

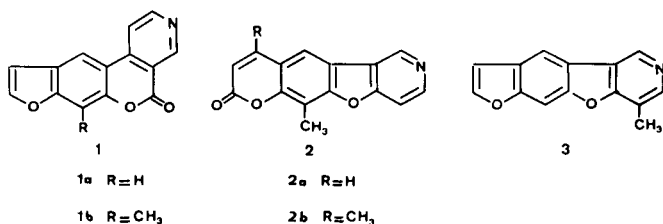
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4-Methylfuro[3',2':5,6]benzofuro[3,2-c]pyridine (**3**) was synthesized from 2-acetylfuro[3,2-f]benzo[*b*]furan (**4**) or from 2-acetyl-5,6-dihydrofuro[3,2-f]benzo[*b*]furan (**10**). The key step involves a rearrangement-cyclization of azides **6** and **12** to form 4-methylfuro[3',2':5,6]benzofuro[3,2-c]pyridin-1(2*H*)-one (**7**) and 8,9-dihydro-4-methylfuro[3',2':5,6]benzofuro[3,2-c]pyridin-1(2*H*)-one (**13**). Introduction of an aminoalkyl chain on carbon 1 was effected by substitution of 1-chloro-4-methylfuro[3',2':5,6]benzofuro[3,2-c]pyridine (**8**).

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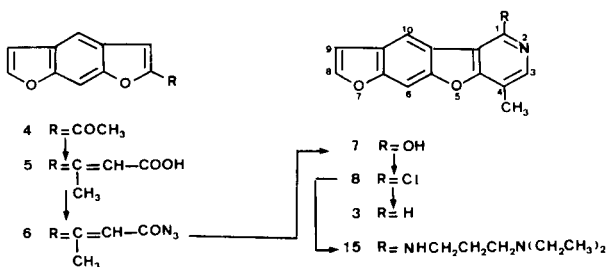
Recently we described the synthesis of 5*H*-furo[3',2':5,6]benzopyrano[3,4-*c*]pyridin-5-one (**1**) and 6-methyl-8*H*-pyrano[3',2':5,6]benzofuro[3,2-*c*]pyridin-8-one (**2**) [1], a new class of psoralen derivatives behaving as monofunctional DNA photobinding agents [2]. These compounds in combination with 365 nm light exhibit high antiproliferative activity [3]. In addition, **1a** and **1b** have been shown to possess photochemotherapeutic effectiveness in the topical treatment of psoriasis [4].



As a further development, we intended to prepare 4-methylfuro[3',2':5,6]benzofuro[3,2-*c*]pyridine (**3**), a new planar tetracyclic heterocycle in which the α -pyrone ring of the pyridopsoralen skeleton is replaced by a furan ring, with a view to evaluate the effect of this modification on photobiological activities.

The synthesis of the title compound has been accomplished by using 2-acetylfuro[3,2-*f*]benzo[*b*]furan (**4**) as starting material (Scheme 1). The sodium salt of triethylphosphonoacetate was condensed with ketone **4**. Subsequent hydrolysis gave acid **5** in 71% yield as a 1/2 mixture

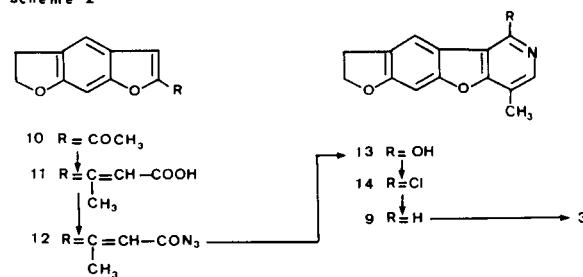
Scheme 1



of *Z* and *E* isomers. This crude isomeric mixture was converted to the acid azide **6** by the mixed anhydride method [5]. Rearrangement of the azide **6** with concomitant cyclization was accomplished by a modified Eloy and Deryckere reaction [6,7] to afford compound **7** in 74% yield, which was transformed into the chloro derivative **8** by refluxing in phosphorus oxychloride. The target compound **3** was obtained from **8** by reduction with zinc and acetic acid in 57% yield.

