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HETEROCYCLIC COMPOUNDS—V[1]

THE SYNTHESIS OF CASIMIROIN

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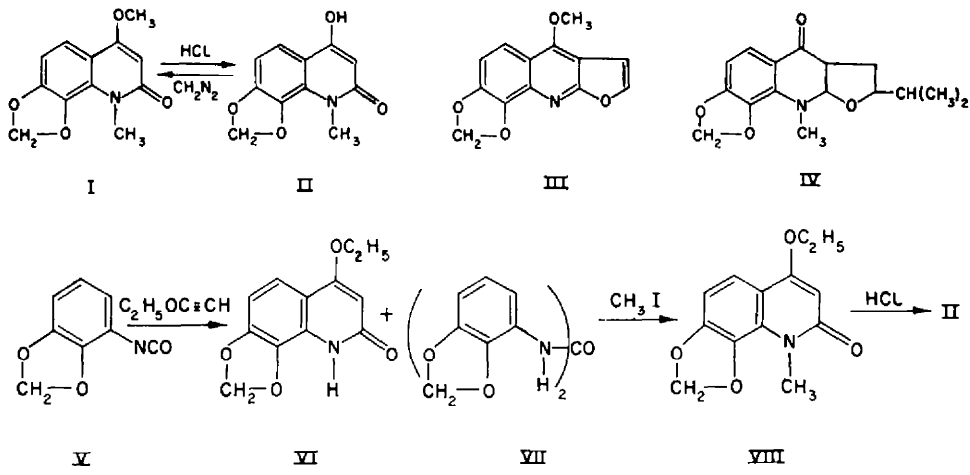
Abstract—Ethoxyacetylene was added to 2,3-methylenedioxyphenyl isocyanate to yield 4-ethoxy-7,8-methylenedioxy-2-quinolone. N-Methylation of the quinolone followed by hydrolysis of the ethoxy group and treatment with diazomethane gave 4-methoxy-1-methyl-7,8-methylenedioxy-2-quinolone. This reaction sequence furnished a synthesis of the naturally occurring compound, casimiroin.

CASIMIROIN (I), a constituent of the seed and the bark of the tree *Casimiroa edulis* Llave *et* Lex., was shown by chemical degradation to be 4-methoxy-1-methyl-7,8-methylenedioxy-2-quinolone.[2–4] In the original proof of structure casimiroin was cleaved by hot, dilute hydrochloric acid to afford casimiroinol (II). In turn, treatment of casimiroinol with diazomethane gave casimiroin. The ready availability of casimiroinol would allow it to be used as an intermediate in a synthesis of several furoquinoline alkaloids[5,6]—for example, kokusagine (III)[7] and lunine (IV).[8] The introduction of a new reactive center in casimiroinol would be analogous to the route in which 2,4-dihydroxyquinoline was condensed with chloroform under Reimer–Tiemann conditions to yield 1,2-dihydro-4-hydroxy-2-oxo-3-quinolinecarboxyaldehyde (nordictamnal).[9] A related compound, 6,7-methylenedioxynordictamnal, was prepared by this same reaction.[10,11]

Several years ago one solution to a simple preparation of casimiroinol was suggested in a study on the chemistry of acetylenic ethers.[12] A mixture of phenyl isocyanate and ethoxyacetylene in nitromethane in a sealed tube at room temperature formed in moderate quantity 4-ethoxy-2-quinolone after a six-week reaction period. A higher temperature was unfavorable for this cyclization, as there were produced large amounts of uncharacterized brown oils. If one assumes that other appropriately substituted aromatic isocyanates can react with acetylenic ethers to form quinolones, then a general route exists for the preparation of casimiroin as well as similar

