COMMUNICATIONS

The total synthesis of coccinelline and precoccinelline

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Received February 12, 1976

WILLIAM A. AYER and KIMIAKI FURUICHI. Can. J. Chem. **54**, 1494 (1976).

The synthesis of the ladybug defensive substances precoccinelline and coccinelline, starting from 2,6-lutidine, is described.

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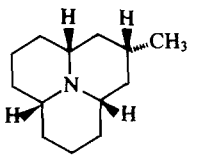
On décrit la synthèse à partir de la lutidine-2,6 des substances défensives des coccinelles soit la precoccinelline et la coccinelline.

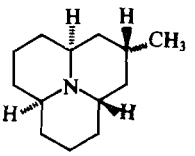
[Traduit par le journal]

Recently we have described the synthesis from 2,4,6-collidine of the ladybug defensive substances myrrhine (**1**) hippodamine (**2**), and convergine (**3**) (1). The key step in the synthesis of these substances involved the cyclization of the ketoaldehyde **4***a* (which is isolated as the carbinolamine ketol **5***a*) to furnish the ketones **6***a* and **7***a*. Removal of the oxygen function from **6***a* provided myrrhine (**1**), and from **7***a*, hippodamine (**2**). The ketone **8**, a potential precursor of precoccinelline (**9**) and thus also of coccinelline (**10**), could not be obtained from **4***a* (1). Coccinelline (**10**) (2) is the major defensive substance of several species of Coccinellidae (ladybugs) (3) and thus its synthesis remained a challenge. As noted previously (1) the ketone **7***b* (=**11**), potentially available from the ketoaldehyde **4***b*, is an attractive precursor of precoccinelline (**9**). We now report the synthesis of **11** (= **7***b*) and its transformation to precoccinelline (**9**) and coccinelline (**10**).

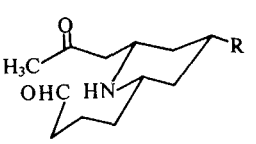
The synthesis of **4***b* followed the same pathway as the synthesis of **4***a* except that 2,6-lutidine was utilized as starting material rather than 2,4,6-collidine. Treatment of the monolithium



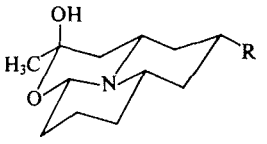
1



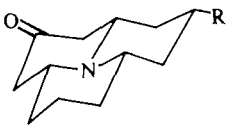
2
3 *N*-oxide of **2**



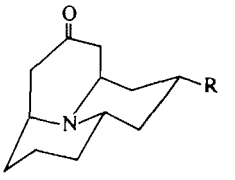
4*a* R = CH_3
4*b* R = H



5*a* R = CH_3
5*b* R = H



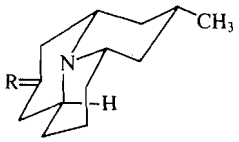
6*a* R = CH_3
6*b* R = H



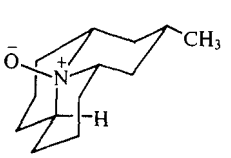
7*a* R = CH_3
7*b* R = H

derivative of 2,6-lutidine (1 equiv.) with β-bromopropionaldehyde dimethyl acetal (1 equiv.) (4) in ether in the presence of excess 2,6-lutidine (2 equiv.) gave the acetal **12**,[1] bp 85–90 °C/0.3 torr, in 76% yield (based on alkylating agent). Treatment of an ether solution of **12** with phenyllithium, followed by the slow (over 4 h) addition of an ethereal solution of acetonitrile (1 equiv.) (1) provided after work-up the crude ketone **13** which was immediately transformed (ethylene glycol – benzene – *p*-toluenesulfonic acid) to the diacetal **14** (bp 110–120 °C/0.1 torr)[1]. The overall

[1]All new compounds reported, with the exception of **16**, gave satisfactory combustion analyses. Nuclear magnetic resonance, ir, and mass spectra were obtained on all new compounds and are completely consistent with the structures formulated.



