1-FUNCTIONALIZED 5,6-DIMETHYL-6H-PYRIDO [4,3-b] CARBAZOLES (ELLIPTICINES) AND ANALOGUES : A NEW RAPID SYNTHESIS.

Emile Bisagni+*, Marilys Rautureau+, and Christiane Huel++

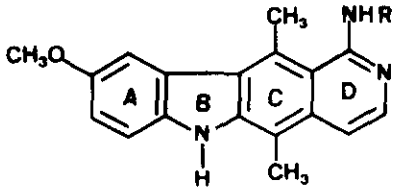
+UA 533 CNRS, Laboratoire de synthèse Organique and ++U. 219 INSERM, Biophysique,
Institut Curie, Section de Biologie, Bâtiments 110-112, 15, rue Georges Clémenceau 91405 ORSAY, FRANCE

Abstract — 4-Acetyl-2-chloro-3-lithiopyridine ethylene glycol ketal reacts with 3-formyl-5-methoxy-1-methylindole and 3-formyl-1-methyl-1H-pyrrolo [3,2-c] pyridine, giving the expected alcohols whose triethylsilane-trifluoroacetic acid reduction at room temperature followed by ketal hydrolysis and cyclisation in acidic medium leads in one step to 1-chloro-9-methoxy-5,6-dimethyl-6H-pyrido [4,3-b] carbazole and 10-chloro-5,6-dimethyl-5H-pyrido [3',4' : 4,5] pyrrolo [2,3-g] isoquinoline respectively, in 30 % overall yields.

1-Functionalized 11-nor-ellipticines and analogues are thus obtained via a two-step convergent pathway which appears to be particularly attractive for the rapid synthesis of various condensed heterocyclic systems.

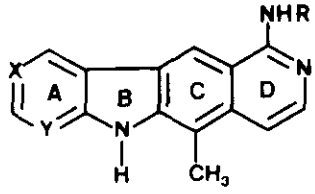
The remarkable antitumor properties of compounds 1 and 2 in rodents[1,2] prompted the clinical evaluation of these drugs for the treatment of human cancer. Phase I studies for compound 2 (BD-40) were quite promising[3] and stimulated further trials. Compound 1 (BD-84) is also currently under clinical evaluation. These two compounds are the most potent anticancer agents known among the ellipticine and 9-aza-ellipticine series. Some analogues with another dibasic side chain at the D nucleus are also of interest from the pharmacological point of view[4], but the nature of the A nucleus is determining with regard to tumor cell growth inhibition. For example, compound 3 and 7-hydroxyellipticine as well, have been reported to be inactive in vitro and in vivo[5,6].

Screening a number of analogues is a necessity to get further information about the key structural factors involved in metabolism and activity of these new drugs. However, no general method was available for the synthesis of such tetracyclic conjugated systems. For instance, compound 1 was obtained by a synthesis of the 6H-pyrido [4,3-b] carbazole system starting from the A nucleus[7], whereas compounds 2 and 3 were synthesized beginning from the C nucleus[5,8]. Transposition of these multi-step procedures proved to be difficult or unsuccessful in other series. We were therefore urged on finding a convergent pathway for these 1-functionalized heterocyclic systems. First attempts starting from 2-(2-methoxy-4-pyridyl)-4,4-dimethyl-2-oxazoline, led to the synthesis of 1-chloro-5-methylisoquinolines that could be fused via their [g] bond to various aromatic systems[9]. This method still suffered from a limited applicability but, with modifications, we were finally able to obtain the desired compounds using 2-chloro-4-acetylpyridine ethylene glycol ketal[10] as precursor[11]. In this paper we report on the application of this new protocol to the synthesis of 1 and 2 analogues.