Alternatively compound **3** could also be obtained by palladium-charcoal dehydrogenation of the dihydro derivative **9** which was prepared from 2-acetyl-5,6-dihydrofuro[3,2-*f*]benzofuran (**10**) following the same general procedure employed for the synthesis of **3** (Scheme 2). However, the former route (Scheme 1) proved to be more convenient as it did not involve the dehydrogenation step required in the procedure outlined in Scheme 2. Furthermore this would allow the introduction of an aminoalkyl

Scheme 2



side chain on carbon 1 which is expected to increase the affinity of the molecule toward DNA. This was illustrated by the nucleophilic substitution of the chloro derivative **8** with excess of 3-(diethylamino)propylamine affording the [3-(diethylamino)propyl]amino derivative **15**.

EXPERIMENTAL

Melting points were determined with a Reichert hot-stage microscope and are uncorrected. The ir spectra were recorded on a Perkin-Elmer double beam spectrometer model 21. The nmr spectra were obtained

with a Varian XL100 (100-MHz) spectrometer operating in the Fourier transform mode. Mass spectra were recorded on a MS30 AEI Kratos apparatus equipped with a computer Varian 100MS. Elemental analyses were performed by the Service Central de Microanalyses du C.N.R.S.

6-Hydroxy-5-benzofurancarboxaldehyde [8].

This known compound was obtained from 2,3-dihydro-6-hydroxy-5-benzofurancarboxaldehyde [9] with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in refluxing dioxane, as previously described [10] for oxidation of 2,3-dihydro-6-hydroxy-7-methoxy-5-benzofurancarboxaldehyde to 6-hydroxy-7-methoxy-5-benzofurancarboxaldehyde.

2-Acetylfuro[3,2-*f*]benzo[*b*]furan (4).

6-hydroxy-5-benzofurancarboxaldehyde was converted to compound 4 as described in the literature [11] in 75% yield, mp 169-170° (lit mp [11] 169°).

2-Acetyl-5,6-dihydrofuro[3,2-*f*]benzo[*b*]furan (10).

Compound 10 was prepared from 2,3-dihydro-6-hydroxy-5-benzofurancarboxaldehyde [9] following the same procedure as described for 4 [11]. 2,3-Dihydro-6-hydroxy-5-benzofurancarboxaldehyde (6.56 g, 40 mmoles) was treated with chloroacetone (4.18 g, 45 mmoles) in 2-butanone (72 ml) in presence of potassium carbonate (12 g) at reflux for 30 minutes. Work-up followed by recrystallization from ethanol gave 6.2 g (76%) of 10, mp 157°; nmr (deuteriochloroform): δ 2.54 (s, 3H, COCH₃), 3.28 (t, 2H, J = 8.5 Hz, 5-CH₂), 4.68 (t, 2H, J = 8.5 Hz, 6-CH₂), 6.93 (1H, d, J = 0.4 Hz, 3-H), 7.4 (d, 1H, J = 0.8 Hz, 4-H), 7.43 (m, 1H, 8-H).

Anal. Calcd. for C₁₂H₁₀O₃: C, 71.28; H, 4.99. Found: C, 70.94; H, 4.90.

3-[2'(Furo[3,2-*f*]benzo[*b*]furyl)]crotonic Acid (5).

