Monatshefte für Chemie 123, 473–475 (1992)

Monatshefte für Chemie
Chemical Monthly

Printed in Austria

Short Communication

Acetylene Chemistry, Part XXII [1, 2]: Synthesis of Noracronycine and Some of its Analogs via Mitsunobu-Reaction

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Summary. The natural product noracronycine as well as some of its analogs were synthesized by Mitsunobu-etherisation, using propinol derivatives.

Keywords. Acridone alkaloids; Analogs of noracronycine; Chromene synthesis; Noracronycine; Mitsunobu-etherisation.

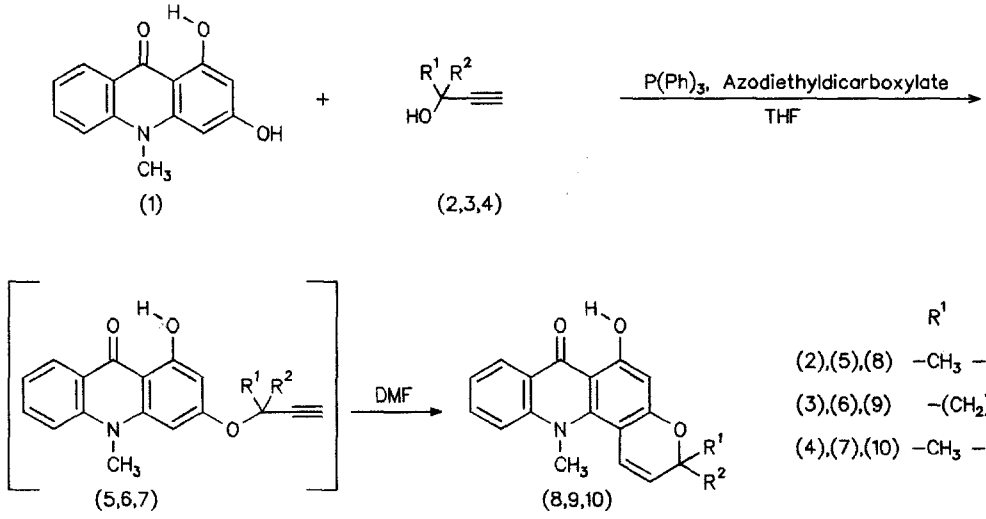
Acetylenchemie, 22. Mitt.: Synthese von Noracronycin und einiger Analoga mittels Mitsunobu-Reaktion (Kurze Mitt.)

Zusammenfassung. Der Naturstoff Noracronycin sowie einige seiner Analoga konnten durch Mitsunobu-Veretherung unter Verwendung von Propinol-Derivaten synthetisiert werden.

There is an increasing number of many natural products with a 2*H*-dimethylpyrane ring in their structure [3]. For the formation of this ring system, a strategy developed by Späth [4] (Späth's chromene synthesis) has been used. This concept has been varied in many ways without cognition of its origin (compare with [5, 6]). One of the disadvantages of these variations is the use of 1-dialkylated 1-chloropropyines for etherisation, since these substances are potentially unstable and with possible health hazards [7].

The direct etherisation of a phenolic group with an alcohol is possible if using the Mitsunobu-reaction [8]. Within the scope of our investigations into the structure-activity-relationship on noracronycine (**8**) [9, 10] this method was used for the first time in the synthesis of this natural product.

1,3-Dihydroxy-N-methyl-acridin-9(10H)-one (**1**) was easily prepared by a combination of synthetic methods [11, 12] and subsequent demethylation using 48% HBr. The reaction of **1** with the propinol derivatives **2**–**4** in the presence of triphenylphosphine and azodiethyldicarboxylate was carried out in *THF* [8]. The



resulting yields depend on the type of alcohol and were usually between 20 and 27%.

In case of the 1-ethynyl-1-cyclohexanol the linear isomer of the noracronycine derivative **9** could also be isolated, but its yield, compared with the amount of the angular form, was very low. This could be attributed to the type of solvent used [10].

It should be pointed out that some side products may be of great interest [10].

