Tetrahedron Letters,Vol.28,No.42,pp 5029-5032,1987
Printed in Great Britain

0040-4039/87 $3.00 + .00
Pergamon Journals Ltd.

REDUCTION OF THE ANTICANCER DRUG "NITRACRINE". ACCESS TO DIHYDROPYRAZOLO- AND DIHYDROPYRIMIDINO-ACRIDINES

W.M. CHOLODY[1], M.F. LHOMME[2*] and J. LHOMME[2*]

1 - Laboratory of Chemistry and Biochemistry of Antitumor Compounds, Institute of Organic and Food Chemistry and Technology, Polytechnical University, 80952 Gdansk, Poland.
2 - Laboratoire de Chimie Organique Biologique - UA 351 - Université de Lille Flandres Artois, 59655 Villeneuve d'Ascq France.

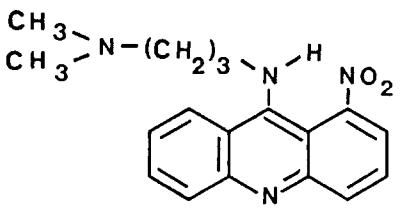
This work is dedicated to the memory of Professor A. LEDOCHOWSKI.

Abstract : Reduction of the anticancer drug nitracrine 1 leads to the dihydropyrazoloacridine 3 by heterocyclisation. New dihydropyrimidinoacridines 8, 9 and 10 are also described.

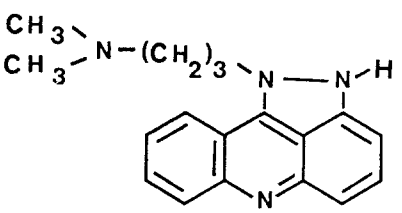
1-Nitro-9-(dimethylaminopropylamino)acridine 1 (generic name nitracrine) was discovered in Poland and is currently used in that country as an anticancer drug (1). Its mode of action is not yet clearly established, but it has been shown to form reversible complexes with DNA *in vitro* and to bind covalently to DNA *in vivo* (2). It has been suggested by Konopa that enzymatic reduction of the nitro group to the hydroxylamino derivative may be responsible for covalent binding (3). In a program devoted to the study of biologically active nitroaromatics (4), we have examined the chemical reduction of nitracrine. We now show that in our conditions the hydroxylaminoderivative is not detected, instead we isolate the reduction cyclisation product 3. The other reduction products 2 and 4 give an access to a new dihydropyrimidinoacridine system 8, 9.

Different conditions have been described to selectively reduce nitroaromatics into hydroxylamines. However the course of the reaction varies greatly depending on the structure of the compounds and the yields frequently drop dramatically due to the instability of the

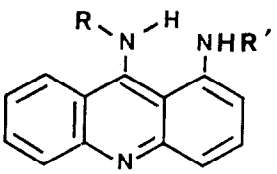
hydroxylamino group. Reductions involving Palladium or Raney nickel catalysts have been used. To provide a general route to arylhydroxylamines of biological interest (as mutagenic and carcinogenic metabolic species) J.G. Westra reported reductions which make use of hydrazine hydrate in the presence of palladium over charcoal in THF as solvent (5). This method is particularly efficent to reduce polycyclic nitroaromatics but is given to fail with monocyclic systems. We treated nitracrine under these conditions and obtained a mixture of mainly three compounds 2, 3 and 4 (6) in ratios depending on the precise conditions : 2 results from total reduction of the nitro group into the amino-group. It is the major compound isolated (50-90 % yield) ; 4 arises from reduction accompanied by substitution of the labile secondary 9-aminogroup. Its ratio increases (90 % yield) with an excess of hydrazine ; the structure was confirmed by independant two-step synthesis, i.e., substitution of 1-nitro-9-chloroacridine by hydrazine hydrate followed by reduction ; the last compound isolated 3 possesses an additional five membered-ring. It is obtained as a minor constituent (20 % yield) when ether is used as a solvent. However changing the reduction conditions to Raney nickel in dry ether gives the latter cyclization product 3 in a 55 % yield along with the amino derivative 2 (45 %). The structure of 3 is deduced from elemental analysis, mass spectrum and ^1H NMR data (7). Compound 3 is unstable in solution (methanol, ether, chloroform...) and in the presence of air and light, giving unidentified mixtures.