[1] Paper IV, W. W. Lee, G. L. Tong, A. P. Martinez, B. Weinstein, M. G. M. Schelstraete, B. R. Baker and L. Goodman, *J. Med. Chem.* **6**, 439 (1963).
[2] F. A. Kincl, J. Romo, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.* 4163 (1956).
[3] J. Iriarte, F. A. Kincl, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.* 4170 (1956).
[4] A. Meisels and F. Sondheimer, *J. Amer. Chem. Soc.* **79**, 6328 (1957).
[5] For earlier review articles on the furoquinolone alkaloids, see: H. T. Openshaw, *The Alkaloids* Vol. VII; p. 229. Academic Press, New York (1960) and J. R. Price, *Fortschr. Chem. Org. Naturstoffe* **13**, 302 (1956).
[6] A totally different approach to the preparations of the furoquinolone alkaloids is exemplified by the reaction between substituted anilines and various diethyl malonate derivatives; see: E. A. Clarke and M. F. Grundon, *J. Chem. Soc.* 438 (1964).
[7] M. Terasaka, T. Ohta and K. Narahaski, *Pharm. Bull., Japan* **2**, 159 (1954).
[8] S. Goodwin, J. N. Schoolery and L. F. Johnson, *J. Amer. Chem. Soc.* **81**, 3065 (1959).
[9] T. Ohta and Y. Mori, *Ann. Rept. Tokyo Coll. Pharm.* **4**, 261 (1954).
[10] T. Ohta and O. Okuda, *J. Pharm. Soc., Japan* **71**, 414 (1951).
[11] T. Ohta and O. Okuda, *Ann. Rept. Tokyo Coll. Pharm.* **1**, 25 (1951).
[12] J. Nieuwenhuis and J. F. Arens, *Rec. Trav. Chim.* **76**, 999 (1957).



compounds.[13] The validity of this approach was demonstrated here by a successful preparation of both casimiroinol and casimiroin.

A solution of ethoxyacetylene[14] and 2,3-*methylenedioxyphenyl isocyanate* (V) in nitromethane was sealed in a glass tube. In a few hours crystals began to deposit in the reaction vessel, and after eleven days, the interior of the tube was partially filled with a solid mass. The tube was opened and the product was separated from the brown mother liquor. Examination of the material revealed that it was a mixture of the desired 4-*ethoxy*-7,8-*methylenedioxy*-2-*quinolone* (VI) as well as *bis*-2,3-*methylenedioxyphenyl urea* (VII). Various attempts to separate the two compounds on a large scale were unsuccessful; therefore, the crude quinolone–urea combination was methylated with methyl iodide to form 4-ethoxy-1-methyl-7,8-methylenedioxy-2-quinolone (VIII). The unaltered urea VII was separated from the desired quinolone VIII by using a combination of chromatography, crystallization, and sublimation processes. Hydrolysis of compound VIII by hot, aqueous hydrochloric acid gave casimiroinol. Finally, II was treated with diazomethane to yield synthetic casimiroin, identical with an authentic specimen.[15]

EXPERIMENTAL[16,17]

2,3-*Dimethoxybenzaldehyde* (o-*Veratraldehyde*). To 260 g (1·71 moles) molten freshly-distilled *o*-vanillin, heated over a steam bath, were added with vigorous stirring simultaneously from separate

[13] Recently, the cuprous salt catalyzed addition of α-acetylenic esters to aromatic amines was reported to give easily separated mixtures of 2- and 4-quinolones; see: J. Reisch, *Angew. Chem.* **75**, 1203 (1963).

[14] Ethoxyacetylene, which is commercially available (Pfister Chemical Works, Inc., Ridgefield, N.J.). was used at this stage rather than methoxyacetylene. Since casimiroinol was desired as an intermediate, the additional reaction step, involving the removal of the ethoxy group, was not considered deleterious.

[15] We wish to thank Dr. Franz Sondheimer, Weizmann Institute of Science, Rehovoth, Israel, for a sample of casimiroin.

[16] All m.ps and b.ps are uncorrected. The IR spectra were obtained on a Perkin-Elmer Model 421 double grating instrument in KBr disks and the UV spectra were taken on a Cary Model 14 spectrophotometer in grain alcohol solution, unless otherwise stated. The microanalyses were performed by the Microanalytical Laboratory, Department of Chemistry, Stanford University.

