# 65. 2-Bis(dimethylamino)phosphinoyl-1-lithio-1,2,3,4-tetrahydroisoquinoline. A Highly Nucleophilic d¹-Reagent for the Preparation of 1-Substituted Tetrahydroisoquinolines

Preliminary communication

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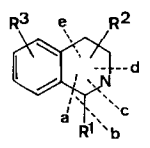
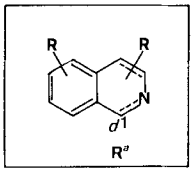
*Summary*

The title compound **4** is generated from the phosphoric amide **5** in tetrahydrofuran with butyllithium. The lithium reagent **4** is stable at room temperature; its reactions with electrophiles furnish the products **6**–**22**, **26**, **27**, see *Table 1* and the *Scheme*. A second alkylation is also possible, see **23**–**25**. The cleavage to tetrahydroisoquinolines is accomplished in refluxing aqueous-methanolic hydrochloric acid, see *Table 2*. Phosphinoylation, lithiation, reaction with electrophiles and cleavage constitute an efficient sequence for 1-alkylation of the isoquinoline nucleus.

The importance of the isoquinoline system in natural products and in physiologically active compounds is appropriately matched by the large variety of synthetic methods for its construction [1]. Thus, all the bonds indicated by a, b, c, d, and e in formula **1** may be formed in key steps of isoquinoline syntheses [1]. The classical method of introducing an R-group with an acceptor reagent in the




**1**




**2**

1-position (see the synthon box **2**) is the alkylation of *Reissert*-compounds [2]. The development of methods of reactivity-*umpolung* of amines [3] has led to alternative processes symbolized by **2**. But like the *Reissert*-reaction, the methods

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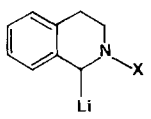
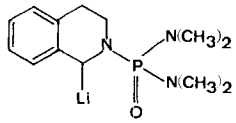
using lithiated isoquinoline derivatives **3** [3–8] are not fully satisfactory for one, or more than one of the following reasons: potentially dangerous intermediates are involved; the nucleophilicity is too low and rivalled by strong basicity; as X in **3**,



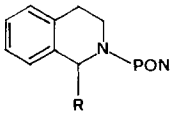
**3a** X = NO [3] [4]
**3b** X = $COC(C_6H_5)_3$ [5] [6]
**3c** X = $COC(CH_3)_3$ [7]



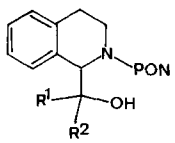
**4**
[$PO(N(CH_3)_2)_2{\equiv}PON$]

groups with high molecular weight are necessary; the reagents are thermally unstable and must be generated *and* used at very low temperatures; expensive bases such as *sec.*- or *tert.*-butyllithium have to be employed; attachment and/or removal of the X-group, following the reaction of **3** with an electrophile, require elaborate techniques, unusual reagents, or tricky conditions. We give here a preliminary account of our experiences with the lithiated phosphoric amide **4**[2]), the use of which seems to overcome the mentioned limitations.

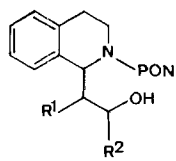
The precursor of **4** is obtained in 90% yield from tetrahydroisoquinoline and commercial bis(dimethylamino)phosphinoyl chloride. Metallation of **5** with butyllithium occurs instantaneously and quantitatively even at dry ice temperature to give deeply wine red tetrahydrofuran (THF) solutions of **4**, which are stable at room temperature for several days. Reactions with electrophiles are accompanied by decolorization; they are complete within minutes, except with neopentyl bromide and epoxides which require reaction times of many hours at temperatures above 0°. The reagent **4** can be alkylated with primary and secondary halides[3]) (products **7–14**), it adds to aldehydes and ketones ($\alpha$-hydroxyalkylated products **15–20**), and it opens up epoxides ($\beta$-hydroxyalkylations to give **21**, **22**). In the *Scheme*, the structures of the products obtained with cycloaliphatic electrophiles, the result of phenylation with benzenetricarbonylchromium [9], and of the dimerization with iodine are shown. With the methylated derivative **7**, we have shown that geminal