8 R = O
9 R = H, H



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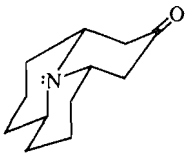
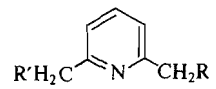


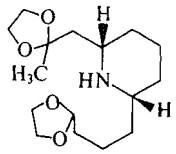
11

yield of **14** from **12** was 48%, with 27% of **12** (as the ethylene acetal) recovered.

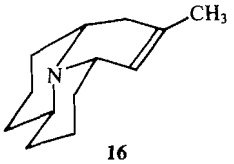
Reduction of **14** using sodium – isoamyl alcohol followed by careful chromatography over silicic acid gave the *cis* piperidine **15** (bp 135–140 °C/0.05 torr, hydrochloride mp 118–119 °C)[1] in 63% yield. The *trans*-isomer of **15** was isolated in 25% yield. The stereochemistry of the major product was assigned on the basis of: (*1*) its mode of formation (thermodynamically favored product); (*2*) a comparison of its cmr spectrum with that of the *trans*-isomer (*cf.* ref. 1); (*3*) trans-



12 R′ = H
R = $CH_2CH_2CH(OCH_3)_2$
13 R′ = $COCH_3$
R = $CH_2CH_2CH(OCH_3)$
14 R′ = —C(O)—CH_3
R = CH_2CH_2CH(dioxolane)



15



16

formation to the carbinolamine ketol **5***b*. Hydrolysis of **15** with 5% aqueous hydrochloric acid gave the ketol **5***b* (mp 87–88.5 °C)[1] which shows OH absorption and strong Bohlmann bands in the ir, a methyl signal at δ 1.48 (s, 3H) in the pmr and at δ 30.3 in the cmr, and thus must have the structure and stereochemistry shown in **5***b* (*cf.* **5***a*, ref. 1).

Cyclization of **5***b* (closed form of **4***b*) using pyrrolidine (1 equiv.) and acetic acid (2 equiv.) in refluxing tetrahydrofuran (1) gave a 1:1 mixture of ketones **6***b* and **7***b* (= **11**) in 86% yield. The mixture of ketones was separated by chromatography over silicic acid (eluant $CHCl_3$–MeOH–$NHMe_2$, 100:10:1); **6***b* (bp 75–80 °C/0.2 torr)[1] shows carbonyl absorption at 1730 cm^{-1} and *strong Bohlmann bands* in the ir; **7***b* (= **11**) (mp 82–84 °C)[1] shows carbonyl absorption at 1710 cm^{-1} and *no Bohlmann bands*.

Treatment of ketone **7***b* with methyllithium in ether followed by dehydration of the resulting carbinol with thionyl chloride in methylene chloride yielded the air sensitive olefin **16** (pmr, δ 1.66 (bs, 3H), 5.15 (bs, 1H)) which was hydrogenated (Pt, CH_3OH, room temperature, 1 atm) to give precoccinelline **9** (27% yield from **7***b*), identical (ir, pmr, ms, tlc) with an authentic sample.[2] Oxidation of synthetic precoccinelline with *m*-chloroperbenzoic acid in methylene chloride gave coccinelline (**10**), mp 205–210 °C (dec.), hydrochloride mp 215–220 °C (dec.), identical (mp, ir, ms, tlc) with an authentic sample.[2]

Treatment of ketone **6***b* with methyllithium followed by dehydration ($SOCl_2$–CH_2Cl_2) and hydrogenation gave myrrhine (**1**).

Acknowledgement

We wish to thank the National Research Council of Canada for financial support.

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2. R. Karlsson and D. Losman. Chem. Commun. 626 (1972).
3. J. M. Pasteels, C. Deroe, B. Tursch, J. C. Braekman, D. Daloze, and C. Hootele. J. Insect Physiol. **19**, 1771 (1973).
4. A. Kirrmann, M. Goudard, and M. Chahidzadeh. Bull. Soc. Chim. Fr. **2**, 2148 (1935).

[2]We wish to thank Prof. B. Tursch for samples and spectra of precoccinelline and coccinelline.