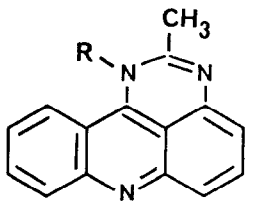


1



3





2	: R = $(CH_2)_3N(CH_3)_2$	R' = H
4	: R = NH_2	R' = H
5	: R = H	R' = H
6	: R = $(CH_2)_3N(CH_3)_2$	R' = Ac
7	: R = NHAc	R' = Ac

8	: R = $(CH_2)_3N(CH_3)_2$
9	: R = NHAc
10	: R = H

Under no reaction conditions could we isolate the hydroxylamino derivative resulting from reduction of the nitro group. A possible explanation could be partial reduction of the nitrogroup to a species which is trapped intramolecularly by the 9-aminogroup. Several species may be hypothesized, among which the electrophilic nitroso derivative which might cyclize by nucleophilic attack by the aminogroup and then be further reduced. Due to steric compression between the 1 and 9 positions, this scheme seems more probable than further reduction of the nitroso group to the hydroxyl amino derivative followed by cyclization.

Compression factors and proximity effects between positions 1 and 9 were used further to prepare the new tetracyclic skeleton of the dihydropyrimidinoacridines 8, 9 and 10. Acetylation of the reduction derivatives 2 and 4 (Ac_2O, $CHCl_3$, 20°, 2h) gave the acetamides 6 and 7 which were readily cyclized (HCl, MeOH, 20°, 1h) into 8 and 9 (10). The N-9 unsubstituted derivative 10 was similarly prepared starting from 1-nitro-9-aminoacridine. Reduction with hydrazine hydrate (Pd/C, Et_2O, 20°, 3h) gave 1-9-diaminoacridine 5. Treatment with acetic anhydride in chloroform (20°, 3h) gave directly the cyclized compound 10.

The present results further illustrate the peculiarities of the nitracrine system (8), due to compression and proximity effects between positions 1 and 9. The interest resides at two levels : 1/ The inability to detect any hydroxylamine derivative in any of the nitracrine reduction conditions used, and also the isolation of the cyclization-reduction product 3 may be of much biological significance. This result brings into question the possible existence and the involvement of the hydroxylamine derivative as a key metabolite of nitracrine, responsible for covalent binding to DNA. In this respect nitracrine may diverge from the most frequently proposed mode of binding of polycyclic nitroaromatics to DNA (9). The cyclization-reduction product 3 is now examined as a possible metabolite of the drug.
2/ Secondly these results open a route to new tetracyclic dihydropyrazolo- and dihydropyrimidino-acridines having potential DNA-binding properties.

REFERENCES AND NOTES :

* Present adress : LEDSS Bât. 52, UA 332, Université de Grenoble I, B.P. 68 - 38402 St Martin d'Hères Cédex France

1. A. LEDOCHOWSKI, Materia Medica Polona, (1976), 8, 237 ; M. GNIAZDOWSKI, J. FILIPSKI, M. CHORAZY, Antibiotics V/2, (1979) p. 275 - Ed. F.E. FAHN, Springer-Verlag Berlin.
2. J. FILIPSKI, B. MARCZYNSKI, M. CHORAZY, Acta Biochim. Polon., (1975), 22, 119 ; J. FILIPSKI, B. MARCZYNSKI, L. SADZINSKA, G. CHALUPKO, M. CHOROZY, Biophys. Acta, (1977), 478, 33 ; M. GNIAZDOWSKI, E. CIESIELSKA, L. SZMIGIERO, Chem. Biol. Interactions, (1981), 34, 355.
3. J.W. PAWLAK, J. KONOPA, Biochem. Pharmacol., (1979), 28, 3391 ; K. PAWLAK, A. MATUSZKIEWICZ, J.W. PAWLAK, J. KONOPA, Chem. Biol. Interactions, (1983), 43, 131.
4. M. DEMEUNYNCK, N. TOHME, M.F. LHOMME, J.M. MELLOR, J. LHOMME, J. Amer. Chem. Soc., (1986), 108, 3539.

