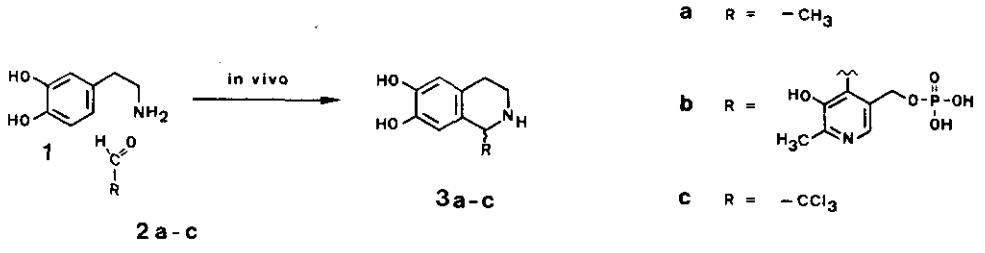
FIRST SYNTHESIS OF 1-TRICHLOROMETHYL-6,7-DIHYDROXY-TETRAHYDRO-ISOQUINOLINE - AN IMAGINABLE CHLORAL-DERIVED MAMMALIAN ALKALOID[1]

Gerhard Bringmann*, Annette Hille, and Marianne Zsiška

Organisch-Chemisches Institut der Universität Münster
Orléansring 23, D-4400 Münster, West Germany

Abstract- 1-Trichloromethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (3c), a potential condensation product from dopamine (1) and chloral (2c), could be prepared for the first time, by a stepwise Bischler-Napieralski pathway, and, more directly, under *special Pictet-Spengler conditions*. The results indicate that 3c is not a probable alkaloid in man.

Reactive carbonyl compounds like acetaldehyde (2a) and pyridoxal phosphate (2b) can undergo spontaneous Pictet-Spengler[2] type condensation reactions with aryl ethylamines like dopamine (1) in mammalians[3], leading to tetrahydroisoquinoline alkaloids. Some of these (like 3a) have already been known, in optically active form, from the plant kingdom, whereas others, e.g. the vitamin B_6 derived pyridoxyl alkaloid 3b, represent completely novel structures[4].

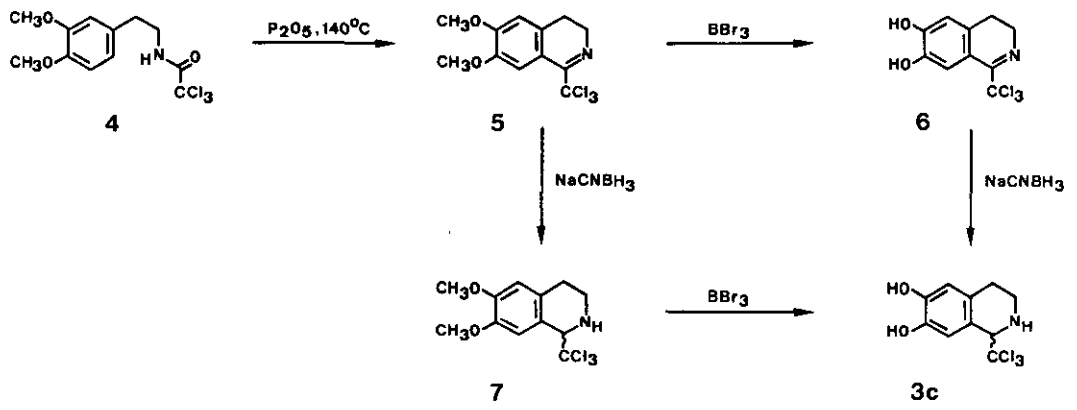


Scheme 1

A formally highly reactive aldehyde, for which the formation of alkaloid-type heterocycles has to be taken into consideration, is chloral (2c), the oldest synthetic narcotic[5]. Obviously still indispensable e.g. for an interruption of the status epilepticus, its hydrate is still administered in gram quantities, even to children - despite well known side effects to heart, kidneys, and liver, and despite the existing danger of addiction[6].