Sodium hydride (50% dispersion in mineral oil) (1.2 g, 25 mmoles) was washed twice with dry hexane under argon. To the dry residue in dry tetrahydrofuran (10 ml) triethylphosphonoacetate (5.67 g, 25.3 mmoles) was added dropwise with stirring and cooling. The reaction mixture was stirred at room temperature for 30 minutes then compound 4 (5.06 g, 25.3 mmoles) in tetrahydrofuran (160 ml) was added over 15 minutes. The red solution was stirred at room temperature for 1 hour and refluxed for 45 minutes. The solvent was evaporated, to the residue was added ethanol (20 ml), 2*N* potassium hydroxide (50 ml) and the mixture was refluxed for 2.5 hours. The cooled solution was diluted with water and extracted with methylene chloride. The aqueous layer was acidified with *N* hydrochloric acid and the resulting precipitate was collected, washed with water, dried and recrystallized from toluene to yield 4.39 g (72%) of acid 5 as a 1/2 mixture of *Z* and *E* isomers (as indicated by the nmr). A portion of this mixture was recrystallized twice from ethanol to give pure *E* isomer as pale yellow needles, mp 238-240°; nmr (DMSO-*d*₆): δ 2.52 (d, 3H, J = 1.3 Hz, CH₃), 6.51 (d, 1H, J = 1.3 Hz, C = CH-COOH), 7.06 (dd, 1H, J = 2.3 Hz, J = 0.7 Hz, 5-H), 7.47 (br s, 1H, 8-H), 7.91 (br s, 2H, 4-H and 3-H), 8.04 (d, 1H, J = 2.3 Hz, 6-H).

Anal. Calcd. for C₁₄H₁₀O₄: C, 69.42; H, 4.16. Found: C, 69.51; H, 4.14.

3-[2'(5',6'-dihydrofuro[3,2-*f*]benzo[*b*]furyl)]crotonic Acid (11).

Compound 11 was prepared following the procedure described above for 5. From the dihydro derivative 10 (5.59 g, 27.6 mmoles) there was obtained after recrystallization from toluene 5.1 g (75%) of acid 11 as a 1/2 mixture of *Z* and *E* isomers. A portion of this mixture was recrystallized twice from ethanol to give pure *E* isomer as pale yellow needles, mp 228-230°; nmr (DMSO-*d*₆): δ 2.46 (d, 1H, J = 1.2 Hz, CH₃), 3.26 (t, 2H, J = 8.5 Hz, 5-CH₂), 4.64 (t, 2H, J = 8.5 Hz, 6-CH₂), 6.38 (d, J = 1.2 Hz, C = CH-COOH), 7.02 (s, 1H, 3-H), 7.28 (s, 1H, 4-H), 7.49 (s, 1H, 8-H).

Anal. Calcd. for C₁₄H₁₂O₄: C, 68.84; H, 4.95. Found: C, 69.14; H, 4.93.

4-Methylfuro[3',2':5,6]benzofuro[3,2-*c*]pyridin-1(2*H*)-one (7).

Ethyl chloroformate (2.20 g, 20 mmoles) in acetone (30 ml) was added dropwise to a stirred solution at 0° of the crude mixture of acids 5 (4.38 g, 18 mmoles) and triethylamine (2.3 ml) in acetone (15 ml). Stirring was continued for 1 hour at 0°, then a solution of sodium azide (1.8 g, 27

mmoles) in water (5 ml) was added. The solution was poured in ice-water (200 ml). The resulting precipitate formed was filtered off and dried to afford 4 g (83%) of azide 6; ir (nujol): 2.150 cm⁻¹ (N₃).

A solution of the crude azide 6 (3.97 g, 14.8 mmoles) in diphenyl ether at 30° (50 ml) was added dropwise to a rapidly stirred mixture of diphenyl ether (50 ml) and tributylamine (5 ml) at 250° over 20 minutes. Stirring was continued for 15 minutes at 250°, then the solution was concentrated under reduced pressure to ca 70 ml and after cooling hexane was added. The precipitate was filtered off, washed with hexane and dried to afford 3.24 g (91%) of crude 7. Recrystallization from toluene gave colourless crystals, mp > 290° dec; nmr (DMSO-*d*₆): δ 2.32 (d, 3H, J = 1 Hz, 4-CH₃), 7.15 (dd, 1H, J = 2.2 Hz, J = 1 Hz, 9-H), 7.39 (br s, 1H, 10-H), 8.10-8.07 (m, 2H, 6-H and 8-H), 8.26 (br s, 1H, 3-H), 8.87 (m, 1H, NH).

Anal. Calcd. for C₁₄H₉NO₃: C, 70.29; H, 3.79; N, 5.86. Found: C, 70.56; H, 4.13; N, 5.59.

8,9-Dihydro-4-methylfuro[3',2':5,6]benzofuro[3,2-*c*]pyridin-1(2*H*)-one (13).