1

R=$CH_2CH_2CH_2N(CH_2CH_3)_2$



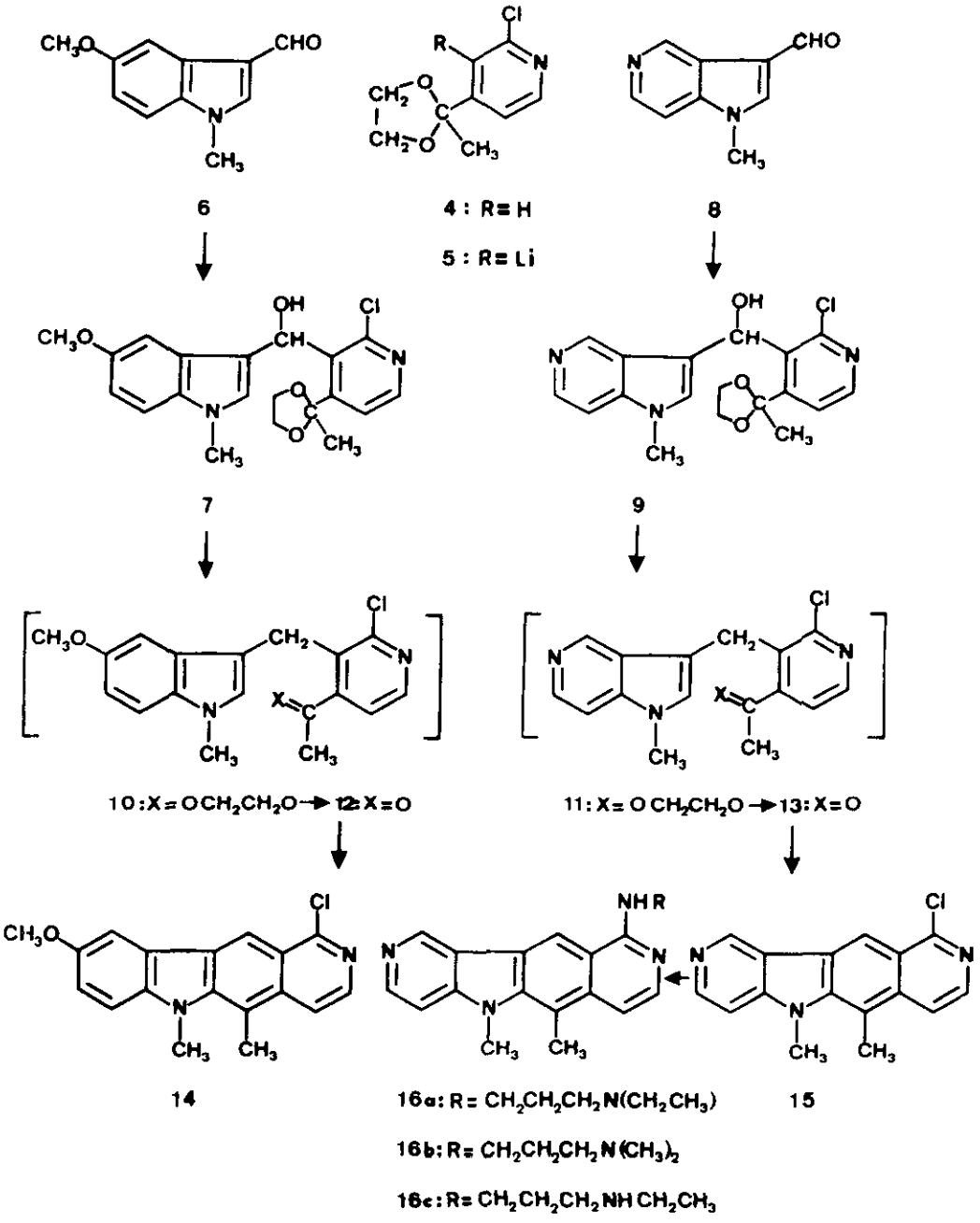
2 : X = N ; Y = CH

3 : X = CH ; Y = N

As described earlier[11], lithiation of 4-acetyl-2-chloropyridine ethylene glycol ketal 4 prepared as described[10] gave the 3-lithio derivative 5. The 4-acetyl-2-chloro-3-[α-3-(5-methoxy-1-methylindolyl)α-hydroxy] methylpyridine ethylene glycol ketal 7 was then obtained in 65 % yield upon reaction of 5 with 3-formyl-5-methoxy-1-methylindole 6 (prepared by Vilsmeier formylation of 5-methoxy-1-methylindole[12]). The reaction of 3-formyl-1-methyl-1H-pyrrolo [3,2-c] pyridine 8 (prepared from hexamethylene tetramine-trifluoroacetic acid formylation of 1-methyl-1H-pyrrolo [3,2-c] pyridine[13-15]) also led to the expected compound 9 (59 % yield).