An examination of the reactivity of chloral (2c) towards dopamine (1) is interesting not only with respect to the mentioned chloral therapy, but also on account of the expected trichloromethyl tetrahydroisoquinoline alkaloid 3c - an unprecedented structural type with possibly remarkable physiological properties: 3c simultaneously bears the pharmacophoric aryl ethylamine element like its neurotransmitter precursor dopamine (1), and the huge, lipophilic CCl_3 group, common to the insecticide DDT and to a small number of natural products, e.g. from marine organisms[7].

However, condensation experiments reveal that dopamine (1) does not form tetrahydroisoquinolines with chloral[8] under "physiological conditions", not even at elevated temperature, or under water-free conditions, starting from non-hydrated chloral (2c), itself. In order to be able to identify even trace amounts of 3c that might, nonetheless be formed *in vivo*, as well as for an analysis of potential decomposition products and for an investigation of its biological activity, we consequently have developed a first, stepwise, but "secure"[9] pathway to 3c, involving a Bischler-Napieralski ring closure (see Scheme 2):

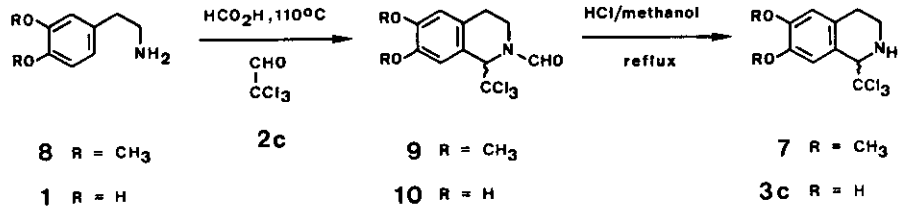


Scheme 2

The trichloroacetamide 4[10], prepared from homoveratrylamine and trichloroacetyl chloride (97 %) proves to be astonishingly stable, e.g. towards $POCl_3$ in refluxing toluene. It can, nonetheless, quite conveniently be ring closed under more drastic Bischler-Napieralski conditions, e.g. using P_2O_5/seasand in refluxing xylene, to give 5[11] (colourless crystals of mp 122°C) in 42 % yield (44 % of 4 reisolated by crystallization from cyclohexane). 5 is thermally stable but rapidly decomposes photochemically. From 5, the target compound 3c can be obtained by two different pathways: O-Demethylation of 5 with BBr_3 in dichloromethane gives 6[11] as yellow crystals (hydrobromide; mp >205°C [decomp.], yield 93 %), sensitive to light and air. Further reduction with $NaBH_4$, or, far better, with $NaCNBH_3$ (yield 93 %) affords the free tetrahydroisoquinoline 3c[11] as colourless crystals (mp >130°C [decomp.]). Better yields, starting from 5, are obtained, by first performing the reduction step ($NaCNBH_3$) to give the still protected tetrahydroisoquinoline 7[11,12] (mp 116°C, yield 92 %), which can then easily be O-demethylated, again with BBr_3, to afford 3c in 97 % yield.

With this reference compound 3c now readily available, and in view of its thermal stability, especially under acidic conditions, we looked more closely at more direct synthetic strategies, using special Pictet-Spengler conditions, such as ring closure reactions via N-acyliminium ions, which have been found to be suited even

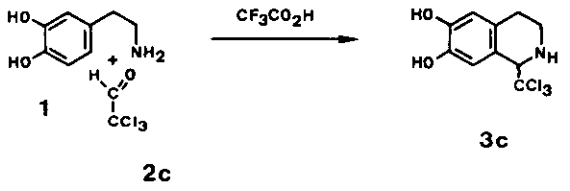
for the synthesis of tetrahydroisoquinolines entirely lacking oxygen functions[13]. Thus, refluxing homoveratrylamine (8) in formic acid and subsequent addition of water-free chloral (2c) (1 equivalent) indeed affords the corresponding tetrahydroisoquinoline formamide 9[11] (mp 110°C, yield 85 %) (see Scheme 3):



Scheme 3

Encouraged by this first successful Pictet-Spengler condensation with chloral (2c), we have analogously reacted unprotected dopamine (1), to afford 10[11] (mp >198°C [decomp.], yield 89 %), thus saving a subsequent O-demethylation step. N-Deformylation of 10 by treatment with 0.5 N hydrochloric acid in methanol (reflux) yields 3c (88 %), identical with the material obtained above in the four-step Bischler-Napieralski synthesis.