Compound 13 was prepared following the procedure described above for compound 7. From the crude mixture of acids 11 (5.59 g, 19.26 mmoles) there was obtained 4.41 g (85%) of azide 12; ir (nujol): 2.150 cm⁻¹ (N₃).

The azide 12 (4.3 g, 16 mmoles) gave 3.20 g (84%) of compound 13. Recrystallization from toluene afforded colourless needles, mp > 290° dec; nmr (deuteriochloroform): δ 2.34 (d, 3H, J = 1 Hz, CH₃), 3.35 (t, 2H, J = 8.5 Hz, 9-CH₂), 4.71 (t, 2H, J = 8.5 Hz, 8-CH₂), 7.01 (s, 1H, 6-H), 7.18 (d, 1H, J = 1 Hz, 3-H), 7.99 (s, 1H, 10-H).

Anal. Calcd. for C₁₄H₁₁NO₃: C, 69.70; H, 4.59; N, 5.80. Found: C, 69.98; H, 4.55; N, 6.03.

1-Chloro-4-methylfuro[3',2':5,6]benzofuro[3,2-*c*]pyridine (8).

Compound 7 (3 g, 11.67 mmoles) was refluxed with phosphorus oxychloride (80 ml) for 6 hours. Excess of phosphorus oxychloride was removed under reduced pressure. The residue was taken up in methylene chloride, treated with aqueous sodium carbonate and the mixture was stirred for 1 hour. The aqueous solution was extracted with methylene chloride. Evaporation of the solvent gave a residue which was recrystallized from toluene to give 1.6 g of compound 8, mp 202-203°; nmr (deuteriochloroform): δ 2.56 (d, 3H, J = 1 Hz, 4-CH₃), 6.96 (dd, 1H, J = 2.2 Hz, J = 1 Hz, 9-H), 7.73 (d, 1H, J = 1 Hz, 6-H), 7.74 (d, 1H, J = 2.2 Hz, 8-H), 8.22 (d, 1H, J = 0.7 Hz, 10-H), 8.46 (d, 1H, J = 1 Hz, 3-H).

Anal. Calcd. for C₁₄H₈ClNO₂: C, 65.25; H, 3.13; Cl, 13.77; N, 5.44. Found: C, 65.36; H, 3.09; Cl, 13.58; N, 5.21.

Chromatography of the mother liquor on silicagel with methylene chloride-ethanol (98/2) gave after recrystallization from toluene an additional crop of 0.36 g (overall yield 61%) of 8.

1-Chloro-8,9-dihydro-4-methylfuro[3',2':5,6]benzofuro[3,2-*c*]pyridine (14).

Compound 14 was synthesized following the procedure described above for the preparation of 8. From 13 (3.1 g, 12.8 mmoles) there was obtained 1.45 g (43%) of compound 14 as colourless crystals (from toluene), mp 180°; nmr (deuteriochloroform): δ 2.52 (d, 3H, J = 0.8 Hz, 4-CH₃), 3.38 (t, 2H, J = 8.5 Hz, 9-CH₂), 4.74 (t, 2H, J = 8.5 Hz, 8-CH₂), 7.02 (s, 1H, 6-H), 8.03 (1H, s, 10-H), 8.14 (d, 1H, J = 0.8 Hz, 3-H).

Anal. Calcd. for C₁₄H₁₀ClNO₂: C, 64.75; H, 3.88; N, 5.39. Found: C, 64.68; H, 3.91; N, 5.71.

8,9-Dihydro-4-methylfuro[3',2':5,6]benzofuro[3,2-*c*]pyridine (9).