[17] The conversion of 2,3-dimethoxybenzaldehyde to 2,3-methylenedioxybenzoyl chloride was previously described in the lit., but generally only in brief detail; see: W. H. Perkin, Jr. and V. M. Trikojus, *J. Chem. Soc.* 2925 (1926).

funnels at the rate of 2 drops/sec, 206 ml (275 g, 2·20 moles) dimethyl sulphate and a solution of 140 g (2·50 moles) KOH in 200 ml water (similar to the method for the preparation of 3,4-dimethoxybenzaldehyde[18]). The solution was maintained basic (brownish) throughout the reaction period by beginning the addition of the KOH aq for 30 sec before commencing the introduction of the dimethyl sulphate. The mixture was further stirred, with continued heating, for an additional hr and then poured into a dish to cool overnight. The resulting crystalline mass was crushed in 500 ml ice water, collected by filtration, dried ($CaCl_2$) and vacuum distilled to yield 255 g (90%) product. The analytical sample was recrystallized from hexane and was sublimed *in vacuo*; m.p. 52·5–53·5° (lit. m.p. 54°[17]); IR, 6·04 μ (C=O); UV, λ_{max} 219 μm (log ϵ 4·32), 258 mμ (log ϵ 3·99), and 318 mμ (log ϵ 3·45).

2,3-*Dimethoxybenzoic acid* (*o-veratric acid*). To 121 g (0·73 mole) 2,3-dimethoxybenzaldehyde in 1 l. water maintained at 70–80° was added over 1 hr with vigorous stirring a saturated aq solution containing 202 g (1·28 moles) $KMnO_4$. After an additional hr, the hot solution was filtered, and the precipitate washed with boiling water. The filtrates were combined, cooled, then acidified with conc. HCl aq. The resulting white precipitate was filtered, washed with cold water and was dried *in vacuo* (P_2O_5) to yield 104 g (78%) product. Concentration of the mother liquors yielded, after drying, an additional 3 g acid; total yield, 81%. The analytical sample was recrystallized from water and sublimed *in vacuo*; m.p. 124–125° (lit. m.p. 125°[19] and 122°[20]); IR, 5·79 μ (C=O); UV, λ_{max} 225 mμ (weak shoulder) and 291 mμ (log ϵ 3·29).

2,3-*Dihydroxybenzoic acid* (*o-pyrocatechuic acid*). A solution of 104 g (0·57 mole) 2,3-dimethoxybenzoic acid in 650 g 47% HI was refluxed (air condenser) for 3·5 hr. The solution was cooled in ice, and the resulting solid filtered and washed with ice water. Recrystallization of the acid from 4 l. water, followed by drying *in vacuo* (P_2O_5), resulted in a yield of 66 g (75%). Workup of the mother liquors yielded an additional 5 g; total yield, 81%. The analytical sample of the acid was sublimed *in vacuo*; m.p. 208–209° (lit. m.p. 204°[17] and 206°[21]); IR, 6·06 mμ (C=O); UV, λ_{max} 245 mμ (log ϵ 3·93) and 316 mμ (log ϵ 3·59).

2,3-*Methylenedioxybenzoic acid* (*o-piperonylic acid*). To a rapidly stirred slurry of 30·8 g (0·20 mole) 2,3-dihydroxybenzoic acid in 60 ml water, under a N_2 atm., was added very slowly with cooling a solution of 33·4 g (0·60 mole) KOH in 130 ml water, followed by a heterogeneous mixture of 51 g (0·19 mole) methylene iodide and 82 ml 95% ethanol. The mixture was refluxed with vigorous stirring for 65 hr. After removal of the unreacted methylene iodide by steam distillation, the resulting solution was cooled, acidified with conc. HCl, and the precipitate removed by filtration to yield a slightly gummy brown solid. Direct sublimation of the dried material at 170° *in vacuo* afforded 13·5 g pale yellow crystals, m.p. 228–232° (positive phenol test). Several recrystallizations from 95% ethanol, followed by another sublimation *in vacuo*, yielded 10 g (30%) white crystals, m.p. 229–230° (sealed tube) (lit. m.p. 227°[17]), (negative phenol test); IR, 5·97 μ (C=O) and 10·75 μ (CH_2O_2=); UV, λ_{max} 233 mμ (shoulder) (log ϵ 3·92) and 312 mμ (log ϵ 3·56).

