Pergamon

Tetrahedron Letters, Vol. 36, No. 11, pp. 1845-1848, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00138-7

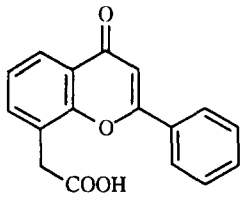
Synthesis of the 3-aminoflavone-8-acetic acid

Daniel Dauzonne* and Laetitia Martinez

Laboratoire de Chimie associé au CNRS,
Institut Curie, Section de Biologie, 26 rue d'Ulm, 75231 PARIS Cedex 05, France.

Abstract: The synthesis of the so far unknown 3-amino-4-oxo-2-phenyl-4*H*-1-benzopyran-8-acetic acid (3-aminoflavone-8-acetic acid) starting from 2-hydroxy-3-(prop-2-ene)benzaldehyde and (*Z*)-(2-chloro-2-nitroethenyl)benzene is described.

Flavone-8-acetic acid (**1**; FAA, NSC 347512, LM 975, Mitoflaxone) has aroused considerable attention since the discovery, in the mid-eighties, of its exceptional and selective activity on several murine solid tumors that are resistant to most chemotherapeutic drugs.[1] Unfortunately, these promising properties were not confirmed in man and the exploratory clinical trials conducted with this compound led to disappointing results.[1f, 2]



Flavone-8-acetic acid (1)

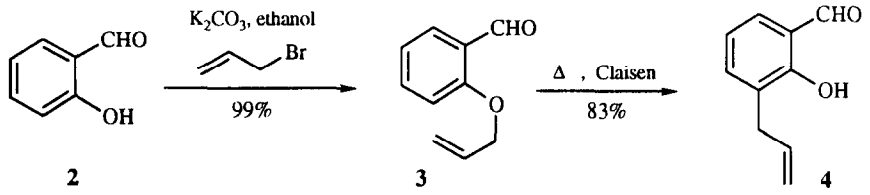
The observed discrepancies in activity between animal and man are still difficult to explain since , at the present time, the mechanism of action of FAA remains unclear in spite of an abundant literature dealing with extensive studies of its biological properties and its pharmacokinetical behaviour.[3] Furthermore, no structure-activity relationships are yet apparent although a number of works have been devoted to several derivatives of FAA itself[1a-c, 4] or to related series such as 2-phenylquinoline-8-carboxamides,[5] flavone-8-carboxylic acids,[6] (2-styrylchromon-8-yl)acetic acids,[7] xanthenone-4-acetic acids,[8] 9-oxo-9,10-dihydroacridines-4-acetic acids[9] and various other topologically connected compounds.[10] However, to our knowledge, no modified FAA bearing a nitrogen atom at the 3-position is hitherto known.

In this context, we considered the synthesis of the title compound to be an attractive project with the aim of evaluating the biological potentiality of such 3-amino derivatives of **1**.

This undertaking was all the more interesting for us, since this type of product could be prepared by adapting a methodology developed in our laboratory a few years ago to provide access to 2-aryl-3-nitro-4*H*-1-benzopyran-4-ones (3-nitroflavones) *via* the 2-aryl-3-chloro-3,4-dihydro-4-hydroxy-3-nitro-2*H*-1-benzopyrans.[11] This synthesis uses 2-hydroxybenzaldehydes and (*Z*)-β-chloro-β-nitrostyrenes as starting materials. In the present case, the choice of a conveniently substituted 2-hydroxybenzaldehyde is primordial, because it must bear in the 3-position (the future 8-position of the flavone), a substituent susceptible of giving rise to a carboxymethyl group.

In this connection, we thought that an allyl substituent could be a better precursor than the halomethyl groups previously employed as intermediates in the preparation of other FAA derivatives.[1c, 4e, 10] In fact, the herein reported strategy reduces the number of operations because it necessitates only one oxidation step to obtain the desired carboxylic acid, instead of the multistep procedures involving successive substitutions followed by hydrolysis of a cyano group which have been usually described.[1c, 4e, 7a, 8b-e, 10]