Reduction of the alcohols 7 and 9 was performed in triethylsilane-trifluoroacetic acid medium[16]. This procedure, however, yielded complex mixtures due to partial hydrolysis of the ketals 10 and 11 into the ketones 12 and 13, followed by spontaneous acid-catalyzed cyclisation resulting in traces of the tetracyclic derivatives 14 and 15, as shown by thin layer chromatography. For the above-mentioned transformation to go to completion, the crude mixtures were evaporated and the residues treated with 50 % v/v sulfuric acid. After a 4 h incubation at 60°C and usual work-up, the mixture derived from 7 gave a 54 % yield of 1-chloro-9-methoxy-5,6-dimethyl-6H-pyrido [4,3-b] carbazole 14. This product is identical to that prepared earlier using an eleven-step procedure[4]. Upon treating the reduced mixture from 9 with 50 % v/v sulfuric acid for 24 h at room temperature, the novel 10-chloro-5,6-dimethyl-5H-pyrido [3',4': 4,5] pyrrolo [2,3-g] isoquinoline 15 was obtained in a 48 % yield.

SCHEME I


6
4 : R= H
5 : R= Li
8
7
9
10 : X = O CH2CH2O → 12 : X = O
11 : X = O CH2CH2O → 13 : X = O
14
16a : R = CH2CH2CH2N(CH2CH3)
16b : R = CH2CH2CH2N(CH3)2
16c : R = CH2CH2CH2NH CH2CH3
15

The overall yields for the 6 → 14 and 8 → 15 transformations were 35.1 % and 28.3 %, respectively.

Thus, 1-chloro-substituted derivatives of ellipticine and related compounds can now be obtained in only two steps by reaction of the lithio ketal 5 with the aldehydes 6 and 8. Furthermore, the preparation of the precursor aldehydes is no problem, even in large amounts. This will undoubtedly facilitate the production of large series of new products with antitumor potential. This will also permit selective ^{14}C-radiolabeling of drugs for use in transport, metabolic and pharmacokinetic studies. On the other hand, the 1-chloro function must be substituted by alkylamino chains for greater biological efficiency[1,2,4]. Compounds 16a-16c have been prepared accordingly and are currently under comparative tests with their N-5 non-methylated analogues in cell cultures and in animal tumor models.

EXPERIMENTAL

All melting points (uncorrected) were determined with a Kofler apparatus. ^1H nmr spectra were recorded with a Varian XL100 spectrometer. Me_4Si was used as internal standard and chemical shifts are reported on the δ scale, with peak multiplicities. Elemental analysis were performed by the Service Central de Microanalyses du CNRS (91190 Gif-sur-Yvette, FRANCE).

3-Formyl-5-methoxy-1-methyl-indole (6).

To dimethylformamide (DMF, 35 ml) maintained below 15°C with an ice bath, phosphorous oxychloride (9 ml) was progressively added, under stirring. A solution of 5-methoxy-1-methyl-indole[12] (14.1 g) in DMF (25 ml) was then added at once. The heterogeneous mixture was heated to 110°C for 5 min and then maintained under stirring at 65°C for a 30 min period. The cooled mixture was decomposed by water (200 ml) and basified with a 5N sodium hydroxide solution. The resulting solid was filtered, washed with water and recrystallized from ethanol to afford 14.53 g (87 %) of colorless needles, mp 134°C.

Anal. Calc. for $C_{11}H_{11}NO_2$: C, 69.82 ; H, 5.86 ; N, 7.40. Found : C, 69.84 ; H, 7.71 ; N, 7.4.