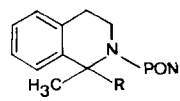
**5** R = H
**6** R = D
**7** R = $H_3C$
**8** R = $C_4H_9$
**9** R = $(CH_3)_2CH$
**10** R = $(H_2C)_5CH$
**11** R = $(CH_3)_3C{-}CH_2$
**12** R = $CH_2{=}CH{-}CH_2$
**13** R = $C_6H_5{-}CH_2$
**14** R = 3,4-$(CH_2O_2){-}C_6H_3{-}CH_2$



**15** $R^1 = C_2H_5$, $R^2$ = H
**16** $R^1 = C(CH_3)_3$, $R^2$ = H
**17** $R^1 = C_6H_5$, $R^2$ = H
**18** $R^1$ = 3,4-$(CH_2O_2){-}C_6H_3$, $R^2$ = H
**19** $R^1/R^2 = (CH_2)_4$
**20** $R^1 = R^2 = C_6H_5$



**21** $R^1$ = H, $R^2 = CH_3$
**22** $R^1/R^2 = (CH_2)_4$



**23** R = Li
**24** R = $CH_3$
**25** R = $CH_2C_6H_5$

[2]) The 2-(diethoxyphosphinoyl)-1,2,3,4-tetrahydroisoquinoline could not be metallated.
[3]) The alkylation can be carried out also with methyl *p*-toluenesulfonate.

Scheme. *Cycloalkylation, phenylation, and dimerization of* **4**

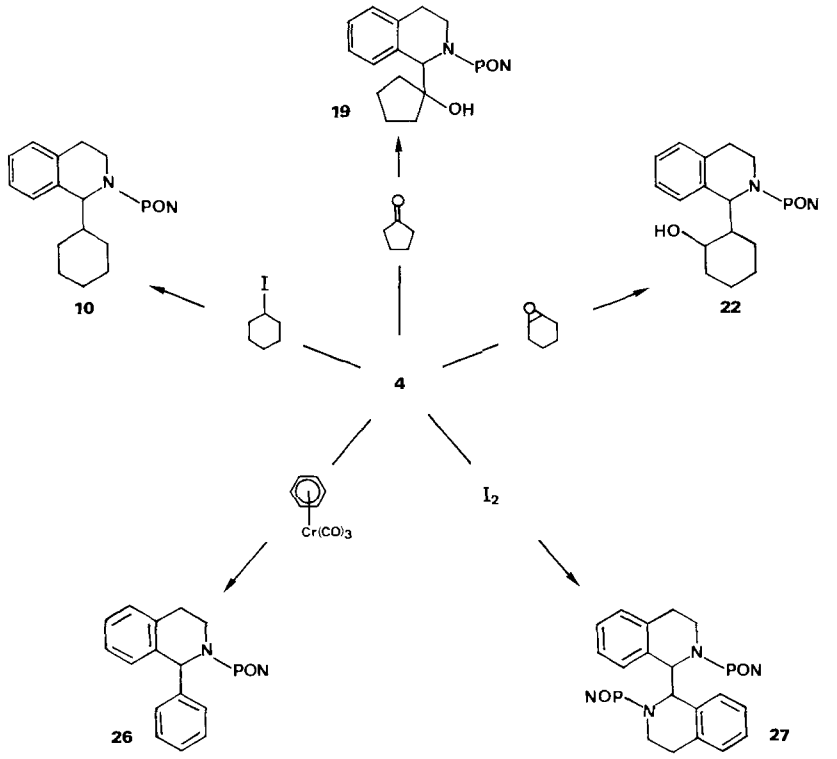



Table 1. *Non-optimized yields, $^1$H-NMR., and other characteristic physical data of the alkylation products of* **4** *and* **23**. (The boiling points have been determined during *Kugelrohr* distillations. The $^1$H-NMR. chemical shifts (ppm) refer to TMS as internal standard, coupling constants are given in Hz)

*2-Bis(dimethylamino)phosphinoyl-1,2,3,4-tetrahydroisoquinoline* (**5**): 91% from tetrahydroisoquinoline and $ClP(O)(NMe_2)_2$ in ether/$Et_3N$. B.p. 175°/0.02 Torr.

*2-Bis(dimethylamino)phosphinoyl)-1-deuterio-1,2,3,4-tetrahydroisoquinoline* (**6**): >95% from **4** and $D_2O$. – $^1$H-NMR.: 4.25 (*d*, $J$(P,H) = 6, 1 H, CHD).