Still more rationally, the Pictet-Spengler condensation of 1 with water-free chloral (2c) can be performed in refluxing trifluoroacetic acid (95 %), then directly leading to unprotected 3c (see Scheme 4)!



Scheme 4

This successful one-step synthesis of 3c allows the facile preparation of this potential mammalian alkaloid for extended physiological tests, and as a reference substance for its search in body liquids of patients treated with chloral hydrate.

The lacking tendency of chloral (2c) to react with dopamine (1) spontaneously and nonenzymatically under physiological conditions, combined with the pronounced instability of 3c at neutral and basic pH-values, however, indicates that the occurrence of 1-trichloromethyltetrahydroisoquinolines does not have to be expected.

ACKNOWLEDGEMENT

This work was supported by the Minister für Wissenschaft und Forschung des Landes Nordrhein-Westfalen and by the Fonds der Chemischen Industrie.

REFERENCES AND NOTES

1. "Endogenous Alkaloids in Man", part 5, for part 4, see ref. 3e.

2a. A. Pictet and T. Spengler, Ber., 44, 2030 (1911).
b. W. Whaley and T. Govindachari, Org. React., 6, 151 (1951).

3a. A. Brossi, Heterocycles, 3, 343 (1975).
b. M.A. Collins, "Alcohol and Opiates", ed. by K. Blum, Academic Press, New York, 1977, p. 155.
c. G. Bringmann, Naturwissenschaften, 66, 22 (1979).
d. M.A. Collins, "The Alkaloids", Vol. XXI, ed. by A. Brossi, Academic Press, New York, 1983, p. 329.
e. G. Bringmann, S. Schneider, and A. Hille, Nachr. Chem. Tech. Lab., 34, 222 (1986).

4. G. Bringmann and S. Schneider, Angew. Chem., 98, 167 (1986); Angew. Chem. Int. Ed. Engl., 25, 177 (1986).

5a. C. Stumpf, "Neuropharmakologie", 3rd ed., Springer-Verlag, Wien, 1985, p. 56.
b. W. Pschyrembel, "Klinisches Wörterbuch", 255th ed., de Gruyter, Berlin, 1985, p. 272.

6a. G. Kuschinsky and H. Lüllmann, "Kurzes Lehrbuch der Pharmakologie und Toxikologie", 8th ed., Thieme Verlag, Stuttgart, 1978, p. 210.
b. E. Mutschler, "Arzneimittelwirkungen", 8th ed., Wissenschaftliche Verlagsgesellschaft, Stuttgart, 1986, p. 160.

7. For a recent review, see: D.J. Faulkner, Nat. Prod. Rep., 1986, 1.

8. A similar lack of reactivity of chloral towards aryl ethyl amines had been described for tryptophan: H.R. Snyder, C.H. Katz, S.M. Parmerter, and E.C. Spaeth, J. Am. Chem. Soc., 70, 219 (1948).

9. However, also for Bischler-Napieralski-type reactions, difficulties had to be expected, due to the report[2b] that trichloroacetamides had failed to give the desired cyclization products.

10. C. Viel, J.-M. Arnaud, R. Dorme, A. Cheutin, and P. Rumpf, Bull. Soc. Chim. France, 1967 (2), 431.

11. All new compounds have been fully characterized by spectroscopic and analytic methods. Details will be reported in a full paper.

12. 7 had previously been prepared by trichloromethylation of 6,7-dimethoxy-3,4-dihydroisoquinoline. However, no experimental, physical, or spectroscopic data had been denoted: S. Queroix and J. Gardent, C. R. Acad. Sci. Paris (C), 276, 703 (1973).

13. L.K. Lukanov, A.P. Venkov, and N.M. Mollov, Synthesis, (in press).

Received, 5th June, 1987