhC-9a), 170.1* (2-CO), 170.3* (COOEt) ppm. – MS (EI): $M^{+\cdot}$ = 316, (CI): $(M+H)^{+\cdot}$ = 317.

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