*2-Bis(dimethylamino)phosphinoyl-1-methyl-1,2,3,4-tetrahydroisoquinoline* (**7**): 89% from **4** and $CH_3I$, 87% from **4** and methyl-*p*-toluenesulfonate. B.p. 140°/0.02 Torr. – $^1$H-NMR.: 4.67 (*pent.*, $J$ = 7, 1 H, CHN); 1.47 (*d*, $J$ = 7, 3 H, $CH_3$).

*2-Bis(dimethylamino)phosphinoyl-1-butyl-1,2,3,4-tetrahydroisoquinoline* (**8**): >95% from **4** and 1-chloro-butane. B.p. 165°/0.01 Torr. – $^1$H-NMR.: 4.47 (br. *qa*, 1 H, CHN); 2.6 (*d*, 12 H, 4 $PNCH_3$).

*2-Bis(dimethylamino)phosphinoyl-1-isopropyl-1,2,3,4-tetrahydroisoquinoline* (**9**): 86% from **4** and 2-iodo-propane. B.p. 155°/0.07 Torr. – $^1$H-NMR.: 4.10 (*d*×*d*, $J_1 = J_2 = 9$, 1 H, CHN); 0.90 (*d*, $J$ = 6, 3 H, $CHCH_3$); 1.1 (*d*, $J$ = 6, 3 H, $CHCH_3$).

*2-Bis(dimethylamino)phosphinoyl-1-cyclohexyl-1,2,3,4-tetrahydroisoquinoline* (**10**): 52% from **4** and iodo-cyclohexane. B.p. 205°/0.01 Torr. – $^1$H-NMR.: 4.0–4.3 (*m*, 1 H, CHN).

*2-Bis(dimethylamino)phosphinoyl-1-neopentyl-1,2,3,4-tetrahydroisoquinoline* (**11**): 60% from **4** and 1-bromo-2,2-dimethylpropane (neopentyl bromide). B.p. 180°/0.01 Torr. – $^1$H-NMR.: 4.63–4.97 (*m*, 1 H, CHN); 1.03 (*s*, 9 H, $C(CH_3)_3$).

*2-Bis(dimethylamino)phosphinoyl-1-allyl-1,2,3,4-tetrahydroisoquinoline* (**12**): >95% from **4** and 1-chloro-2-propene (allyl chloride). B.p. 175°/0.03 Torr. – $^1$H-NMR.: 4.63 (br. *qa*, 1 H, CHN), $J$(P,H) = 7.5 (by decoupling of side chain $CH_2$).

Table 1 (continued)

*2-Bis(dimethylamino)phosphinoyl-1-benzyl-1,2,3,4-tetrahydroisoquinoline* (**13**): >95% from **4** and benzyl chloride. B.p. 215°/0.01 Torr. – $^1$H-NMR.: 4.77 (br. *qa*, 1 H, CHN).

*2-Bis(dimethylamino)phosphinoyl-1-(3,4-methylenedioxybenzyl)-1,2,3,4-tetrahydroisoquinoline* (**14**): 63% from **4** and 3,4-methylenedioxybenzyl bromide. B.p. 250°/0.01 Torr. – $^1$H-NMR.: 4.5–4.8 (*m*, 1 H, CHN).

*2-Bis(dimethylamino)phosphinoyl-1-(1-hydroxypropyl)-1,2,3,4-tetrahydroisoquinoline* (**15**): >95% from **4** and propanal, diastereomeric mixture *ca.* 1:1.

*2-Bis(dimethylamino)phosphinoyl-1-[di(t-butyl)-hydroxymethyl)]-1,2,3,4-tetrahydroisoquinoline* (**16**): 90% from **4** and 2,2-dimethylpropanal (pivalaldehyde). M.p. 154–164°. – $^1$H-NMR.: 4.47 (*t*, $J_1 = J(P,H) = 9$, 1 H, CHN).

*2-Bis(dimethylamino)phosphinoyl-1-(α-hydroxybenzyl)-1,2,3,4-tetrahydroisoquinoline* (**17**): 81% from **4** and benzaldehyde, diastereomeric mixture *ca.* 1:1. M.p. 154–175°. – $^1$H-NMR.: 4.3–4.8 (*m*, 1 H, CHN); 4.9–5.2 (*m*, 1 H, C*H*OH).

*2-Bis(dimethylamino)phosphinoyl-1-(α-hydroxypiperonyl)-1,2,3,4-tetrahydroisoquinoline* (**18**): >95% from **4** and 3,4-methylenedioxybenzaldehyde (piperonal), diastereomeric mixture *ca.* 3:2, partially crystalline material. – $^1$H-NMR.: 4.2–4.8 (*m*, 1 H, CHN); 4.8–5.3 (*m*, 1 H, C*H*OH).