^1H nmr ($CDCl_3$) δ : 3.82 + 3.90 (2s, 2 x 3H, NCH_3 + OCH_3), 6.97 (d, 1H, 6-H, J_{6-7}= 8.3 Hz, J_{6-4}= 2.5 Hz), 7.24 (d, 1H, 7-H), 7.80 (d, 1H, 4-H), 9.94 (s, 1H, CHO).

3-Formyl-1-methyl-1H-pyrrolo [3,2-c] pyridine (8).

A mixture of 1-methyl-1H-pyrrolo [3,2-c] pyridine[13] (2.64 g, 20 mmol), hexamethylenetetramine (5.6 g, 40 mmol) and trifluoroacetic acid (35 ml) was refluxed for 3 h. After addition of 3N-hydrochloric acid (100 ml) heating at reflux was continued for 3 h and the mixture was evaporated to dryness under reduced pressure. The residue was taken up in water (75 ml) and neutralized by 1N sodium hydroxide solution. The mixture was saturated with sodium chloride and extracted with methylene chloride (3 x 50 ml). Evaporation of solvent gave a solid residue which was recrystallized twice in ethyl acetate to give 2.3 g (72 %) of colourless crystals, mp 109-110°C.

Anal. Calc. for $C_9H_8N_2O$: C, 67.50 ; H, 5.0 ; N, 17.50. Found : C, 67.46 ; H, 5.08 ; N, 17.34.

^{1}H nmr ($CDCl_3$) δ : 3.83 (s, 3H, CH_3), 7.21 (dd, 1H, 7-H, J_{7-6}= 5.7 Hz, J_{7-4}= 1 Hz), 7.65 (s, 1H, 2-H), 8.42 (d, 1H, 6-H), 9.45 (d, 1H, 4-H), 9.93 (s, 1H, CHO).

4-Acetyl-2-chloro-3-[α-3-(5-methoxy-1-methylindolyl) α-hydroxy] methylpyridine ethylene glycol ketal (7).

To anhydrous tetrahydrofuran (THF, 100 ml) cooled in ice and maintained under argon, a 1.6 N solution of n-butyllithium in hexane (15 ml, 24 mmol) and anhydrous diisopropylamine (3.36 ml, 24 mmol) were added successively under stirring. This mixture was maintained at 0°C for 1 h, then cooled down to -70°C, and 4-acetyl-2-chloropyridine ethylene glycol ketal 4[10] (4 g, 20 mmol, in 10 ml of THF) was added in one portion. After 4 h under stirring at -70°C, a solution of aldehyde 6 (3.78 g, 20 mmol) in THF (20 ml) was added dropwise. The resulting mixture was stirred at -70°C for a further 2 h period, then at ambient temperature for 15 h, poured in water (200 ml) and extracted with methylene chloride (3 x 60 ml). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was crystallized in ethyl acetate (20 ml) and the filtered solid was recrystallized in the same solvent to give 5.05 g (64 %) of colourless crystals, mp 125°C.

Anal. Calc. for $C_{20}H_{21}ClN_2O_4$: C, 61.78 ; H, 5.44 ; N, 7.21 ; Cl, 9.12. Found : C, 61.98 ; H, 5.30 ; N, 7.31 ; Cl, 9.42.

^{1}H nmr ($CDCl_3$) δ : 1.73 (s,3H,CH_3), 3.66 (s,3H,NCH_3), 3.58-3.95 (m,2 x 2H,CH_2CH_2), 3.85 (s,3H,OCH_3), 4.24 (d,1H,OH,J_{OH-CH} = 11.6 Hz), 6.39 (s,1H,2-H,Ar), 6.89 (m,2H,CH-OH + 6-H Ar), 7.15-7.27 (m,2H,4-H Ar + 7-H Ar), 7.60 (d,1H,5-H py, J_{5-6} = 5.3Hz), 8.37 (d,1H,6-H py).

4-Acetyl-2-chloro-3-[α-3-(1-methyl-1H-pyrrolo [3,2-c] pyridyl)-α-hydroxy]-methylpyridine ethylene glycol ketal (9).