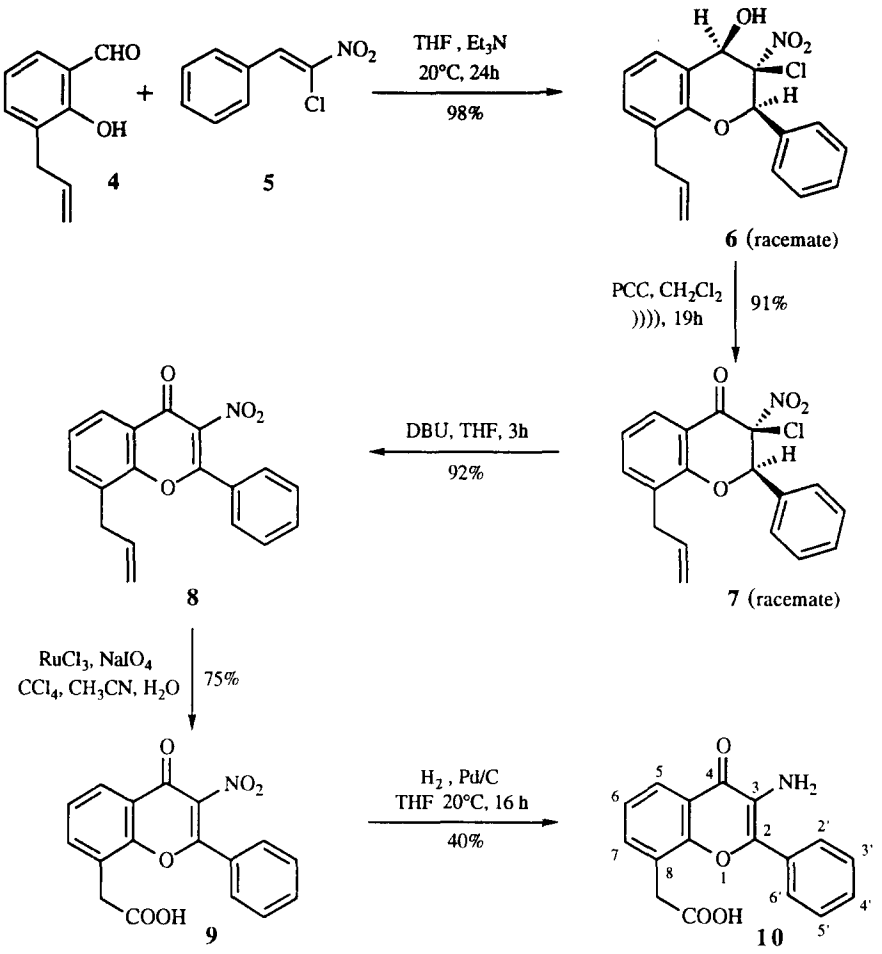
The required starting 2-hydroxy-3-(prop-2-ene)benzaldehyde (**4**) was easily obtained on a large scale from salicylaldehyde (**2**), *via* a Claisen rearrangement of the intermediate 2-allyloxybenzaldehyde (**3**), according to a known procedure[12] outlined in Scheme 1 below :



2 3 4

Scheme 1

Further reactions leading to the wanted 2-aminoflavone-8-acetic acid (**10**) are depicted in Scheme 2. Condensation of **4** with (2-chloro-2-nitroethenyl)benzene (**5**) in tetrahydrofuran in the presence of triethylamine gave the benzannelated oxygen-containing heterocycle **6**, as a racemate, in the exclusive relative configuration 2*R*, 3*R*, 4*R*.[11a] Subsequent ultrasound-assisted oxidation of **6** by pyridinium chlorochromate in dichloromethane yielded the oxo-derivative **7** (with the relative configuration 2*R*, 3*S*) which was then converted into the nitroflavone **8** by treatment with diazabicyclo[5.4.0]undec-7-ene in tetrahydrofuran. Oxidative cleavage of the allylic double bond of **8** was achieved by adapting a procedure reported by Sharpless and co-workers, using the system ruthenium (III) chloride / sodium periodate in the ternary mixture carbon tetrachloride / acetonitrile / water as solvent,[13] to provide the 3-nitro-4-oxo-2-phenyl-4*H*-1-benzopyran-8-acetic acid (**9**) in good yield. Finally, catalytic reduction of the nitro group by hydrogen in the presence of palladium on charcoal in tetrahydrofuran gave the expected 3-amino-4-oxo-2-phenyl-4*H*-1-benzopyran-8-acetic acid (**10**; 3-aminoflavone-8-acetic acid).[14]



Scheme 2

Additional experiments, carried out with the object of improving the yield of the aminoflavone **10** starting from the nitro compound **9**, are currently being conducted.