2,3-*Methylenedioxybenzoyl chloride* (*o-piperonyloyl chloride*). A solution of 5·9 g (0·036 mole) 2,3-methylenedioxybenzoic acid in 10 ml thionyl chloride was refluxed 45 min. Excess thionyl chloride was removed by distillation and the residual solid recrystallized from benzene–pet. ether (30–60°) and then sublimed *in vacuo* to yield 6·3 g (96%) light tan crystals, m.p. 116·5–118·5° (lit. m.p. 116°[17]); IR, 5·73 μ (C=O) and 10·92 μ (CH_2O_2=); UV, $\lambda_{max}^{C_6H_{12}}$ 229 mμ (log ϵ 4·27), 243 mμ (log ϵ 3·98), 248 mμ (log ϵ 4·00), 2·53 mμ (shoulder), 256 mμ (log ϵ 4·12) and 337 mμ (log ϵ 3·61).

2,3-*Methylenedioxybenzoyl azide*. To a stirred solution of 2·0 g (0·031 mole) sodium azide in 25 ml water at 0–5° was added dropwise 4·25 g (0·023 mole) 2,3-methylenedioxybenzoyl chloride in 50 ml warm acetone. After allowing the solution to stir at this temp for 2–3 hr, excess ice water was added, and the intermediate azide collected by filtration and dried in the absence of light. The crude product has m.p. 53–54° (dec) and, on standing in the presence of light, developed a pink coloration. The azide was recrystallized, without change in m.p., from acetone by adding ice water, to give white crystals; IR, 4·67 μ (—N_3), 5·93 μ (C=O) and 10·72 μ (CH_2O_2=); UV, λ_{max} 228 mμ (log ϵ 4·27), 261 mμ (log ϵ 4·21), and 340 mμ (log ϵ 3·53).

[18] G. Barger and R. Silberschmidt, *J. Chem. Soc.* 2919 (1928).
[19] J. Shinoda and S. Sato, *J. Pharm. Soc., Japan* **540**, 25 (1927).
[20] W. H. Perkin, Jr. and R. Robinson, *J. Chem. Soc.* **105**, 2376 (1914).
[21] E. Späth and H. Hoffer, *Ber. Dtsch. Chem. Ges.* **60**, 1891 (1927).

2,3-*Methylenedioxyphenyl isocyanate* (V).[22] The crude azide (3·8 g, 0·020 mole) was slowly added to 25 ml benzene at 70–80°. The solution was then refluxed 30 min, concentrated, and the oily residue distilled to yield 2·4 g (64% from acid chloride) of a colorless oil, b.p. 76° at 2 mm. On standing, the isocyanate slowly solidified, m.p. 37–38°; IR, (film) 4·46 μ (—NCO), 10·86 μ (CH_2O_2=) UV, $\lambda_{max}^{C_6H_{13}}$ 210 mμ (log ϵ 4·59), 232 mμ (shoulder) (log ϵ 4·0), and 287 mμ (log ϵ 3·39). (Found: C, 59·28; H, 3·28; N, 8·64, $C_8H_5NO_2$ requires: C, 58·90; H, 3·09; N, 8·59%).

4-*Ethoxy*-7,8-*methylenedioxy*-2-*quinolone* (VI). A solution of 2·0 g (0·012 mole) 2,3-methylenedioxyphenyl isocyanate and 1·2 g (0·017 mole) ethoxyacetylene in 8·5 ml nitromethane was mixed and allowed to stand in a sealed tube at room temp. Filtration of the mixture after 11 days gave 0·8 g crude product, and an additional 0·4 g was obtained after 1 month. A thin-layer chromatogram (silica gel–acetone) revealed the presence of considerable *bis*-2,3-*methylenedioxyphenyl urea* (m.p. 303–306°). The crude brown material was only sparingly soluble in methanol or acetone, and was purified by crystallization from triethylene glycol. The analytical sample was sublimed *in vacuo* at 220° to give white crystals, m.p. 322–324° (sealed tube); IR, 6·12 μ (C=O), 10·80 μ (CH_2O_2=); UV, λ_{max} 228 mμ (log ϵ 4·49), 232 mμ (shoulder) (log ϵ 4·39), 239 mμ (shoulder) (log ϵ 4·35), 251 mμ (log ϵ 4·35), 258 mμ (log ϵ 4·33), 305 mμ (log ϵ 3·86), and 315 (weak shoulder). (Found: C, 61·65; H, 4·93; N, 6·16. $C_{12}H_{11}NO_4$ requires: C, 61·80; H, 4·75; N, 6·01%).

