

A General Method for Alkylation and Alkenylation of Heterocycles

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Abstract: A new procedure is described for the direct introduction of alkyl and alkenyl substituents into heterocyclic nuclei. A suitable leaving group on the heterocycle is displaced by an alkylidenephosphorane (Wittig reagent), and the resulting heterocyclic ylide is converted *in situ* either by hydrolysis into an alkyl derivative of the heterocycle or by reaction with a carbonyl compound into an alkenyl derivative of the heterocycle. The scope, limitations, and specific advantages of this new functionalization procedure are detailed, and its synthetic potential illustrated by "one-pot" syntheses of papaverine (from 1-chloro-6,7-dimethoxyisoquinoline), a series of 6-alkyl- and 6-alkenylpurines (from 6-chloro-9-(tetrahydro-2-pyranyl)purine), and the Cinchona alkaloids ruban, 6-methoxyruban, and deoxyquinine-deoxyquinidine (from 4-chloroquinoline and 4-chloro-6-methoxyquinoline, respectively).

Despite well-developed and versatile methodology for the alkylation and alkenylation of aromatic substrates,^{2,3} comparable procedures unfortunately do not exist in the field of heterocyclic chemistry.^{4,5} We describe in the present paper a facile method for the introduction of alkyl and alkenyl groups into a wide range of heterocyclic nuclei which is both general and regiospecific.⁶ This new procedure involves the displacement of a suitable leaving group on the heterocycle (**1**, X = Cl, Br, SO₂CH₃, etc.) by an alkylidenephosphorane (Wittig reagent) (**2**). The resulting phosphonium salt (**3**) undergoes transylidation by reaction with a second equivalent of the initial Wittig reagent, and the heterocyclic ylide thus formed (**4**) is then converted *in situ* either by hydrolysis into an alkyl derivative of the heterocycle (**5**) or by reaction with a carbonyl compound into an alkenyl derivative (**6**).⁷ This new approach to the functionalization of heterocycles *via* Wittig reagents is depicted in general terms in Scheme I; representative conversions are summarized in Table I.

The following comments can be made about this new procedure.

(1) It is applicable both to five- and six-membered systems, and to monocyclic as well as polycyclic heterocycles.

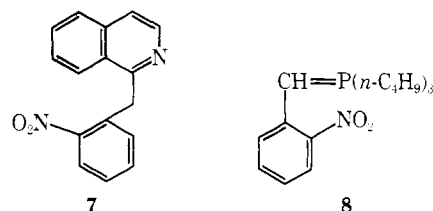
(2) Although the new substituent can be introduced only into a position previously occupied by the leaving group, this restriction simultaneously confers regiospecificity to the alkylation and alkenylation reactions. Thus, although 3-substituted quinolines cannot be prepared by this procedure, either 2- or 4-substituted derivatives can be prepared selectively, starting with an appropriately substituted precursor.

(3) The requisite chloro or methylsulfonyl precursors number among the most accessible derivatives in heterocyclic chemistry.

Although most of the simple heterocycles (e.g., pyridine, quinoline, and isoquinoline) are readily available without substituents already present on the ring, in many heterocyclic systems (e.g., quinazoline) the parent, unsubstituted heterocycle is less accessible than are substituted derivatives.⁴ The chloro compound, in fact, is often an intermediate in the formation of the unsubstituted system. Furthermore, since chloro compounds are usually prepared by the action of phosphorus oxychloride or similar reagents on the corresponding lactams, which in turn are often the immediate product of a ring closure reaction, the position of substitution is also assured.

(4) Since a variety of leaving groups can be employed successfully, substrates which prove unreactive to displacement (*i.e.*, 2-chloropyridine and 2-methylthioquinoline)⁸ can be converted to substrates which undergo displacement readily (*i.e.*, 2-bromo- or 2-methylsulfonylpyridine, and 2-chloro- or 2-methylsulfonylquinoline). This flexibility in the choice of the leaving group greatly extends the versatility of the procedure.

(5) Flexibility is also possible in the choice of the nucleophilic alkylidenephosphorane. Methylene-, ethylidene-, and *n*-butylidenetriphenylphosphorane have all been used successfully. Furthermore, although 2-chloroquinoline failed to react with benzylidenetriphenylphosphorane, it reacted satisfactorily with benzylidene(tri-*n*-butyl)phosphorane, which is more nucleophilic. An attempt to prepare the aporphine alkaloid precursor **7** *via* the reaction of 1-chloroisoquinoline with the Wittig reagent **8**, however, was unsuccessful.



(6) Since the intermediate heterocyclic ylide reacts with aliphatic and aromatic aldehydes, and with ketones ranging in reactivity from acetone to benzophenone, a broad variety of alkenyl groups (and, by reduction, alkyl groups) may be selectively introduced into the heterocyclic substrate.

(7) The alkenylation method appears to lead stereospecifically to *trans* olefins ($J_{\text{vinyl}} \sim 16$ Hz). Since the heterocyclic phosphonium ylides are stabilized, their addition to carbonyl compounds is an endergonic process which proceeds