Compound 14 (0.772 g, 2.98 mmoles) in ethyl acetate (100 ml) was hydrogenated at room temperature and atmospheric pressure in presence of anhydrous sodium acetate (0.24 g) using 10% palladium on charcoal (0.080 g) as catalyst. After 7 hours the catalyst was filtered off and washed with ethyl acetate. The filtrate was evaporated to dryness and the residue recrystallized from ethanol to afford 0.483 g (72%) of the dihydro derivative 9 as colourless needles, mp 174-175°; nmr (deuteriochloroform): δ 2.54 (s, 3H, 4-CH₃), 3.35 (t, 2H, J = 8.5 Hz, 9-CH₂), 4.72 (t, 2H, J = 8.5 Hz, 8-CH₂), 7.02 (s, 1H, 6-H), 7.75 (s, 1H, 10-H), 8.37 (s,

1H-3-H), 8.96 (br s, 1H, 1-H).

Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.60; H, 5.03; N, 6.33.

4-Methylfuro[3',2':5,6]benzofuro[3,2-c]pyridine (**3**).

Method A.

The chloro derivative **8** (0.23 g, 0.89 mmole) in acetic acid (3 ml) was refluxed with powdered zinc (0.36 g) for 2 hours. After cooling, the reaction mixture was filtered off and the solid washed with acetic acid. The filtrate was evaporated under reduced pressure, the residue was taken up in water and made alkaline with 20% aqueous sodium hydroxide. The aqueous solution was extracted with methylene chloride. Evaporation of the solvent gave a residue which was recrystallized from aqueous methanol to afford 0.114 g (57%) of compound **3** as colourless needles, mp 167-169°; nmr (deuteriochloroform): δ 2.59 (s, 3H, 4-CH₃), 6.92 (dd, 1H, J = 2 Hz, 9-H), 7.73 (m, 2H, 6-H and 8-H), 8.16 (s, 1H, 10-H), 8.46 (s, 1H, 3-H), 9.11 (s, 1H, 1-H); ms: M^+ (m/e) 233.

Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 75.32; H, 4.06; N, 6.28. Found: C, 74.88; H, 4.28; N, 5.94.

Method B.

A mixture of compound **9** (0.24 g, 1.06 mmoles), 10% palladium on charcoal (0.22 g) and diphenyl ether (2.5 ml) was refluxed for 4 hours; it was then filtered whilst hot and the catalyst washed with hot ethanol. After removal of the ethanol the mixture was chromatographed on silica gel (10 g), eluting the diphenyl ether with methylene chloride. Fractions eluted with methylene chloride-ethanol (95/5) were recrystallized from ethanol to afford 0.12 g (50%) of compound **3** identical in all respects to the sample obtained in A.

1-[3-(Diethylamino)propylamino]-4-methylfuro[3',2':5,6]benzofuro[3,2-c]pyridine (**15**).

A mixture of compound **8** (0.247 g, 0.96 mmoles) and 3-(diethylamino)propylamine (5 ml) was refluxed for 6 hours. Excess of amine was removed under reduced pressure, the residue was taken up in 1N sodium hydroxide and extracted with methylene chloride. Evaporation of the solvent gave a residue which was chromatographed on neutral alumina (30 g) with methylene chloride to give 0.315 g (89%) of **15**; nmr (deuteriochloroform): δ 1.13 (t, 2 x 3H, CH₃-CH₂), 1.93 (m, 2H, β -CH₂), 2.43 (d, 3H,

J = 0.7 Hz, 4-CH₃), 2.8-2.6 (m, 3 x 2H, γ -CH₂ and N-CH₂-CH₃), 3.78 (m, 2H, α -CH₂), 7.03 (br s, 1H, NH), 6.85 (dd, 1H, J = 2.2 Hz, J = 0.7 Hz, 9-H), 7.68-7.69 (m, 2H, 8-H and 6-H), 7.97 (d, 1H, J = 0.9 Hz, 10-H), 8.02 (s, 1H, 3-H).

To a stirred solution of maleic acid (0.15 g, 1.29 mmoles) in acetone (1 ml) was added amine **15** (0.167 g, 0.475 mmole) in the minimum of acetone. The resulting precipitate was filtered off, washed with acetone and recrystallized from ethanol to yield 0.197 g of the dimaleate salt of amine **15**, mp 176-177°.

Anal. Calcd. for $C_{29}H_{33}N_3O_4$: C, 59.68; H, 5.70; N, 7.20. Found: C, 59.96; H, 5.71; N, 7.35.

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