The reaction was performed as described in the preceding paragraph, with the same ratios of solvent and compounds but starting from aldehyde 8 (3.2 g, 20 mmoles). After the usual work-up, 4.24 g (59 %) of colourless crystals, mp 150°C, were obtained.

Anal. Calc. for $C_{18}H_{18}ClN_3O_3$: C, 60.09 ; H, 5.04 ; N, 11.68 ; Cl, 9.85. Found : C, 59.92 ; H, 5.22 ; N, 11.62 ; Cl, 9.84. ^{1}H nmr ($CDCl_3$) δ : 1.74 (s,3H,CH_3), 3.59-3.96 (m,2 x 2H, CH_2-CH_2), 3.72 (s,3H,NCH_3), 4.35 (br s,1H,OH), 6.61 (s,1H,2-H Ar), 6.82 (broad s,1H,CH-OH), 7.20 (d,1H,7-H Ar, J_{6-7} = 6Hz), 7.61 (d,1H,5-H py, J_{5-6} = 5.5Hz), 8.33 (d,1H,6-H Ar), 8.38 (d,1H,6-H py), 8.81 (s,1H,4-H Ar).

1-chloro-9-methoxy-5,6-dimethyl-6H-pyrido [4,3-b] carbazole (14).

A mixture of compound 7 (388 mg, 1 mmol) triethylsilane (0.18 ml, 1.1 mmol) and trifluoroacetic acid (2 ml) was stirred at ambient temperature for 20 h and evaporated to dryness under reduced pressure. To the residue, water (5 ml) and sulfuric acid d = 1.86 (5 ml) were added successively ; the mixture was heated to 60°C for 4 h, then allowed to stay at ambient temperature for 15 h under stirring. The solution was diluted with water (50 ml),

basified with ammonia and extracted with methylene chloride (5 x 50 ml). Evaporation of solvent led to a semi-solid residue which was taken up and recrystallized in the minimum amount of ethyl acetate, giving 170 mg (55 %) of yellow microcrystals, mp 206°C. This compound was identical to that already described but obtained by a 11 step sequence[4].

^{1}H nmr (not described in ref. 4) ($CDCl_3$) δ = 3.07 (s,3H,5-CH_3), 3.99 + 4.13 (2s,2 x 3H,OCH_3 + NCH_3), 7.28-7.38 (m,2H,7-H + 8-H), 7.72 (dd,1H,10-H,J_{10-8} = 2.5Hz, J_{10-7} = 0.7Hz), 7.83 (dd,1H,4-H,J_{4-3} = 6.1Hz,J_{4-11} = 1Hz), 8.21 (d,1H,3-H), 8.90 (d,1H,11-H).

10-Chloro-5,6-dimethyl-5H-pyrido [3',4, : 4,5] pyrrolo [2,3-g] isoquinoline (15).

Reduction of compound 9 (720 mg, 2 mmol) was performed with triethylsilane (0.64 ml, 4 mmol) in trifluoroacetic acid (4 ml) at ambient temperature for 24 h. The residue from evaporation was stirred in 50 % aqueous sulfuric acid (20 ml) at room temperature for 24 h and basified with ammonia. Extraction with methylene chloride (6 x 50 ml) and evaporation of solvent gave a residue which was taken up and recrystallized in the minimum volume of ethyl acetate. 271 mg (48 %) of pale yellow crystals, mp 256°C were obtained in this preparation.

Anal. Calc. for $C_{16}H_{12}ClN_3$: C, 68.21 ; H, 4.29 ; N, 14.92 ; Cl, 12.58. Found : C, 67.93 ; H, 4.23 ; N, 14.98 ; Cl, 12.51.

^{1}H nmr ($(CD_3)_2SO$) δ : 3.14 (s,3H,5-CH_3), 4.03 (s,3H,NCH_3), 7.70 (dd,1H,4-H,J_{4-3} : 5.9Hz,J_{4-1} = 0.6Hz), 8.14 (dd,1H,7-H,J_{7-8} = 6Hz,J_{7-11} = 0.8Hz), 8.29 (d,1H,8-H), 8.66 (d,1H,3-H), 9.14 (br s,1H,11-H), 9.63 (br s,1H,1-H).