Scheme I

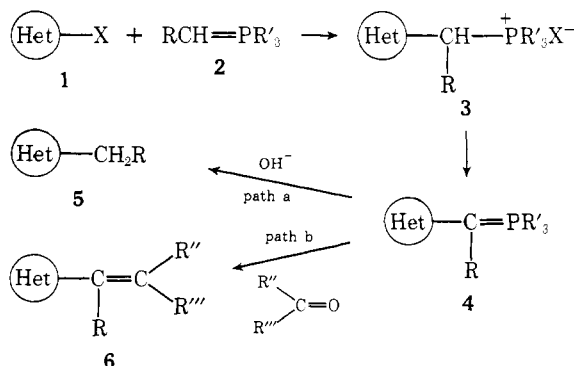


Table I. Synthesis of Alkyl- and Alkenyl-Substituted Heterocycles

Starting material	Reacting ylide	Reaction time, hr	Alkyl deriv (method)	Yield, %	Alkenyl deriv	Yield, %
2-Bromopyridine	$\text{CH}_2=\text{PPh}_3$	72 ^a			2-Styrylpyridine ^c	32
2-Methylsulfonylpyridine	$\text{CH}_2=\text{PPh}_3$	4 ^a			2-Styrylpyridine ^c	46
2-Chloropyrazine	$\text{PhCH}=\text{P}(n\text{-C}_4\text{H}_9)_3$	18 ^a	2-Benzylpyridine (A) ^d	57	2-(1-Butenyl)pyrazine ^e	35
	$\text{CH}_2=\text{PPh}_3$	6 ^a			2-Styrylpyrazine ^f	52
2-Chloroquinoline	$\text{CH}_2=\text{PPh}_3$	16 ^a	Quinaldine (A) ^g	82	2-(1-Butenyl)quinoline ^h	62
					2-Styrylquinoline	65
					1-(2-Thienyl)-2-(2-quinolyl)-ethylene ⁱ	52
					2-(2-Methyl-1-propenyl)-quinoline ^j	55
					2-Quinolylidenecyclohexane ^k	54
					2-(α -Methylstyryl)quinoline ^l	46
					1,1-Diphenyl-2-(2-quinolyl)-ethylene ^m	47
	$\text{CH}_3\text{CH}=\text{PPh}_3$	16 ^a	2-Ethylquinoline (A)	75		
	$n\text{-C}_5\text{H}_7\text{CH}=\text{PPh}_3$	16 ^a	2- <i>n</i> -Butylquinoline (A) ⁿ	58		
	$\text{PhCH}=\text{P}(n\text{-C}_4\text{H}_9)_3$	16 ^a	2-Benzylquinoline (B) ^o	72		
4-Chloro-2-methylquinoline	$\text{CH}_2=\text{PPh}_3$	24 ^a	2,4-Dimethylquinoline (A) ^p	79	2-Methyl-4-styrylquinoline ^q	69
1-Chloroisoquinoline	$\text{CH}_2=\text{PPh}_3$	16 ^a			1-Styrylisoquinoline ^r	68
	$\text{PhCH}=\text{P}(n\text{-C}_4\text{H}_9)_3$	16 ^a	1-Benzylisoquinoline (B) ^s	76		
1-Chloro-6,7-dimethoxyisoquinoline	$3,4\text{-(CH}_3\text{O)}_2\text{C}_6\text{H}_3\text{-CH}=\text{P}(n\text{-C}_4\text{H}_9)_3$	18 ^a	Papaverine	74		
2-Chlorobenzoxazole	$\text{CH}_2=\text{PPh}_3$	4 ^b			2-Styrylbenzoxazole ^t	72
2-Chloroquinoxaline	$\text{CH}_2=\text{PPh}_3$	4 ^b			2-(1-Butenyl)quinoxaline ^u	42
					2-Styrylquinoxaline ^v	53
4-Chloroquinazoline	$\text{CH}_2=\text{PPh}_3$	3 ^b			4-Styrylquinazoline ^w	48
6-Chloro-9-(tetrahydro-2-pyranyl)purine	$\text{CH}_2=\text{PPh}_3$	4 ^b	6-Methylpurine	73	1-(2-Furfuryl)-2-(6-purinyl)-ethylene	63
					6-Styrylpurine	55
					1-(3,4,5-Trimethoxyphenyl)-2-(6-purinyl)ethylene	70
	$\text{CH}_3\text{CH}=\text{PPh}_3$	4 ^b	6-Ethylpurine	66		
	$\text{PhCH}=\text{P}(n\text{-C}_4\text{H}_9)_3$	6 ^c	6-Benzylpurine	72		

^a Refluxing 1,2-dimethoxyethane. ^b Room temperature. ^c Mp 172–174°; lit. mp 177° [H. Baurath, *Ber.*, **21**, 818 (1888)]. ^d Bp₁₅ 147–148°; lit. bp₁₆ 148–149° [W. L. C. Veer and St. Goldschmidt, *Recl. Trav. Chim. Pays-Bas*, **65**, 793 (1946)]. ^e Bp₁₂ 90–91° (picrate mp 100–101°); nmr (CDCl₃) δ 1.09 (t, 3, J = 7 Hz), 2.30 (distorted pentuplet, 2, J = 7 Hz), 6.43 (d, 1, J = 16 Hz), 6.96 (t of d, 1, J = 7, 16 Hz), 8.39 (m, 3). ^f Anal. Calcd for C₁₄H₁₃N₅O₇ (picrate): C, 46.28; H, 3.61; N, 19.28. Found: C, 46.46; H, 3.47; N, 19.52. ^g Mp 74–76°; lit. mp 79–82° [S. Yamada and T. Ueda, Japanese Patent 3367 (1961); *Chem. Abstr.*, **57**, 3458e (1962)]; mp (picrate) 144–145°. ^h Bp₁₂ 113–114°; lit. bp₁₆ 119–121° [W. G. Dauben and C. W. Vaughan, Jr., *J. Amer. Chem. Soc.*, **75**, 4651 (1953)]. ⁱ Bp_{0.06} 93–94° (mp (picrate) 149–150°); nmr (CDCl₃) δ 1.08 (d of t, 3, J = 0.5, 7 Hz), 2.25 (m, 2), 6.75 (m, 2), 7.25 (d, 1, J = 8.5 Hz), 7.44 (m, 3), 7.81 (d, 1, J = 8.5 Hz), 8.09 (distorted d, 1, J = 9 Hz). ^j Anal. Calcd for C₁₉H₁₆N₄O₇ (picrate): C, 55.34; H, 3.91; N, 13.59. Found: C, 55.35; H, 3.93; N, 13.65. ^k Mp 84–86°; lit. mp 89° [W. Ried and S. Hinsching, *Justus Liebigs Ann. Chem.*, **600**, 47 (1956)]. ^l Picrate mp 170–171°; lit. mp 171–172° [P. Bednarek, R. Bodalski, J. Michalski, and S. Musierowicz, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **11**, 507 (1963); *Chem. Abstr.*, **60**, 5546g (1964)]. ^m Picrate mp 155–156°; nmr (CDCl₃) δ 1.58 (broad s, 6), 2.32 (broad s, 2), 2.80 (broad s, 2), 6.42 (broad d, 1), 7.15 (d, 1, J = 8.5 Hz), 7.49 (m, 3), 7.87 (d, 1, J = 8.5 Hz), 8.08 (distorted, d, 1, J = 9 Hz). ⁿ Anal. Calcd for C₂₂H₂₀N₄O₇ (picrate): C, 58.40; H, 4.46; N, 12.39. Found: C, 58.69; H, 4.66; N, 12.27. ^o Mp 95–97° (picrate mp 167–168°); nmr (CDCl₃) δ 2.62 (d, 3, J = 1.5 Hz), 6.96 (q, 1, J = 1.5 Hz), 7.69 (m, 11). ^p Anal. Calcd for C₂₄H₁₈N₄O₇ (picrate): C, 60.76; H, 3.82; N, 11.81. Found: C, 60.83; H, 3.99; N, 11.88. ^q Mp 85–87°. ^r Anal. Calcd for C₂₃H₁₇N₃: C, 89.86; H, 5.58; N, 4.56. Found: C, 89.71; H, 5.74; N, 4.50. ^s Bp_{0.25} 89–91°; lit. bp₄ 153° [K. Ziegler and H. Zeiser, *Justus Liebigs Ann. Chem.*, **485**, 174 (1931)]. ^t Mp (HCl salt) 142–143°; picrate mp 158–159°; lit. mp 158–159° [F. M. Elkobaisi and W. J. Hickenbottom, *J. Chem. Soc.*, 1286 (1960)]. ^u Bp₁₂ 135–137°; lit. bp₁₅ 143° [E. Knoevenagel, *Ber.*, **55**, 1912 (1922)]. ^v Mp 95–96°; nmr (CDCl₃) δ 2.72 (s, 3), 7.44 (m, 10), 8.03 (m, 2). ^w Anal. Calcd for C₁₈H₁₅N₃: C, 88.13; H, 6.16; N, 5.71. Found: C, 87.78; H, 6.01; N, 5.87. ^x Mp 109–110°; lit. mp 111° [W. H. Mills and J. L. B. Smith, *J. Chem. Soc.*, **121**, 2732 (1922)]. ^y Mp (HCl salt) 169–171°; lit. mp 170–172° [S. Sugawara and R. Tachikawa, *Tetrahedron*, **4**, 205 (1958)]. ^z Mp 80–81°; lit. mp 80–81.5° [K. Nakagawa, H. Onoue, and J. Sugita, *Chem. Pharm. Bull.*, **12**, 1135 (1964)]. ^{aa} Bp_{0.03} 88–89° (HgCl₂ salt mp 143–144° dec); nmr (CDCl₃) δ 1.10 (d of t, 3, J = 0.5, 7 Hz), 2.28 (d of pentuplet, 2, J = 1, 7 Hz), 6.57 (d of d, 1, J = 16, 1 Hz), 7.04 (t of d, 1, J = 7, 16 Hz), 7.84 (m, 4), 8.69 (s, 1). ^{ab} Anal. Calcd for C₁₂H₁₂N₂HgCl₂: C, 31.62; H, 2.65; N, 6.15. Found: C, 31.77; H, 2.70; N, 6.09. ^{ac} Mp 99–103°; lit. mp 105° [J. K. Landquist and G. J. Stacey, *J. Chem. Soc.*, 2822 (1953)]. ^{ad} Mp 94–95°; nmr (CDCl₃) δ 7.32 (d, 1, J = 16 Hz), 7.82 (m, 9), 8.30 (d, 1, J = 16 Hz), 9.31 (s, 1). ^{ae} Anal. Calcd for C₁₆H₁₂N₂: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.87; H, 5.37; N, 12.02.