The biological investigations for the FAA derivatives **9** and **10** are still in progress and their results will be reported in the near future together with those obtained for other related products.

References and Notes

1. (a) Briet, P.; Berthelon, J.-J.; Collonges, F. *Eur. Pat.* **1983**, 80934 ; *Chem. Abstr.* **1983**, *99*, 175594. (b) Briet, P.; Berthelon, J.-J.; Collonges F. *Fr. Demande* **1984**, 2536397; *Chem. Abstr.* **1984**, *101*, 230357. (c) Atassi, G.; Briet, P.; Berthelon, J.-J.; Collonges, F. *Eur. J. Med. Chem.-Chim. Thér.* **1985**, *20*, 393-402. (d) Plowman, J.; Narayanan, V.L.; Dykes, D.; Szarvasi, E.; Briet, P.; Yoder, O.C.; Paull, K.D. *Cancer Treat. Rep.* **1986**, *70*, 631-5. (e) O'Dwyer, P.J.; Shoemaker, D.; Zaharko, D.S.; Grieshaber, C.; Plownan, J.; Corbett, T.; Valeriote, F.; King, S.A.; Cradock, J.; Hoth, D.F.; Leyland-Jones, B. *Cancer Chemother. Pharmacol.* **1987**, *19*, 6-10. (f) Armand, J.P.; De Forni M.; Recondo G.; Cals L.; Cvitkovic E.; Munck J.N. in: *Progress in Clinical and Biological Research*, Vol. 280, *Plants Flavonoids in Biology and Medicine II*, Cody, V.;Middleton, E.; Harborne, J.B.; Beretz, A. (eds.), Alan, R., Liss. Inc., New York, **1988** 235-41.

(g) Bibby M.C.; Double J.A.; Phillips R.M.; Loadman P.M.; Gummer J.A. in Ref.1f p. 243-6. (h) Desoize, B.; Carpentier, Y.; Guerrier, D. *Anticancer Res.* **1989**, *9*, 1701-5. (i) Bowler, K.; Pearson, J.A. *Anticancer Res.* **1992**, *12*, 1275-80.