Experimental Part

In a 100 ml three-necked flask 482 mg (2 mmol) **1** was suspended in 25 ml abs. *THF* and 789 mg (3 mmol) triphenylphosphine was added. After subsequent addition of 3 mmol of a 1-dialkylated propinol derivative (**2**, **3** or **4**), the suspension was kept under nitrogen atmosphere. Then 502 mg (3 mmol) azodiethyldicarboxylat, dissolved in 12 ml *THF*, was added dropwise (ca. 1 h). The reaction was stopped after 24 h and the solvent evaporated in vacuo. Column chromatography ($CHCl_3$) was used to separate the mixture of noraconycine derivative, the corresponding propargylether and other side products from excess reagents and starting materials. The final cyclisation of the propargylether to the corresponding noracronycine derivative was carried out by heating the mixture of products in *DMF* at 130°C for 5 h. The expected product was isolated by column chromatography (toluene).

Using 2-methyl-3-butyn-2-ol (**2**), noracronycine (**8**) (122 mg, 20%) was obtained, while with 1-ethynyl-1-cyclohexanol (**3**) spiro[6-hydroxy-12-methyl-3 H-pyrano[2,3-c]acridin-7(12 *H*)-on-3,1′-cyclohexane] (**9**) (212 mg, 27%) was isolated and 2-methyl-4-pentyn-2-ol (**4**) gave 157 mg (22%) 3-ethyl-6-hydroxy-3,12-dimethyl-3 *H*-pyrano[2,3-c]acridin-9(10 *H*)-one (**10**).

Noracronycine (**8**)

The spectroscopic data of **8** were identical with those given in [13].

Spiro[6-hydroxy-12-methyl-3 H-pyrano[2,3-c]acridin-7(12 H)-on-3,1′-cyclohexane] (**9**)

R_f: 0.35 ($CHCl_3$), 0.21 (toluene). M.p. 167°C. IR (KBr): $\nu = 3\,440\,cm^{-1}$ (br., 6-OH), 2930, 2860 (v, C–H), 1640 (s, C=O), 1585, 1555, 1540 (m, arom. C=C), 1355 (m, C–H), 1275 (s, OH), 1135 (s, C–O), 745 (s, 4 vic. arom. H). UV (methanol): λ_{max} (log ε) = 418.0 nm (3.404), 286.0 (4.441), 256.5

(4.346), 228.0 (4.098). ^{1}H-NMR ($CDCl_3$): $\delta = 1.60$ (m, 10 H, 2'-H, 3'-H, 4'-H, 5'-H, 6'-H), 3.90 (s, 3 H, N$-CH_3$), 5.53 (d, $J_{2-1} = 10.64$ Hz, 1 H, 2-H), 6.30 (s, 1 H, 5-H), 6.56 (d, $J_{1-2} = 10.64$ Hz, 1 H, 1-H), 7.30 (dd, $J_{9-8} = 8.01$ Hz, $J_{9-10} = 7.64$ Hz, 1 H, 9-H), 7.42 (d, $J_{11-10} = 8.65$ Hz, 1 H, H-11), 7.71 (dd, $J_{10-9} = 7.64$ Hz, $J_{10-11} = 8.65$ Hz, 1 H, 10-H), 8.37 (dd, $J_{8-9} = 8.01$ Hz, $J_{8-10} = 1.30$ Hz, 1 H, 8-H), 14.72 (s, 1 H, 6-OH). ^{13}C-NMR ($CDCl_3$): $\delta = 21.7$ (C-4'), 25.3 (C-3', C-5'), 35.2 (C-2', C-6'), 43.6 (N$-CH_3$), 76.4 (C-3), 97.9 (C-5), 101.6 (C-12 b), 107.3 (C-6 a), 116.1 (C-11), 121.7, 122.1, 122.4 (C-2, C-9, C-1), 126.3 (C-8), 133.9 (C-10), 144.4 (C-12 a), 144.9 (C-11 a), 161.5 (C-6), 165.3 (C-4 a), 181.2 (C-7). MS (70 eV): m/z (%) = 347 (42), 304 (100), 289 (21), 276 (10), 234 (8), 152 (8), 102 (4), 77 (9). $C_{22}H_{21}NO_3$: calc. 347.152144; found 347.1512648.