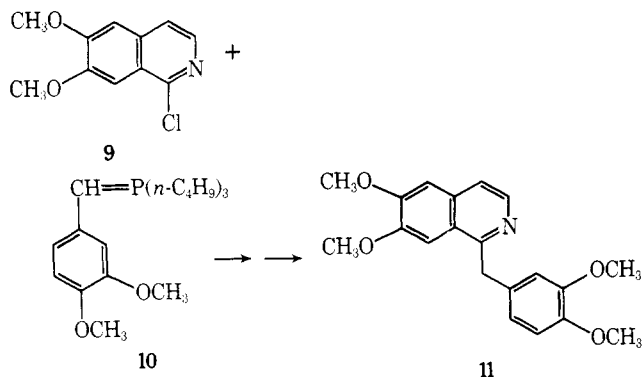
via the reversible formation of an intermediate betaine, leading predictably to trans stereochemistry in the resulting olefin.⁹

The versatility of this new procedure for heterocyclic functionalization is further illustrated by the specific illustrations given below.

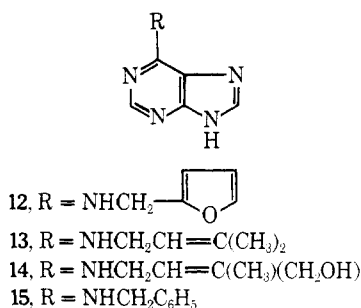
(a) **The Synthesis of Papaverine (11).** In the years since 1909, when Pictet and Gams reported the first synthesis of papaverine (11),¹⁰ numerous alternate syntheses of this alkaloid have been reported. With the exception of the recent application of the Reissert reaction (which gives papaverine

in only 17% yield from 6,7-dimethoxyisoquinoline, however),¹¹ these procedures require a ring-closure reaction as one of the final steps in a relatively long reaction sequence. The utility of our alkylation procedure is demonstrated by the direct synthesis of papaverine in 74% yield in one step by the reaction of 1-chloro-6,7-dimethoxyisoquinoline (9) with the Wittig reagent 10, prepared from veratryl chloride and tri-*n*-butylphosphine.

(b) **The Synthesis of Cytokinin Analogs.** A number of 6-alkylaminopurines [6-furfurylaminopurine (kinetin) (12), 6-(γ,γ -dimethylallylamino)purine (13), 6-(4-hydroxy-3-



methyl-*trans*-2-butenylamino)purine (zeatin) (**14**), and 6-benzylaminopurine (**15**)] belong to that important class of