2. (a) Kerr, D.J.; Maughan, T.; Newlands, E.; Rustin, G.; Bleehen, N.M.; Lewis, C.; Kaye, S.B. *Br. J. Cancer* **1989**, *60*, 104-6. (b) Kaye, S.B.; Clavel, M.; Dodion, P.; Monfardini, S.; ten Bokkel-Huinink, W.; Wagener, D.T.; Gundersen, S.; Stoter, G.; Smith, J.; Renard, J. van Glabbeke, M.; Cavalli, F. *Invest. New Drugs* **1990**, *8*, S95-9. (c) Olver, I.N.; Webster, L.K.; Bishop, J.F.; Stokes, K.H. *Cancer Chemother. Pharmacol.* **1992**, *29*, 354-60.
3. (a) Cummings, J.; Kerr, D.J.; Kaye, S.B.; Smyth, J.F. *J. Chromatogr.* **1988**, *431*, 77-85. (b) Cummings, J.; Smyth, J.F. *Cancer Chemother. Pharmacol.* **1989**, *24*, 269 and references cited therein. (c) Baguley, B.C.; Calveley, S.B.; Crowe, K.K.; Fray, L.M.; O'Rourke, S.A.; Smith, G.P. *Eur. J. Cancer Clin. Oncol.* **1989**, *25*, 263-9. (d) Ching, L.M.; Baguley, B.C. *Eur. J. Cancer Clin. Oncol.* **1989**, *25*, 1513-5. (e) Rabinovitz, M. *J. Natl. Cancer Inst.* **1989**, *81*, 962. (f) Sayers, T.J.; Wiltrout, T.A.; McCormick, K.; Husted, C.; Wiltrout, R.H. *Cancer Res.* **1990**, *50*, 5414-20. (g) Triozzi, P.L.; Rinehart, J.-J.; Malspeis, L.; Young, D.C.; Grever, M.R. *Cancer Res.* **1990**, *50*, 6483-5. (h) Thomsen, L.L.; Ching L.M.; Baguley, B.C. *Cancer Res.* **1990**, *50*, 6966-70. (i) Futami, H.; Hornung, R.L.; Back, T.T.; Bull, R.; Gruys, E.; Wiltrout, R.H. *Cancer Res.* **1990**, *50*, 7926-31. (j) De Neve, W.; Evelhoch, J.; Everett, C.; Simpson, N.; Bissery, M.C.; Corbett, T.; Valeriote, F. *Int. J. Radiat. Oncol. Biol. Phys.* **1990**, *18*, 1359-65. (k) Elitsur, Y.; Bull, A.W.; Luk, G.D. *Clin. Immunol. Immunopathol.* **1990**, *57*, 96-104. (l) Damia, G.; Garofalo, A.; Rossi, C.; Giavazzi, R.; D'Incalci, M. *Anticancer Res.* **1990**, *10*, 437-9. (m) Brodfuehrer, J.; Valeriote, F.; Chan, K.; Heilbrun, L.; Corbett, T. *Cancer Chemother. Pharmacol.* **1990**, *27*, 27-32. (n) Damia, G.; Tagliabue, G.; Allavena, P.; D'Incalci, M. *Cancer Immunol. Immunother.* **1990**, *32*, 241-4. (o) Wurm, G. *Dtsch. Apoth. Ztg.* **1990**, *130*, 2306-12 and references cited therein. (p) Bibby, M.C. *Br. J. Cancer* **1991**, *63*, 3-5 and references cited therein. (q) Pratesi, G.; Manzotti, C.; Tortoreto, M.; Audisio, R.A., Zunino, F. *Br. J. Cancer* **1991**, *63*, 71-4. (r) Thurston, G.; Smith, K.A.; Murray, J.C. *Br. J. Cancer* **1991**, *64*, 689-92. (s) Wiltrout, R.; Horning, R. *U.S. Pat.* **1991**, 533442; *Chem. Abstr.* **1991**, *115*, 85412. (t) Hill, S.A.; Williams, K.B.; Denekamp, *J. Int. J. Radiat. Biol.* **1991**, *60*, 379-84. (u) Smith, K.A.; Thurston, G.; Murray, J.C. *Int. J. Radiat. Biol.* **1991**, *60*, 389-93. (v) Chabot, G.G.; Gouyette, A. *Biochem. Pharmacol.* **1991**, *42*, 1145-8. (w) Murray, J.C.; Clauss, M.; Denekamp, J.; Stern, D. *Int. J. Cancer* **1991**, *49*, 254-9. (x) Ching, L.M.; Joseph, W.R.; Li, Z.; Atwell, G.J.; Rewcastle, G.W.; Denny, W.A.; Baguley, B.C. *Eur. J. Cancer* **1991**, *27*, 79-83. (y) Zwi, L.J.; Baguley, B.C.; Gavin, J.B.; Holdaway, K.M.; Wilson, W.R. *Oncol. Res.* **1992**, *4*, 333-9. (z) Thomsen, L.L.; Baguley, B.C.; Wilson, W.R. *Cancer Chemother. Pharmacol.* **1992**, *31*, 151-5. (aa) Thomsen, L.L.; Ching, L.M.; Joseph, W.R.; Gavin, G. B. *Biochem. Pharmacol.* **1992**, *43*, 2401-6. (ab) Veszelovsky, E.; Thomsen, L.L.; Zhuang, L.; Baguley, B.C. *Eur. J. Cancer* **1993**, *29A*, 404-8. (ac) Candeias, L.P.; Everett, S.A.; Wardman, P. *Free Radical Biol. Med.