3-Ethyl-6-hydroxy-3,12-dimethyl-3 H-pyrano[2,3-c]acridin-7(12 H)-one (**10**)

R_f: 0.32 ($CHCl_3$), 0.20 (toluene). M.p. 183°C. IR (KBr): $\nu = 3440$ cm^{-1} (br., OH), 3000, 2940 (v, C$-$H), 1635 (s, C$=$O), 1595, 1555, 1505 (m, arom. C$=$C), 1460 (m, C$-$H), 1330 (s, OH), 1150 (s, C$-$O), 745 (s, 4 vic. arom. H). UV (methanol): λ_{max} (log ε) = 405.0 nm (3.643), 270.5 (4.570), 223.5 (4.217). ^{1}H-NMR ($CDCl_3$): $\delta = 0.99$ (t, $J_{14-13} = 7.5$ Hz, 3 H, 14-H), 1.47 (s, 3 H, 15-H), 1.84 (q, $J_{13-14} = 7.5$ Hz, 2 H, 13-H), 3.89 (s, 3 H, N$-CH_3$), 5.47 (d, $J_{2-1} = 9.7$ Hz, 1 H, 2-H), 6.25 (s, 1 H, 5-H), 6.57 (d, $J_{1-2} = 9.7$ Hz, 1 H, 1-H), 7.27 (dd, $J_{9-10} = 7.7$ Hz, $J_{9-8} = 8.1$ Hz, 1 H, 9-H), 7.40 (dd, $J_{11-10} = 8.6$ Hz, 1 H, 11-H), 7.69 (ddd, $J_{10-11} = 8.6$ Hz, $J_{10-9} = 7.7$ Hz, $J_{10-8} = 1.6$ Hz, 1 H, 10-H), 8.34 (dd, $J_{8-9} = 8.1$ Hz, $J_{8-10} = 1.6$ Hz, 1 H, 8-H), 14.72 (s, 1 H, 6-OH). ^{13}C-NMR ($CDCl_3$): $\delta = 8.2$ (C-14), 24.6 (C-15), 32.8 (C-13), 43.7 (N$-CH_3$), 79.0 (C-3), 97.8 (C-5), 101.0 (C-12 b), 106.9 (C-6 a), 116.3 (C-11), 121.8, 121.9, 122.0 (C-2, C-9, C-1), 126.2 (C-8), 133.9 (C-10), 144.3 (C-12 a), 144.9 (C-11 a), 161.8 (C-6), 165.2 (C-4 a), 181.1 (C-7). MS: m/z (%) = 321 (27) [M^+], 306 (19), 292 (100), 278 (32), 264 (14), 250 (10), 241 (53), 212 (31), 184 (14), 140 (9), 77 (20). $C_{20}H_{19}NO_3$: calc. 321.136494; found 321.137368.

References

[1] Also: Natural Product Chemistry, Part 151

[2] Acetylene Chemistry, XXI: Reisch J., Kaiserling-Buddemeier I., Baader A. (1991) Acta Pharm. Turcica **33**: 99; Natural Product Chemistry, Part 150: Reisch J., Top M. (1991) Acta Pharm. Turcica **23**: 71

[3] Schweizer E. E., Meeder-Nycz D. (1977) in: Ellis G. P. (ed), Chromenes, Chromanones and Chromones. Wiley, New York

[4] Späth E., Hillel R. (1939) Chem. Ber. **72**: 963 u. 2093

[5] Reisch J., Salehi-Artimani R. A. (1985) Monatsh. Chem. **116**: 1099

[6] Reisch J., Salehi-Artimani R. A., Bathe A., Müller M. (1988) Monatsh. Chem. **119**: 781

[7] Reisch J. (1965) Pharmazie **20**: 271

[8] Mitsunobu O. (1981) Synthesis: 1

[9] Reisch J., Dziemba P. (1991) Arch. Pharm. (Weinheim) **324**: 67

[10] Voerste A. A. W.: A part of the Ph.D. Thesis, Münster

[11] Smolders R. R., Hanuise J., Lepoint T., Vogelet N. (1984) Tetrahedron **40**: 5181

[12] Claisen L., Eisler O. (1913) Lieb. Ann. **401**: 29

[13] Hlubuček J., Ritchie E., Taylor W. (1979) Aust. J. Chem. **23**: 1881

Received October 16, 1991. Accepted November 5, 1991

Verleger: Springer-Verlag KG, Sachsenplatz 4-6, A-1201 Wien. — Herausgeber: Österreichische Akademie der Wissenschaften, Dr.-Ignaz-Seipel-Platz 2, A-1010 Wien, und Gesellschaft Österreichischer Chemiker, Eschenbachgasse 9, A-1010 Wien. — Redaktion: Währinger Straße 38, A-1090 Wien. — Hersteller: Adolf Holzhausens Nachfolger, Kandlgasse 19-21, A-1070 Wien. — Verlagsort: Wien. — Herstellungsort: Wien. — Printed in Austria.