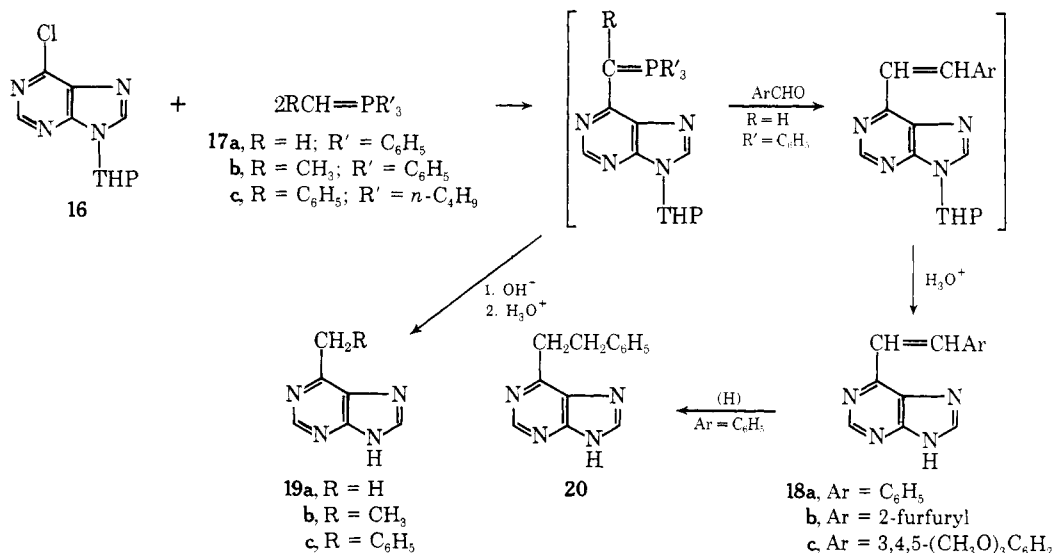
highly active stimulants of cell division and organ formation in plant tissues known as cytokinins.¹²⁻¹⁵ Replacement of the -NHCH₂- linkage in these compounds by a -CH=CH- or -CH₂CH₂- grouping might give analogs¹⁶ which would be resistant to *in vivo* cleavage by adenine deaminases, and which might therefore exhibit interesting and potentially useful biological properties. We have prepared a number of such potential cytokinin analogs by our new alkenylation and alkylation procedure. Thus, reaction of 6-chloro-9-(tetrahydro-2-pyranyl)purine (**16**)¹⁷ with 2 equiv of methylenetriphenylphosphorane (**17a**), addition of an excess of an aromatic aldehyde, and subsequent removal of the tetrahydropyranyl protecting group with aqueous acid gave the desired trans olefins **18a-c** in good yield (Scheme II). The 6-alkyl substituted purines **19a-c** were readily prepared in a single step by treatment of **16** with 2 equiv of the appropriate Wittig reagent (**17a-c**), followed

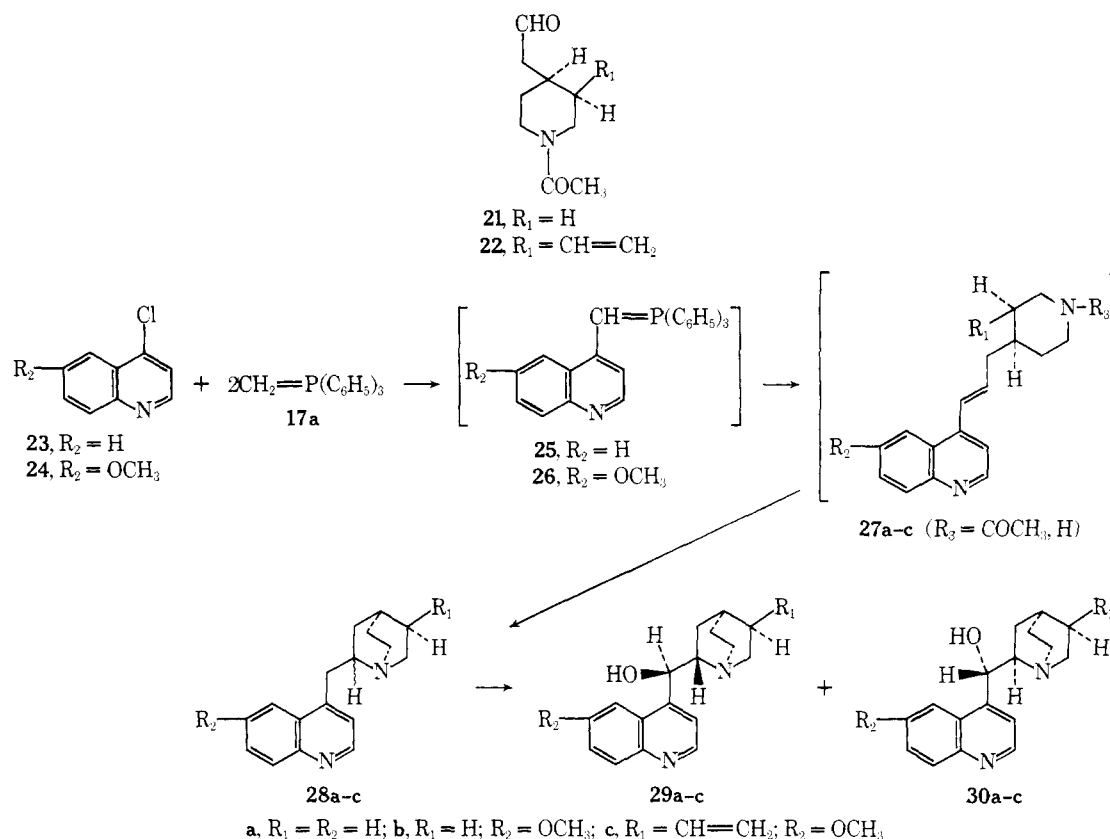
by hydrolysis (first with base and then with acid). Catalytic reduction of **18a** gave 6-(2-phenylethyl)purine (**20**). In preliminary tests,¹⁸ **18a** and **18b** proved toxic to three plant species: pinto beans, cucumbers, and blue grass; inhibition of growth was observed only with blue grass. It is interesting to note that the saturated derivative **20** was less active than the unsaturated styryl derivative **18a**.

(c) **Synthesis of the Cinchona Alkaloids.** Continuing interest in the development of more efficient total synthetic approaches to the Cinchona alkaloids¹⁹⁻²⁷ has culminated in several successful, extremely ingenious recent syntheses of quinine (**29c**) and quinidine (**30c**) by Uskoković²⁰ and by Gates.²¹ Both groups prepared the olefin **27c** (R₃ = H) which, by intramolecular Michael addition of the piperidine nitrogen to the conjugated vinyl grouping, was converted to a mixture of deoxyquinine and deoxyquinidine (**28c**). Since the reported syntheses of this key olefinic intermediate required numerous steps,^{20,21} we have examined its possible preparation by our new heterocycle alkenylation procedure. We report below one-step conversions of 4-chloroquinoline (**23**) to *rac*-ruban (**28a**) and of 4-chloro-6-methoxyquinoline (**24**) to *rac*-6-methoxyruban (**28b**), as well as the direct conversion of **24** to a mixture of deoxyquinine and deoxyquinidine (**28c**). All of these "one-step" reactions involve the formation of the intermediate olefins **27a-c** (R₃ = H) and their subsequent capture *in situ* by Michael addition (Scheme III).