* **1993**, *15*, 385-94. (ad) Relling, M.V.; Evans, R.R.; Groom, S.; Crom, W.R.; Pratt, C.B. *J. Pharmacokinet. Biopharm.* **1993**, *21*, 639-51. (ae) Bibby, M.C.; Double, J.A. *Anti-Cancer Drugs* **1993**, *4*, 3-17 and references cited therein. (af) Smit, J.A.; Stark, J.H.; *Radiat. Res.* **1994**, *137*, 84-8. (ag) Ching, L.M.; Joseph, W.R.; Crosier, K.E.; Baguley, B.C. *Cancer Res.* **1994**, *54*, 870-2. (ah) Everett, S.A.; Candéias, L.P.; Denny, W.A.; Wardman, P. *Anti-cancer Drug Design* **1994**, *9*, 68-72.
4. (a) Aono, T.; Mizuno, K. *Eur. Pat.* **1988**, 283761; *Chem. Abstr.* **1989**, *110*, 75319. (b) Briet, P.; Berthelon, J.-J.; Collonges, F. *Eur. Pat.* **1989**, 341104; *Chem. Abstr.* **1990**, *113*, 23516. (c) Aristoff, P.A.; *P.C.T. Int.* **1990**, 9008143; *Chem. Abstr.* **1991**, *114*, 42387. (d) Wiltrout, R.H.; Hornung, R. *US. Pat.* **1992**, 5126129; *Chem. Abstr.* **1992**, *117*, 184852. (e) Aitken, R.A.; Bibby, M.C.; Double, J.A.; Phillips, R.M.; Sharma, S.K. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2313-6.
5. Atwell, G.J.; Baguley, B.C.; Denny, W.A. *J. Med. Chem.* **1989**, *32*, 396-401
6. Cutler, S.J.; El-Kabbani, F.M.; Keane, C.; Fisher-Shore, S.L.; McCabe, F.L.; Johnson, R.K.; DeWitt Blanton Jr, C. *Eur. J. Med. Chem.* **1993**, *28*, 407-14.
7. (a) Zammattio, F.; Brion, J.D.; Belachmi, L.; Le Baut, G. *J. Heterocyclic Chem.* **1991**, *28*, 2013-9. (b) Brion, J.D.; Le Baut, G.; Zammattio, F.; Pierre, A.; Atassi, G.; Belachmi, L. *Eur. Pat.* **1991**, 454587; *Chem. Abst.* **1992**, *116*, 106092.
8. (a) Denny, W.A.; Baguley, B.C.; Atwell, G.J.; Rewcastle, G.W. *Eur. Pat.* **1988**, 278176; *Chem. Abst.* **1989**, *110*, 8048. (b) Rewcastle, G.W.; Atwell, G.J.; Baguley, B.C.; Calveley, S.B.; Denny, W.A. *J. Med. Chem.* **1989**, *32*, 793-9. (c) Atwell, G.J.; Rewcastle, G.W.; Baguley, B.C.; Denny, W.A. *J. Med. Chem.* **1990**, *33*, 1375-9. (d) Rewcastle, G.W.; Atwell, G.J.; Zhuang, L.; Baguley, B.C.; Denny, W.A; *J. Med. Chem.* **1991**, *34* , 217-22. (e) Rewcastle, G.W.; Atwell, G.J.; Palmer, B.D.; Boyd, P.D.W.; Baguley, B.C.; Denny, W.A. *J. Med. Chem.* **1991**, *34*, 491-6. (f) Ching, L.M.; Joseph, W.R.; Baguley, B.C. *Biochem. Pharmacol.* **1992**, *44*, 192-5.
9. Gamage, S.A. Rewcastle, G.W.; Atwell, G.J.; Baguley, B.C.; Denny, W.A. *Anti-Cancer Drug Design* **1992**, *7*, 403-14.
10. Atwell, G.J.; Rewcastle, G.W.; Baguley, B.C.; Denny, W.A. *Anti-cancer Drug Design* **1989**, *4*, 161-9.
11. (a) Dauzonne, D.; Demerseman, P. *Synthesis* **1990**, 66-70. (b) Dauzonne, D.; Grandjean, C. *Synthesis* **1992**, 677-80.
12. Claisen, L.; Eisleb, O. *Justus Liebigs Ann. Chem.* **1913**, *40*, 21-119.
13. Carlsen, P.H.J.; Katsuki, T.; Martin, V.S.; Sharpless, K.B. *J. Org. Chem.* **1981**, *46*, 3936-8.
14 Selected data for **10**: m.p. 190-192°C. microanalysis (Found: C, 68,98; H, 4,34; N, 4,91; $C_{17}H_{13}NO_4$ requires C, 69,15; H, 4,44; N 4,74). MS: (DCI / NH_3, m/z) = 296 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ (ppm / TMS): 3,92 (s, 2H, CH_2) ; 4,79 (br. s, 2H, NH_2) ; 7,39 (t, 1H, H-6, J = 7,3Hz) ; 7,50-7,60 (m, 3H, H-3', H-4', H-5') ; 7,69 (dd, 1H, H-7, J = 1,1 and 7,3 Hz) ; 8,00 (d, 2H, H-2', H-6' J = 7,5 Hz) ; 8,04 (dd, 1H, H-5, J = 1,1 and 7,3 Hz) ; (the signal of the acidic proton is indiscernible).

(*Received in France* 16 *December* 1994; *accepted* 16 *January* 1995)