10-[1-(3-Diethylamino)-propylamino]-5,6-dimethyl-5H-pyrido [3',4': 4,5] pyrrolo [2,3-g] isoquinoline (16a).

Compound 15 (400 mg) in 3-diethylaminopropylamine (20 ml) was heated in an oil-bath to 160°C for 6 h. Excess 3-diethylaminopropylamine was then eliminated by evaporation under reduced pressure. The residue was taken up in water (100 ml), basified with an N-sodium hydroxide solution and extracted with methylene chloride (3 x 100 ml). Evaporation of solvent left a residue which was recrystallized twice in cyclohexane to give 476 mg (89 %) of a grey solid corresponding to the hydrate of 16, mp 149°C.

Anal. Calc. for $C_{23}H_{29}N_5.H_2O$: C, 70.23 ; H, 7.89 ; N, 17.81. Found : C, 70.80 ; H, 7.74 ; N, 17.65. ^{1}H nmr ($(CD_3)_2SO$) δ : 1.02 (t,2 x 3H,$(CH_2\underline{CH_3})_2$), 1.86 (m,2H,β-CH_2), 2.45-2.66 (m,6H,$(\underline{CH_2}CH_3)_2$ + γ-CH_2), 2.99 (s,3H,6-CH_3), 3.61 (m,2H,α-CH_2), 4.17 (s,3H,5-$N\underline{CH_3}$), 7.14 (d,1H,7-H,J_{7-8} = 6.3Hz), 7.59 (broad s,1H,NH), 7.62 (dd,1H,4-H,J_{4-3} = 5.8Hz, J_{4-1} = 0.8Hz), 8.57 (d,1H,3-H), 9.01 (s,1H,11-H), 9.29 (d,1H,1-H).

Trimaleate of 16a : The solution of the preceding base (406 mg) in boiling acetone (50 ml) was added at once to a solution of maleic acid (415 mg) in acetone (50 ml) and the mixture was heated at reflux for 1 min. After cooling the resulting solid was filtered and air dried to give 736 mg (94 %) of grey microcrystals of the trimaleate salt dihydrate, mp 193°C.

Anal. Calc. for $C_{35}H_{41}N_5O_{12}.2H_2O$: C, 55.33 ; H, 5.93 ; N, 9.22. Found : C, 55.18 ; H, 5.80 ; N, 9.05.

10-[1-(3-dimethylamino) propylamino]-5,6 dimethyl-5H-pyrido [3',4': 4,5] pyrrolo [2,3-g] isoquinoline (16b).

Compound 15 (2 g) was heated in 3-dimethylaminopropylamine (100 ml) at reflux for 48 h and excess amine was evaporated in vacuo. The residue was taken up in water, basified with N-sodium hydroxide solution and extracted with methylene chloride. After evaporation of solvent, the residue was recrystallized from cyclohexane, then from toluene to give 1.14 g of a solid. This solid was treated with an excess of maleic acid as indicated above to afford 2.16 g (43.8 %) of trimaleate salt dihydrate, mp 170°C.

Anal. Calc. for $C_{33}H_{37}N_5O_{12}$, H_2O : C, 55.54 ; H, 5.47 ; N, 9.82. Found : C, 55.60 ; H, 5.43 ; N, 9.89.

^{1}H nmr (D_2O) δ : 2.4 (m,2H,β-CH_2), 3.04 (s,2 x 3H,N$(CH_3)_2$), 3.07 (s,3H,6-CH_3), 3.5 (m,2H,γ-CH_2), 3.84 (t,2H,α-CH_2), 4.3 (s,3H,5-NCH_3), 6.07 (s,6H,CH = CH maleate), 7.55 (d,1H,7-H,J_{7-8} = 7.7Hz), 7.69 (d,1H,8-H), 8.05 (d,1H,4-H,J_{4-3} = 7Hz), 8.74 (d,1H,3-H), 9.15 (s,1H,11-H), 9.47 (s,1H,1-H).