Thus, the ylide **25**, which was prepared by treatment of 4-chloroquinoline (**23**) with 2 equiv of methylenetriphenylphosphorane (**17a**), was treated with *N*-acetyl-4-piperidineacetaldehyde (**21**) to give the olefin **27a** (R₃ = COCH₃). Removal of the *N*-acetyl group *in situ* by base-catalyzed hydrolysis gave **27a** (R₃ = H), which cyclized spontaneously to *rac*-ruban (**28a**) (36% overall yield). The small amount (13%) of the olefin **27a** (R₃ = H) which was also isolated could, in principle, be recycled to **28a**. Base-catalyzed hydroxylation of **28a** (in dimethyl sulfoxide-*tert*-butyl alcohol containing potassium *tert*-butoxide with dry oxygen)²⁰ gave a mixture of *rac*-*erythro*-rubanol (**29a** and **30a**) and *rac*-*threo*-rubanol (*ca.* 5:1 ratio, 67% overall yield). Furthermore, treatment of the ylide **26**, produced *in situ* from 4-chloro-6-methoxyquinoline (**24**) and 2 equiv of methylenetriphenylphosphorane, with *N*-acetyl-4-piperidineacetaldehyde (**21**) gave the olefin **27b** (R₃ = COCH₃), which was converted by a similar sequence of operations to *rac*-6-methoxyruban (**28b**) (35%); again some uncyclized

Scheme II





olefin (**27b**, $\text{R}_3 = \text{H}$) could be obtained (17%). Base-catalyzed hydroxylation, as before, afforded a mixture of *rac-erythro*-6-methoxyrubanol (**29b** and **30b**) and *rac-threo*-6-methoxyrubanol (*ca.* 5:1 ratio, 71% overall yield).

Finally, treatment of the ylide **26** with *N*-acetyl-3(*R*)-vinyl-4(*S*)-piperidineacetaldehyde (**22**) gave the *N*-acetylaminoquinoline **27c** ($\text{R}_3 = \text{COCH}_3$) which, after hydrolysis to **27c** ($\text{R}_3 = \text{H}$), cyclized spontaneously to a mixture of deoxyquinine and deoxyquinidine (**28c**) (38%). A small amount (6%) of the uncyclized olefin **27c** ($\text{R}_3 = \text{H}$) was isolated in this case as well. Introduction of the hydroxyl group at C-9 as previously described²⁰ gave quinine (**29c**) (33%), quinidine (**30c**) (30%), and a mixture of epiquinine and epiquinidine (10%).

Experimental Section

General Procedures. A. For the Preparation of Heterocyclic Phosphonium Ylides. To a stirred suspension of the appropriate phosphonium salt (2.2 equiv) in anhydrous 1,2-dimethoxyethane (DME) under dry nitrogen at -30 to -35° was added *n*-butyllithium in hexane (2.2 equiv); the reaction mixture was stirred for 1 hr, and the appropriate heterocycle (1 equiv) in anhydrous DME was added. The mixture was allowed to warm slowly (about 1 hr) to room temperature and then stirred either under reflux or at room temperature as specified in Table I.

B. For Hydrolysis of Heterocyclic Ylides. Formation of Alkyl-Substituted Heterocycles. Sodium carbonate (1 equiv) in water was added to the above solution of the heterocyclic ylide; the mixture was refluxed for 3 hr, evaporated under reduced pressure, and then worked up by one of the following procedures.

Method A. The mixture was suspended in chloroform or ether and extracted with dilute aqueous hydrochloric acid, the combined aqueous layers were made alkaline with sodium hydroxide, and the resulting mixture was extracted with ether. The combined ether extracts were dried and evaporated, and the product was purified by distillation or recrystallization.

Method B. The mixture was extracted several times with hot ether, the combined ether extracts were concentrated under re-

duced pressure, and the residual material was treated with an excess of mercuric chloride in 25% aqueous ethanol. The precipitated salt was then collected by filtration and washed, and the heterocycle was freed by treatment of the mercuric chloride salt with hydrogen sulfide gas and sodium carbonate in 10% aqueous ethanol. The crude product was purified by distillation or recrystallization.

C. For Wittig Reactions of Heterocyclic Ylides. Formation of Alkenyl-Substituted Heterocycles. The reaction mixture containing the heterocyclic ylide was treated with an excess (about 4 equiv) of an appropriate aldehyde or ketone in anhydrous DME. In order to minimize side reactions (aldol condensations), the addition of aliphatic aldehydes and ketones to the solution of the heterocyclic ylide was performed at -30° . The reaction mixture was then stirred for 24 hr at room temperature and filtered, and the excess solvent was removed under reduced pressure. The residue was treated in accordance with method B above.

The general procedure for the synthesis of alkyl-substituted heterocycles is illustrated in detail by the following representative example.

2-Ethylquinoline. To a stirred suspension of ethyltriphenylphosphonium bromide (4.97 g, 13.40 mmol) in 75 ml of anhydrous DME under dry nitrogen at -30 to -35° was added 5.8 ml of 2.32 *N*-butyllithium in hexane, the reaction mixture stirred for 1 hr, and 2-chloroquinoline (1.00 g, 6.11 mmol) in 10 ml of anhydrous DME was added. The reaction mixture was allowed to warm slowly (about 1 hr) to room temperature and then refluxed for 16 hr.

Sodium carbonate (0.65 g, 6.11 mmol) in 10 ml of water was added, refluxing continued for an additional 3 hr, and the excess solvent removed under reduced pressure. Chloroform (*ca.* 50 ml) was added to the residue and the organic layer extracted with 5% aqueous hydrochloric acid (4×50 ml). The combined extracts were made alkaline with sodium hydroxide, and the resulting mixture was extracted with ether (3×50 ml). The combined ether extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure, and the crude product was distilled to give 0.71 g (75%) of a colorless liquid, bp_{12} 117 – 119° , *lit.*²⁹ bp_{13} 128 – 131° .

The remaining alkyl-substituted heterocycles listed in Table I were similarly prepared by hydrolysis of the appropriate heterocyclic ylide except as described in detail below.

The general procedure for the synthesis of alkenyl-substituted heterocycles is illustrated in detail by the following representative example.

2-Styrylquinoline. To a stirred suspension of methyltriphenylphosphonium bromide (4.79 g, 13.40 mmol) in 75 ml of anhydrous DME under dry nitrogen at -30 to -35° was added 5.8 ml of 2.32 *N n*-butyllithium in hexane; the reaction mixture was stirred for 1 hr and 2-chloroquinoline (1.00 g, 6.11 mmol) in 10 ml of anhydrous DME added. The reaction mixture was allowed to warm slowly (about 1 hr) to room temperature and then refluxed for 16 hr.