*2-Bis(dimethylamino)phosphinoyl-1-(1-hydrocyclopentyl)-1,2,3,4-tetrahydroisoquinoline* (**19**): 64% from **4** and cyclopentanone, oil. – $^1$H-NMR.: 4.67 (*d*, $J(P,H) = 10$, 1 H, C*H*N).

*2-Bis(dimethylamino)phosphinoyl-1-(α-hydroxybenzhydryl)-1,2,3,4-tetrahydroisoquinoline* (**20**): >95% from **4** and benzophenone. M.p. 217°. – $^1$H-NMR.: 5.72 (*d*, $J(P,H) = 10$, 1 H, CHN).

*2-Bis(dimethylamino)phosphinoyl-1-(2-hydroxypropyl)-1,2,3,4-tetrahydroisoquinoline* (**21**): >95% from **4** and methyl oxirane (propylene oxide); mixture of diastereomers [11]. – $^1$H-NMR.: 4.5–5.0 (*m*, 1 H, CHN); 1.20 (*d*, 3 H, $CH_3$).

*2-Bis(dimethylamino)phosphinoyl-1-(2-hydroxy-cyclohexyl)-1,2,3,4-tetrahydroisoquinoline* (**22**): >95% from **4** and epoxy-cyclohexane, mixture of diastereomers.

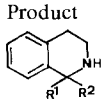
*2-Bis(dimethylamino)phosphinoyl-1,1-dimethyl-1,2,3,4-tetrahydroisoquinoline* (**24**): 56% from **23** and iodo-methane. B.p. 180°/0.07 Torr. – $^1$H-NMR.: 1.80 (*s*, 6 H, $C(CH_3)_2$).

*2-Bis(dimethylamino)phosphinoyl-1-benzyl-1-methyl-1,2,3,4-tetrahydroisoquinoline* (**25**): >95% from **23** and benzyl chloride. B.p. 200°/0.01 Torr. – $^1$H-NMR.: 1.90 (*s*, 3 H, $CH_3$); 3.3 and 4.0 (*2 d*, $J = 13.5$, benzylic $CH_2$).

*2-Bis(dimethylamino)phosphinoyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline* (**26**): 57% from **4** and benzenetricarbonylchromium; work-up with $I_2$, b.p. 230°/0.005 Torr. – $^1$H-NMR.: 5.9 (*d*, $J(P,H) = 9$, 1 H, CHN).

*1,1-Bi(2-bis(dimethylamino)phosphinoyl-1,2,3,4-tetrahydroisoquinoline)* (**27**): 66% from **4** and iodine; one diastereomer [12], m.p. 135°.

Table 2. *Non-optimized yields of acidic hydrolysis of some 2-bis(dimethylamino)phosphinoyl tetrahydroisoquinoline derivatives in 0.5–5N HCl* (the b.p. are from Kugelrohr distillations)

| Starting compound | Conditions | | Product  | | Yield [%] | B.p. [°C/Torr] |
|---|---|---|---|---|---|---|
| | Reflux time [h] | Conc. of HCl (N) | $R^1$ | $R^2$ | | |
| **5** | 3.0 | 0.5 | H | H | 83 | 115/**14** |
| **5** | 3.0 | 2.5 | H | H | 90 | |
| **7** | 1.0 | 1.0 | $CH_3$ | H | 61 | 125/14 |
| **8** | 1.5 | 2.5 | $C_4H_9$ | H | 66 | 110/0.4 |
| **9** | 0.5 | 5.0 | $CH(CH_3)_2$ | H | 71 | 155/14 |
| **9** | 2.0 | 1.0 | $CH(CH_3)_2$ | H | 65 | |
| **13** | 3.0 | 3.0 | $CH_2C_6H_5$ | H | 63 | 170/0.5 [13] |
| **24** | 1.0 | 5.0 | $CH_3$ | $CH_3$ | 64 | 125/14 [14] |

dialkylations are feasible, see the organolithiumcompound **23** and alkylation products obtained from it, **24** and **25**.

The products obtained hitherto from the lithio-derivatives **4** and **23** are listed with yields and some characteristic data in *Table 1*. Most of the reactions have been carried out only once. Many of the products are non-distillable liquids; their yields have been determined NMR.-spectroscopically from non purified, crude materials. With the exception of the dimer **27**, only one isomer of which was detected, diastereomeric product mixtures are formed wherever possible (**15–18**, **21**, **22**).