5. J.W. CRAMER, J.A. BELAND, J. Chem. Soc., (1960), 235, 885 ; J.G. WESTRA, Carcinogenesis, (1981), 2, 355.

6. All new compounds showed satisfactory analysis and spectroscopic data.

7. Typical values for 2 are : MP : 117-118°C ; UV (methanol) : 435 (4300), 269 (30800), 223 (22100) nm ; NMR (DMSO d_6) δ: 1.58-2.29 (m, 4H), 2.06 (s, 6H), 3.81 (t, 2H), 6.09-7.83 (m, 7H), 7.46 (s, 2H), 9.90 (s, 1H) ; $C_{18}H_{22}N_4$: Calc. %C : 73.43, %H : 7.53, %N : 19.04 ; found %C : 73.16, %H : 7.49, %N : 18.95 ; MS : M^+ : 294, m/e : 236, 222.
Typical values for 3 are : MP : 166-168°C ; UV (methanol) : 409 (8700), 343 (17200), 227 (52700) nm ; NMR (DMSO d_6) δ : 1.90-2.35 (m, 4H), 2.05 (s, 6H), 4.50 (t, 2H), 5.70 (d, 1H), 6.30-7.30 (m, 5H), 7.65 (d, 1H), 9.95 (s, 1H) ; $C_{18}H_{20}N_4$: calc. %C ; 73.94, %H : 6.89, %N 19.16 ; found. %C : 74.10, %H : 6.83, %N : 18.91 ; MS : M^+ : 292, m/e : 234, 220, 207, 178, 155, 139.
Typical values for 4 are : MP : 163-164°C ; UV (methanol) : 385 (7800), 318 (7600), 225 (49300) nm ; NMR (DMSO d_6) δ: 5.98 (s, 2H), 6.63 (s, 2H), 6.02-8.28 (m, 7H), 9.36 (s, 1H) ; $C_{13}H_{12}N_4$: calc. %C : 69.62 ; %H : 5.39 ; %N : 24.98 ; found %C : 69.57 ; %H : 5.28 ; %N : 24.90 ; MS : M^+ : 224, m/e : 208, 194, 177.

8. V.B. PETT, M. ROSSI, J.P. GLUSKER, J.J. STEZOWSKI, M. BOGUCKA-LEDOCHOWSKA, Bioorganic Chem., (1982), 11, 443.

9. E. KRIEK, J.G. WESTRA, Chemical Carcinogens and DNA, (1979), 2, 3, Ed. P.L. GROVER, CRC Press. Boca. Raton., Fla. ; B. SINGER, D. GRUNBERGER, Molecular Biology of Mutagens and Carcinogens, (1983), p. 132, Plenum Press, N-Y ; J.B. STENLAKE, Foundations of Molecular Pharmacology, (1979), 2, p 444, The Athlone Press, London.

10. Typical values for 8 are : MP : 121°C ; UV (methanol) : 459 (5400), 341 (3500), 269 (43100), 233 (19700) nm ; NMR (DMSO d_6) δ : 1.60-1.90 (m, 4H), 1.75 (s, 6H), 2.50 (s, 3H), 4.50 (t, 2H), 6.80 (d, 1H), 7.10-7.80 (m, 5H), 8.10 (d, 1H) ; $C_{20}H_{22}N_4$: calc. %C : 75.40, %H : 6.96, %N : 17.59 ; found %C : 75.05, %H : 6.78, %N : 17.26 ; MS : M^+ : 318, m/e : 260, 233, 191, 164, 154.

(Received in France 29 July 1987)