4-*Ethoxy*-1-*methyl*-7,8-*methylenedioxy*-2-*quinolone* (VIII). A solution of 0·75 g NaOH in 15 ml water was added dropwise to a boiling mixture of 3 g impure 4-ethoxy-7,8-methylenedioxy-2-quinolone and 23 g methyl iodide in 45 ml methanol. After refluxing overnight, the solvent was removed *in vacuo* and the solid first washed with water, and the residue extracted with hot acetone. Evaporation of the acetone yielded 0·8 g crude product, which was purified by 2 recrystallizations from acetone–hexane, followed by chromatography on 20 g acidic alumina with elution by 200 ml warm acetone. Finally, recrystallization from acetone–hexane and sublimation *in vacuo* gave 0·7 g white crystals, m.p. 174·5–175·5° (lit. m.p. 170–171°[4]); IR, 6·12 μ (C=O), and 10·75 μ (CH_2O_2=); UV, λ_{max} 227 mμ (log ϵ 4·42), 237 mμ (log ϵ 4·37), 252 mμ (log ϵ 4·30), 260 mμ (log ϵ 4·28) and 302 mμ (log ϵ 3·77). [lit. values[4]: 227 mμ (log ϵ 4·40), 252 mμ (log ϵ 4·23), 260 mμ (log ϵ 4·21) and 303 mμ (log ϵ 3·70)]. (Found: C, 63·11; H, 5·44; N, 5·73. Calc. for $C_{13}H_{13}NO_4$: C, 63·15; H, 5·30; N, 5·67%).

4-*Hydroxy*-1-*methyl*-7,8-*methylenedioxy*-2-*quinolone* (*casimiroinol*) (II). A suspension of 500 mg 4-ethoxy-1-methyl-7,8-methylenedioxy-2-quinolone in 30 ml 20% HCl aq was refluxed for 30 min. After a short time the solid dissolved, but soon a copious white precipitate appeared. The solution was cooled in ice and the product filtered and dried. Crystallization with great difficulty from methanol gave 400 mg (90%) white crystals, m.p. 310–315°, (lit. m.p. 321–323°[2]).

4-*Methoxy*-1-*methyl*-7,8-*methylenedioxy*-2-*quinolone* (*casimiroin*) (I). A suspension of 115 mg of the hydroxyquinolone in 50 ml ether at 0° was treated with excess ethereal diazomethane. The compound failed to dissolve after 30 min; however, addition of 20 ml absolute methanol caused immediate dissolution. After standing at room temp for 4 hr the solution was treated with a small amount of dil. acetic acid to decompose the excess diazomethane. Evaporation of the solution and crystallization of the residue from acetone–hexane gave 91 mg (74%) white needles, m.p. 197–202°. Several recrystallizations from acetone–hexane and finally sublimation *in vacuo* gave the analytical sample, m.p. 202–203°; IR, 2·86 μ (?), 6·18 μ and 6·33 μ (C=O), and 10·76 μ (CH_2O_2=); UV, λ_{max} 227 mμ (log ϵ 4·55), 237 mμ (log ϵ 4·49), 252 mμ (log ϵ 4·38), 260 mμ (log ϵ 4·38) and 301 mμ (log ϵ 3·87). The compound moved as a single spot on thin-layer chromatography (silica gel–acetone), with R_f equivalent to that of an authentic sample of casimiroin. Mutual identification was further established on the basis of a mixture m.p. as well as IR and UV spectral comparisons.[15] (Found: C, 61·98; H, 4·55; N, 6·30. Calc. for $C_{12}H_{11}NO_4$: C, 61·80; H, 4·76; N, 6·01%).

[22] Alternatively, 2,3-methylenedioxyaniline on treatment with phosgene would have yielded V. Unfortunately, the very low yield sequence previously reported for the synthesis of 2,3-methylenedioxyaniline mitigated against further consideration of this route. Some effort was spent in an attempt to improve the preparation, without success.