The cleavage of the phosphoric amides is readily achieved by refluxing with aqueous-methanolic hydrochloric acid, see *Table 2*. This is in contrast to the previously described pivalamides [7] obtained from **3c**, which can only be cleaved reductively.

The use of reagents of type **4** may well turn out to be a useful extension to the methodology of isoquinoline synthesis. Simple open chain phosphoric acid amides, including HMPTA (hexamethylphosphoric triamide) and some of the *N*-allyl- and *N*-benzyl-derivatives, have been successfully metallated before [10].

## REFERENCES

[1] See the books and reviews: *T. Kametani*, 'The Chemistry of Isoquinoline Alkaloids', Hirokawa-Elsevier, Tokyo, Amsterdam 1969. – *F. Šantavý*, 'Alkaloids', Vol. *17*, page 385ff., Academic Press, New York, London 1979. – *T. Kametani & M. Ihara*, Heterocycles *13*, 497 (1979).

[2] Reviews: *F.D. Popp*, Adv. Heterocycl. Chem. *24*, 187 (1979); Heterocycles *14*, 1033 (1980).

[3] Review: *D. Seebach & D. Enders*, Angew. Chem. *87*, 1 (1975); ibid. Int. Ed. *14*, 15 (1975).

[4] *B. Renger, H.-O. Kalinowski & D. Seebach*, Chem. Ber. *110*, 1866 (1977); *D. Seebach & W. Wykypiel*, Synthesis *1979*, 423; *W. Wykypiel & D. Seebach*, Tetrahedron Lett. *1980*, 1927.

[5] Review: *P. Beak & D.B. Reitz*, Chem. Rev. *78*, 275 (1978).

[6] *R. Schlecker, D. Seebach & W. Lubosch*, Helv. Chim. Acta *61*, 512 (1978); *T. Hassel & D. Seebach*, Angew. Chem. *91*, 427 (1979); ibid. Int. Ed. *18*, 399 (1979); *W. Lubosch & D. Seebach*, Helv. Chim. Acta *63*, 102 (1980); *W. Wykypiel*, Diss. Nr. 6682, ETH Zürich 1980.

[7] *J.J. Lohmann. D. Seebach, M.A. Syfrig & M. Yoshifuji*, Angew. Chem. *93*, 125 (1981); ibid. Int. Ed. *20*, 128 (1981).

[8] See also Note added in proof in: *A.I. Meyers & W.T. Hoeve*, J. Am. Chem. Soc. *102*, 7125 (1980).

[9] *M.F. Semmelhack, H.T. Hall, M. Yoshifuji & G. Clark*, J. Am. Chem. Soc. *97*, 1247 (1975); *M.F. Semmelhack, H.T. Hall, R. Farina, M. Yoshifuji, G. Clark, T. Bargar, K. Hirotsu & J. Clardy*, ibid. *101*, 3535 (1979).

[10] *P. Savignac & Y. Leroux*, J. Organomet. Chem. *57*, C47 (1973); *P. Savignac, M. Dreux & Y. Leroux*, Tetrahedron Lett. *1974*, 2651; *A.G. Abatjoglau & E.L. Eliel*, J. Org. Chem. *39*, 3042 (1974); *P. Savignac, Y. Leroux & H. Normant*, Tetrahedron *31*, 877 (1975); *B. Corbel, J.-P. Paugam, M. Dreux & P. Savignac*, Tetrahedron Lett. *1976*, 835; *P. Savignac & M. Dreux*, ibid. *1976*, 2025; *P. Magnus & G. Roy*, Synthesis *1980*, 575.

[11] Cf. *E.M. Kaiser & J.R. McClure*, J. Organomet. Chem. *175*, 11 (1979).

[12] Cf. *M.-A. Siegfried, H. Hilpert, M. Rey & A.S. Dreiding*, Helv. Chim. Acta *63*, 938 (1980).

[13] Cf. *Y. Ban, O. Yonemitsu & M. Terashima*, Chem. Pharm. Bull. Jpn. *8*, 183 (1960).

[14] Cf. *D.M. Bailey, C.G. De Grazia, H.E. Lape, R. Frering, D. Fort & T. Skulan*, J. Med. Chem. *16*, 151 (1973).