10-[1-(3-Ethylamino) propylamino] 5,6-dimethyl-5H-pyrido [3',4': 4,5] pyrrolo [2,3-g] isoquinoline (16c).

A mixture of compound 15 (300 mg) and 3-ethylaminopropylamine (15 ml) was heated in an oil bath at 140°C for 5 h and excess amine was evaporated. The oily residue was treated with an excess of maleic acid as for compound 16a (560 mg ; 73 %) as solid trimaleate hydrate, mp 165-170°C were obtained.

Anal. Calc. for $C_{33}H_{37}N_5O_{12}$. H_2O : C, 55.54 ; H, 5.47 ; N, 9.82. Found : C, 55.37 ; H, 5.58 ; N, 10.17.

^{1}H nmr (D_2O) δ: 1.35 (t,3H,$CH_2\underline{CH_3}$), 2.29 (m,2H,β-CH_2), 2.96 (s,3H,6-CH_3), 3.24 (m,2 x 2H,$\underline{CH_2}CH_3$ + γ-CH_2), 3.75 (t,2H,α-CH_2), 4.21 (s,3H,NCH_3), 6.11 (s,6H,CH = CH-maleate), 7.44 (d,1H,7-H,J_{7-8} = 8Hz), 7.63 (d,1H,8-H), 7.90 (d,1H,4-H,J_{4-3} = 6.9Hz), 8.65 (d,1H,3-H), 8.94 (s,1H,11-H), 9.32 (s,1H,1-H).

REFERENCES

1. C. Ducrocq, F. Wendling, M. Tourbez-Perrin, C. Rivalle, P. Tambourin, F. Pochon, E. Bisagni, and J.-C. Chermann, J.Med. Chem., 1980, **23**, 1212.
2. C. Lidereau, J.-C. Chermann, J. Gruest, L. Montagnier, C. Ducrocq, C. Rivalle, and E. Bisagni, Bull. Cancer, 1980, **67**, 1.
3. M. Marty, C. Jasmin, P. Pouillard, C. Gisselbrecht, G. Gouvenia, and H. Magdelainat, 17th Annual Meeting of Am. Soc. Clin. Oncol.,1981, C-108.
4. C. Rivalle, F. Wendling, P. Tambourin, J.-M. Lhoste, E. Bisagni, and J.-C. Chermann, J. Med. Chem., 1983, **28**, 181.
5. C. Rivalle, C. Ducrocq, J.-M. Lhoste, F. Wendling, E. Bisagni, and J.-C. Chermann, Tetrahedron, 1981, **37**, 2097.
6. C. Auclair and C. Paoletti, J. Med. Chem., 1981, **24**, 289.

7. E. Bisagni, C. Ducrocq, J-M. Lhoste, C. Rivalle, and A. Civier, J. Chem. Soc. Perkin I, 1979, 1706.

8. C. Ducrocq, E. Bisagni, C. Rivalle, and J.-M. Lhoste, J. Chem. Soc. Perkin I, 1979, 142.

9. E. Bisagni and M. Rautureau, Synthesis, 1987, 142.

10. J-L. Lamattina, J. Het. Chem., 1983, 20, 353.

11. E. Bisagni, M. Rautureau, M. Croisy-Delcey, and C. Huel, Can. J. Chem., 1987, 65, 2027.

12. W.A. Remers, G.J. Gibs, C. Pidacks, and M.J. Weiss, J. Org. Chem., 1971, 36, 279.

13. E. Bisagni, J.D. Bourzat, and J. André Louisfert, Tetrehedron, 1970, 26, 2087.

14. A.J. Verbiscar, J. Med. Chem., 1972, 15, 149.

15. N. Balzevic, D. Kolbach, B. Belin, V. Sunjic, and F. Kapfez, Synthesis, 1979, 161.

16. D.N. Kursanow, Z.N. Parmes, and N.M. Loin, Synthesis, 1974, 633.

Received, 29th February, 1988