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SYNTHESIS OF 13-OXOELLIPTICINE

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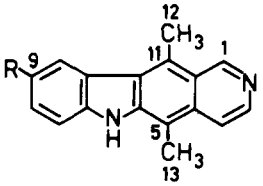
ABSTRACT.—The *Strychnos dinklagei* alkaloid and ellipticine-metabolite 13-oxoellipticine (**8**) has been synthesized from indole (**4**) in seven steps and 38% yield.

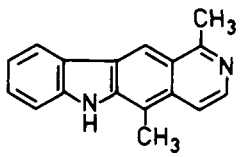
The pyrido[4,3-*b*]carbazole alkaloids ellipticine (**1a**), 9-methoxyellipticine (**1b**), and olivacine (**2**) exhibit pronounced antitumor activity in several animal and human tumor systems (1,2), and a derivative of 9-hydroxyellipticine (**1c**), namely, 2-methyl-9-hydroxyellipticinium acetate (**3**) ("elliptinium"), is currently in Phase II clinical trials (3-5). Consequently, synthetic activity in this area has been vigorous.[1]

In continuation of our own synthetic efforts in this area (7-10), we report herein a synthesis of 13-oxoellipticine (**8**) (also named as 17-oxoellipticine, based on the biogenetic pathway) an alkaloid of chemotaxonomic and biogenetic interest isolated by Koch (11) from the African tree *Strychnos dinklagei*. More recently, **8** was isolated as a metabolite when ellipticine (**1a**) was incubated with plant cell cultures of several *Choisya ternata* strains (12). This pathway differs from bacterial and mammalian metabolism of **1a**, which leads instead to ring hydroxylation at C-8 or C-9 (13,14).

Although we have previously reported the first and only total synthesis of 13-oxoellipticine (9), the overall efficiency of the process is poor.



1a R=H
1b R=OCH_3
1c R=OH



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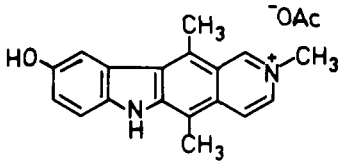

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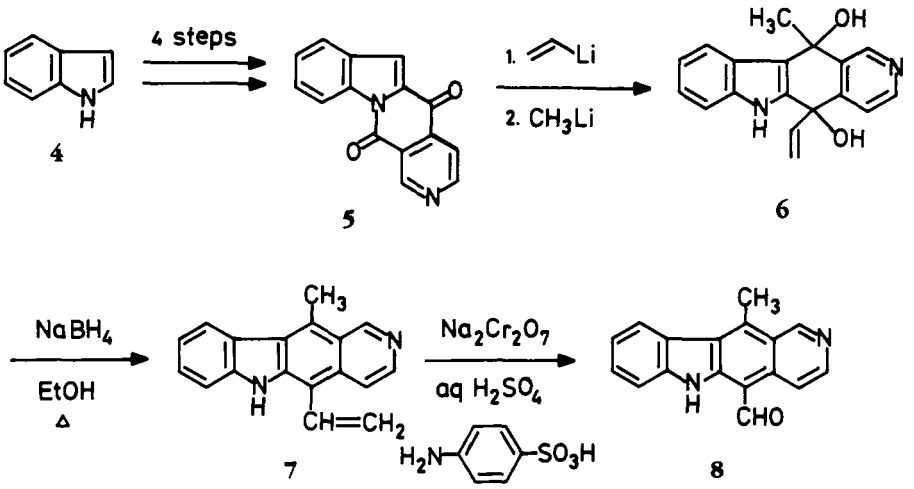
RESULTS AND DISCUSSION

Our greatly improved synthesis of 13-oxoellipticine (**8**) is outlined in Scheme 1. The ketolactam **5** can be prepared in 66% yield in four steps from indole (**4**) through reaction of its 1-(phenylsulfonyl)-2-lithio derivative with 3,4-pyridinedicarboxylic acid anhydride (7,8). Treatment of **5** with 1 equivalent of vinyllithium at $-100°$ followed, after 5 min, by 1 equivalent of methyllithium gave, after reduction of the intermediate diol **6** with $NaBH_4$ and flash chromatography, 5-vinyl-5-demethylellipticine (**7**) in 78% yield. After some exploration, we found that **7** could be smoothly oxidized to 13-oxoellipticine (**8**) in 74% yield using chromic acid in the presence of a dispersing agent (15). The material so obtained was identical (tlc, uv, ir, mp, ^1H nmr) to the natural alkaloid and to material prepared by us earlier (9). In addition, we have recorded the ^{13}C-nmr spectrum of **8**, which is consistent with its structure.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were determined in open capillary tubes with a Mel-Temp Laboratory Devices apparatus and are uncorrected. The ir spectra were recorded on a Per-

[1]For a recent review, see Gribble and Saulnier (6).



kin-Elmer 599 spectrometer. The ^1H- and ^{13}C-nmr spectra were obtained with a Varian XL-300 Fourier transform spectrometer. For ^1H-nmr spectra, chemical shifts are reported in parts per million downfield from TMS as the internal standard. The uv spectra were recorded on a Unicam SP-800A spectrophotometer. Flash chromatography was performed according to the method developed by Still (16). Tlc was performed on precoated (0.2 mm) silica gel 60 F_{254} plastic sheets (E. Merck); spots were visualized under 254 nm uv light. Vinyllithium was purchased as a 2.15 M solution in THF from Sharpe Chemical Company and was standardized by titration against diphenylacetic acid (17). Methyllithium was purchased from Aldrich and standardized by titration against 2,5-dimethoxybenzyl alcohol (18). All reactions were performed in oven-dried (110°) glassware under prepurified nitrogen or argon.