After the mixture was cooled to room temperature, benzaldehyde (2.59 g, 24.4 mmol) in 5 ml of anhydrous DME was added and the mixture stirred for 24 hr at room temperature. The precipitated phosphonium salt was removed by suction filtration, the filtrate concentrated under reduced pressure, and the viscous residue extracted thoroughly with boiling ether (3×75 ml). The combined ether extracts were concentrated under reduced pressure, and the residual material was treated with mercuric chloride (5.0 g) in 15 ml of 25% aqueous ethanol. The precipitated salt was collected by filtration, washed well with ether, and the heterocycle freed by treatment of the mercuric chloride salt with hydrogen sulfide gas and sodium carbonate (2.0 g) in 50 ml of 10% aqueous ethanol for 1 hr at room temperature. The mixture was filtered with the aid of Celite and the filtrate concentrated under reduced pressure to give, after recrystallization from hexane, 0.91 g (65%) of blunt, cream-colored prisms, mp $96-97^\circ$, lit.³⁰ mp $99-100^\circ$.

The remaining alkenyl-substituted heterocycles listed in Table I were similarly prepared from the appropriate heterocyclic ylide and carbonyl compound, except as described in detail below.

Papaverine (11). To a stirred suspension of 3,4-dimethoxybenzyl-(tri-*n*-butyl)phosphonium chloride (prepared from 3,4-dimethoxybenzyl chloride and tri-*n*-butylphosphine) (5.78 g, 14.8 mmol) in 75 ml of anhydrous DME under dry nitrogen at -30 to -35° was added 5.7 ml of 2.6 *N n*-butyllithium in hexane, the reaction mixture stirred for 1 hr, and 6,7-dimethoxy-1-chloroisquinoline (1.50 g, 6.73 mmol) in 20 ml of anhydrous DME added. The mixture was allowed to come slowly (about 1 hr) to room temperature and then refluxed for 18 hr.

Sodium carbonate (0.72 g, 6.73 mmol) in 15 ml of water was added, refluxing continued for an additional 3 hr, and the excess solvent removed under reduced pressure. The residue was suspended in ether (*ca.* 100 ml) and the organic layer extracted with 5% aqueous hydrochloric acid (4×50 ml). The combined aqueous extracts were made alkaline with sodium hydroxide, and the resulting mixture was extracted with ether (3×200 ml). The combined ether extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Conversion of the crude free base to its hydrochloride salt and recrystallization from ethanol-ether gave 1.87 g (74%) of blunt, white needles, mp $223-225^\circ$ dec., identical with an authentic sample (mp, mmp, and ir) of papaverine hydrochloride.

6-Methylpurine (19a). To a stirred suspension of methyltriphenylphosphonium bromide (3.28 g, 9.2 mmol) in 50 ml of anhydrous DME under dry nitrogen at -30 to -35° was added 3.7 ml of 2.5 *N n*-butyllithium in hexane, the reaction mixture stirred for 1 hr, and 6-chloro-9-(tetrahydro-2-pyran)purine¹⁷ (1.00 g, 4.20 mmol) in 10 ml of anhydrous DME added. The reaction mixture was allowed to come slowly (about 1 hr) to room temperature and then stirred at room temperature for 4 hr.

Sodium carbonate (0.44 g, 4.20 mmol) in 10 ml of water was added and the resulting mixture refluxed for 3 hr. After cooling to room temperature, the reaction mixture was acidified to pH ~ 3 with 3 *N* aqueous hydrochloric acid, stirring continued for 2 hr, the excess solvent evaporated under reduced pressure, and water (*ca.* 50 ml) added to the residue. The aqueous layer was washed with chloroform (4×25 ml), evaporated under reduced pressure, and the residue recrystallized from 2-propanol-DME to give 0.41 g (73%) of a yellow powdery solid, mp $234-236^\circ$, lit.³¹ mp 236° .

6-Ethylpurine (19b). Using ethyltriphenylphosphonium bromide to generate the requisite phosphonium ylide, 6-ethylpurine was prepared in an analogous fashion in a yield of 66% as an orange powdery solid, mp $240-243^\circ$. Because this compound was difficult to purify for an analytical sample, it was acetylated with excess acetic anhydride; subsequent evaporation of the excess acetic an-

hydride under reduced pressure and recrystallization from hexane gave 6-ethyl-9-acetylurine as off-white needles, mp $84-85^\circ$: nmr (CDCl_3) δ 1.43 (t, 3), 3.05 (s, 3), 3.22 (q, 2), 8.75 (s, 1), 8.97 (s, 1).

Anal. Calcd for $\text{C}_9\text{H}_{10}\text{N}_4\text{O}$: C, 56.83; H, 5.30; N, 29.46. Found: C, 56.84; H, 5.40; N, 29.74.

6-Benzylpurine (19c). To a stirred suspension of benzyl(tri-*n*-butyl)phosphonium bromide (3.42 g, 9.20 mmol) in 50 ml of anhydrous DME under dry nitrogen at -30 to -35° was added 3.7 ml of 2.5 *N n*-butyllithium in hexane, the reaction mixture stirred for 1 hr, and 6-chloro-9-(tetrahydro-2-pyran)purine (1.00 g, 4.20 mmol) in 10 ml of anhydrous DME added. The reaction mixture was allowed to come slowly to room temperature (about 1 hr) and then stirred at room temperature for 6 hr.

Sodium carbonate (0.44 g, 4.20 mmol) in 10 ml of water was added, the resulting mixture refluxed for 3 hr, and the excess solvent evaporated under reduced pressure. The residue was suspended in water (*ca.* 75 ml) and the mixture extracted with ether (3×50 ml). The combined ether extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure, and the viscous residue was dissolved in a mixture of 25 ml of ethanol and 10 ml of 1 *N* aqueous hydrochloric acid. The resulting solution was stirred at room temperature for 4 hr, the excess acid neutralized with sodium bicarbonate (*ca.* 1 g), and the excess solvent removed under reduced pressure. The residue was chromatographed on 25 g of silica gel (Baker), eluting first with chloroform (200 ml, which were discarded) and then with 2% methanol-chloroform (500 ml). The combined 2% methanol-chloroform eluents were concentrated under reduced pressure, and the crude product was recrystallized from a small volume of ethyl acetate to give 0.63 g (72%) of white needles, mp $165-166^\circ$: nmr (CDCl_3) δ 4.60 (s, 2), 7.37 (m, 5), 8.25 (s, 1), 9.05 (s, 1).

Anal. Calcd for $\text{C}_{12}\text{H}_{10}\text{N}_4$: C, 68.55; H, 4.79; N, 26.65. Found: C, 68.34; H, 4.73; N, 26.64.

6-Styrylpurine (18a). The heterocyclic ylide was prepared in the same manner as described for the preparation of 6-methylpurine (19a) above.

Benzaldehyde (1.78 g, 16.8 mmol) in 10 ml of anhydrous DME was added and the mixture stirred for 24 hr at room temperature. The precipitated phosphonium salt was removed by filtration, the filtrate concentrated under reduced pressure, and the viscous residue dissolved in a mixture of 25 ml of ethanol and 10 ml of 1 *N* aqueous hydrochloric acid. The solution was stirred for 4 hr at room temperature, the excess acid neutralized with sodium bicarbonate (*ca.* 1 g), and the excess solvent removed under reduced pressure. The residue was chromatographed on 25 g of silica gel (Baker), eluting first with chloroform (200 ml, which were discarded) and then with 2% methanol-chloroform (500 ml). The combined 2% methanol-chloroform eluents were concentrated under reduced pressure, and the crude product was recrystallized from chloroform to give 0.51 g (55%) of colorless needles, mp $245-246^\circ$. The analytical sample was recrystallized from ethyl acetate, mp $248-249^\circ$: nmr ($\text{DMSO}-d_6$) δ 7.57 (m, 3), 7.79 (d, 1, $J = 16$ Hz), 7.86 (m, 2), 8.50 (d, 1, $J = 16$ Hz), 8.83 (s, 1), 9.00 (s, 1).

Anal. Calcd for $\text{C}_{13}\text{H}_{10}\text{N}_4$: C, 70.25; H, 4.54; N, 25.21. Found: C, 70.14; H, 4.57; N, 25.00.

The following compounds were prepared analogously. **1-(2-Furfuryl)-2-(6-purinyl)ethylene (18b)** was obtained in 63% yield as pale yellow needles from chloroform, mp $238-240^\circ$ dec. The analytical sample was recrystallized from ethyl acetate, mp $244-245^\circ$ dec: nmr ($\text{DMSO}-d_6$) δ 6.73 (d of d, 1, $J = 1.5, 3.5$ Hz), 7.02 (d, 1, $J = 3.5$ Hz), 7.50 (d, 1, $J = 16$ Hz), 7.94 (d, 1, $J = 1.5$ Hz), 8.31 (d, 1, $J = 16$ Hz), 8.67 (s, 1), 8.93 (s, 1).

Anal. Calcd for $\text{C}_{11}\text{H}_8\text{N}_4\text{O}$: C, 62.25; H, 3.80; N, 26.40. Found: C, 62.35; H, 3.90; N, 26.12.

1-(3,4,5-Trimethoxyphenyl)-2-(6-purinyl)ethylene (18c) (70%) was in the form of bright yellow prisms from chloroform-ether, mp $202-203^\circ$: nmr ($\text{DMSO}-d_6$) δ 3.87 (s, 3), 4.00 (s, 6), 7.19 (s, 2), 7.74 (d, 1, $J = 16$ Hz), 8.43 (d, 1, $J = 16$ Hz), 8.74 (s, 1), 9.00 (s, 1).

Anal. Calcd for $\text{C}_{16}\text{H}_{16}\text{N}_4\text{O}_3$: C, 61.53; H, 5.16; N, 17.94. Found: C, 61.80; H, 5.21; N, 18.20.

6-(β -Phenethyl)purine (20). A suspension of 6-styrylpurine (0.75 g) in 40 ml of ethanol containing 0.1 g of 10% Pd/C was shaken

under 1 atm of hydrogen at room temperature until the hydrogen uptake ceased. The mixture was heated to boiling and filtered through a Celite pad, and the filtrate was evaporated under reduced pressure to give 0.74 g of crude product. Recrystallization from a small volume of benzene gave 0.68 g (90%) of colorless plates, mp 133–134°: nmr (CDCl₃) δ 3.47 (m, 4), 7.22 (s, 5), 8.36 (s, 1), 9.06 (s, 1).

Anal. Calcd for C₁₃H₁₂N₄: C, 69.62; H, 5.39; N, 24.99. Found: C, 69.40; H, 5.25; N, 24.91.

***N*-Benzoyl-4-(carbethoxymethyl)piperidine.** A solution of *N*-benzoyl-4-(carbethoxymethyl)piperidine³² (16.40 g) in 300 ml of ethanol containing 1.0 g of 10% Pd/C was shaken with hydrogen (60 psi) until hydrogen uptake had ceased. The mixture was heated to boiling and filtered with the aid of Celite, and the filtrate was concentrated under reduced pressure. The crude product was distilled to give 15.86 g (97%) of a colorless oil which solidified upon cooling and scratching; bp_{0.20} 176–178°. Recrystallization from hexane gave colorless prisms, mp 47–48°: nmr (CDCl₃) δ 1.23 (t, 3), 4.13 (q, 2; 2 also buried under the q), 1.2–3.2 (broad series of m, 9), 7.36 (s, 5).

Anal. Calcd for C₁₆H₂₁NO₃: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.73; H, 7.63; N, 5.09.

***N*-Acetyl-4-piperidineacetaldehyde (21).** To a stirred solution of *N*-benzoyl-4-(carbethoxymethyl)piperidine (5.00 g, 18.2 mmol) in 50 ml of anhydrous toluene under dry nitrogen at –75° was slowly added (ca. 1.5 hr) a 20% solution of diisobutylaluminum hydride (38.3 ml, 38.3 mmol) in hexane. The solution was stirred an additional 3 hr and the reaction quenched by the addition of 25 ml of 6 *N* aqueous hydrochloric acid. The layers were separated, and the aqueous layer was washed with methylene chloride (3 × 75 ml) and then neutralized with sodium bicarbonate. The amorphous solid was removed by suction filtration with the aid of Celite and the filter pad washed well with water; the combined filtrate and washings were concentrated under reduced pressure (water bath temperature ca. 35°) to about 50 ml. The solution was saturated with sodium chloride and cooled to 0 to 5° in an ice-salt bath, and a solution of sodium acetate (15.0 g) in 15 ml of water and 15 ml of acetic anhydride was added simultaneously with vigorous stirring. The mixture was stirred an additional 30 min, the excess acid neutralized with sodium carbonate, and the aqueous solution extracted with methylene chloride (4 × 75 ml). The combined extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure, and the residual oil was carefully distilled to give 2.31 g (75%) of a colorless liquid, bp_{0.03} 88–90°: nmr (CDCl₃) δ 1.0–4.8 (broad series of m's, 11), 2.05 (s, 3), 9.81 (t, 1, *J* = 1.5 Hz).

Anal. Calcd for C₉H₁₅NO₂: C, 63.55; H, 9.27; N, 7.98. Found: C, 63.88; H, 8.94; N, 8.28.