5-VINYL-11-METHYL-6H-PYRIDO[4,3-*b*]CARBAZOLE (**7**).—To a magnetically stirred solution of ketolactam **5** (7,8) (75.0 mg, 0.302 mmol) in dry THF (15 ml) at −100° was added vinyllithium (1.82 M in THF, 0.17 ml, 0.309 mmol) via syringe. The reaction was kept at −100° for 5 min, then methyllithium (1.0 M, 0.30 ml, 0.30 mmol) was added via syringe. The mixture was maintained at low temperatures (<−95°) for 1 h, then allowed to warm gradually to 20° over 2 h. H_2O (3 ml) was added, and the reaction mixture was stirred for 5 min. The solution was concentrated in vacuo to ca. 5 ml, and then treated with $NaBH_4$ (0.25 g) in EtOH (50 ml). The mixture was refluxed and additional $NaBH_4$ (0.25 g) was added after 14 h at reflux. After 23 h, the mixture was allowed to cool to 20°, the solvent was removed in vacuo, and the residue was treated with H_2O (30 ml) and $CHCl_3$ (30 ml). The phases were separated, and the aqueous portion was alternately acidified and basified, each time followed by extraction with $CHCl_3$ (1×35 ml). This was repeated until the aqueous portion became colorless (ca. three times). The combined extracts were dried (K_2CO_3), filtered, and concentrated in vacuo to afford a yellow solid (92.5 mg). Flash chromatography gave **7** (60.7 mg, 78%), which was recrystallized from MeOH to yield tan needles: mp 259-261° (dec); Rf (THF)=0.44; ^1H nmr ($CDCl_3$) δ 9.5 (s, 1H), 8.5 (m, 1H), 8.35 (d, 1H), 8.3 (d, 1H), 7.8 (d, 1H), 7.5-7.2 (m, 3H), 5.83 (d of d, J=10.8, 1.5 Hz, 1H), 5.81 (d of d, J=17.9, 1.5 Hz, 1H); *Anal.* calcd for $C_{18}H_{14}N_2 \cdot \frac{1}{3} H_2O$: C, 81.79; H, 5.59; N, 10.60. Found: C, 81.99; H, 5.52; N, 10.53; hrms *m/z* 258.1156, calcd for $C_{18}H_{14}N_2$ 258.1157.

13-OXOELLIPTICINE (5-FORMYL-11-METHYL-6H-PYRIDO[4,3-*b*]CARBAZOLE) (**8**).—Vinyl compound **7** (60.0 mg, 0.233 mmol) and sulfanilic acid (149.0 mg, 0.860 mmol) were dissolved in H_2O (17 ml) and H_2SO_4 (0.5 ml). This solution was warmed to 30-40° and treated slowly over 5 min with a solution of $Na_2Cr_2O_7$ (71.1 mg, 0.239 mmol) in H_2O (4 ml). The resulting mixture was stirred at 30-40° for 5 h, then continuously extracted with $CHCl_3$ for 48 h. The extract was concentrated in vacuo to give pure 13-oxoellipticine (**8**) (39.0 mg, 65%). Further continuous extraction (48 h) and then preparative tlc gave additional product (5.4 mg, 9%); combined yield: 44.4 mg, 74%. This material was identical in all respects to an authentic sample of the alkaloid kindly provided by Professor Koch (11); mp 268-270° (dec) [lit. (11) mp 275-276°]; Rf (THF)=0.41; uv (95% EtOH) λ max 354, 283 nm, (95% EtOH+HCl) λ max 305 (sh), 292 nm, (95% EtOH+NaOH) λ max 309, 292 (sh), 284 (sh) nm; ir (KBr) 3360 (m), 1655 (s), 1600 (s), 1570 (m), 1460 (m), 1240 (m), 1190 (w), 1020 (m), 840 (w), 800 (w) cm^{-1}; ^1H nmr ($CDCl_3$) δ 11.1 (broad, 1H), 10.9 (s, 1H), 9.6 (s, 1H), 8.6 (d, 1H), 8.3 (d, 1H), 8.2 (d, 1H), 7.5 (d, 1H), 7.4-7.2 (m, 2H), 3.2 (s, 3H); ^{13}C nmr ($CDCl_3$) δ 188.7, 150.1, 144.2, 143.1, 142.0, 140.1, 135.5, 128.1, 125.2, 123.9, 122.4, 122.1, 121.7, 112.8, 111.6, 106.3, 15.8; hrms *m/z* 260.0953, calcd for $C_{17}H_{12}N_2O$ 260.0950.

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