***N*-Acetyl-3(*R*)-vinyl-4(*S*)-piperidineacetaldehyde (22).** To a stirred solution of *N*-benzoylmerquinene methyl ester¹⁹ (2.50 g, 8.72 mmol) in 30 ml of anhydrous toluene under dry nitrogen at –75° was slowly added (ca. 1 hr) a 20% solution of diisobutylaluminum hydride (18.3 ml, 18.3 mmol) in hexane. The solution was then stirred an additional 3 hr and quenched by the addition of 15 ml of 6 *N* aqueous hydrochloric acid. The layers were separated, and the aqueous layer was washed with ether (3 × 50 ml) and neutralized with sodium bicarbonate. The amorphous solid was removed by suction filtration with the aid of Celite and the filter pad washed well with water, and the combined filtrate and washings were concentrated under reduced pressure (water-bath temperature ca. 35°) to about 25 ml. The solution was saturated with sodium chloride and cooled to 0 to 5° in an ice-salt bath, and a solution of sodium acetate (10.0 g) in 10 ml of water and 10 ml of acetic anhydride was added simultaneously with vigorous stirring. The mixture was stirred for an additional 30 min, the excess acid neutralized with sodium carbonate, and the aqueous solution extracted with methylene chloride (4 × 50 ml). The combined extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residual oil (1.2 g) was carefully distilled to give 0.67 g (40%) of a colorless liquid, bp_{0.04} 110–112°: nmr (CDCl₃) δ 1.0–4.8 (series of broad m's, 10), 2.04 and 2.08 (2 d's, 3, *J* \approx 1 Hz), 5.15 (m, 2), 5.80 (m, 1), 9.78 (perturbed t, 1, *J* \approx 1.5 Hz); exact mass, 195.125313 (calcd for C₁₁H₁₇NO₂, 195.125921).

***rac*-Ruban (28a).** To a stirred suspension of methyltriphenyl-

phosphonium bromide (6.34 g, 17.7 mmol) in 75 ml of anhydrous DME under dry nitrogen at –30 to –35° was added 7.1 ml of 2.5 *N*-butyllithium in hexane; the reaction mixture was stirred for 1 hr and 4-chloroquinoline (1.70 g, 10.35 mmol) in 10 ml of anhydrous DME added. The mixture was allowed to warm slowly (about 1 hr) to room temperature and then refluxed for 24 hr. The reaction mixture was then cooled to –50°, *N*-acetyl-4-piperidineacetaldehyde (1.00 g, 5.92 mmol) in 10 ml of anhydrous DME added, stirring continued for 15 min, the cooling bath removed, and the stirring continued at room temperature for 24 hr. The precipitated phosphonium salts were removed by suction filtration, and the filtrate was concentrated under reduced pressure. The residue was dissolved in a mixture of 25 ml of ethanol and 40 ml of 2 *N* aqueous potassium hydroxide, and the mixture was refluxed gently for 72 hr. The excess ethanol was evaporated under reduced pressure and the aqueous mixture extracted with ether (4 × 50 ml). The combined ether fractions were extracted with saturated sodium chloride solution containing 10% acetic acid (3 × 50 ml), and the combined aqueous extracts were washed with ether (4 × 100 ml) and made alkaline with dilute sodium hydroxide solution. The resulting mixture was extracted with ether (4 × 50 ml), and the combined ether extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 1.01 g of crude product. The crude material was absorbed on 5 g of aluminum oxide (activity grade V, Merck) and chromatographed on 45 g of aluminum oxide (activity grade V, Merck), eluting first with benzene-hexane (1:4) (600 ml; the first 50 ml were discarded). Concentration of the combined eluents under reduced pressure and extraction of the residue with hot hexane gave, after evaporation of the hexane, 0.54 g (36%) of crude *rac*-ruban as a pale yellow oil. Based on tlc, the crude product was ca. 95% pure, containing a trace of a less polar impurity: nmr (CDCl₃) δ 1.35 (broad m's, 7), 3.0 (broad m's, 7), 7.24 (d, 1, *J* = 4.5 Hz), 7.61 (m, 2), 8.08 (m, 2), 8.83 (d, 1, *J* = 4.5 Hz).

Subsequent elution of the column with methylene chloride (300 ml), concentration of the combined eluents under reduced pressure, and extraction of the residue with hot hexane gave, after evaporation of the hexane, 0.20 g (13%) of uncyclized olefin as a yellow oil. This structural assignment is based on the nmr (presence of vinyl protons) and also on a similar, incomplete intramolecular Michael condensation reported independently:³³ nmr (CDCl₃) δ 1.0–3.5 (series of broad m's, 12), 6.48 (m, 1), 7.09 (d, 1, *J* = 16 Hz), 7.3–8.3 (m, 5), 9.00 (d, 1, *J* = 4.5 Hz).

***erythro*- (29a, 30a) and *threo*-Rubanol.** To an equilibrated, stirred solution of crude, *rac*-ruban (0.50 g, 1.98 mmol) in 75 ml of dimethyl sulfoxide-*tert*-butyl alcohol (4:1) in an atmosphere of dry oxygen was added dry potassium *tert*-butoxide (0.33 g, 2.98 mmol) in one lot.²⁰ The mixture was stirred at room temperature for 1 hr; the reaction was then quenched by the addition of water (10 ml) and acetic acid (1 ml). The excess solvent was removed under reduced pressure, the residue dissolved in water (50 ml), the solution made alkaline with dilute sodium hydroxide, and the mixture extracted with methylene chloride (2 × 75 ml). The combined extracts were washed with saturated brine solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give 0.48 g of crude product. Preparative thin layer chromatography on Merck silica gel plates (2 mm) using chloroform-triethylamine-methanol (87.5:10:2.5) gave 294 mg (55%) of *erythro*-rubanol as colorless, blunt prisms from ethanol, mp 227–229 (lit.³⁴ mp 228.5–230.5°), and 62 mg (12%) of the less polar *threo*-rubanol. The *threo*-rubanol was initially obtained as an oil which solidified slowly upon standing, mp 105–115° (lit.³⁴ mp 117–119°).

The *erythro*/*threo* ratio of 4.7:1 is similar to that previously reported by Gates²¹ and Uskoković²⁰ for similar oxidations.

***rac*-6-Methoxyruban (28b).** Using the same mole quantities, 6-methoxyruban was prepared from 4-chloro-6-methoxyquinoline in a similar manner as described for the preparation of ruban. The crude product (1.21 g) was absorbed on 5 g of aluminum oxide (activity grade V, Merck) and chromatographed on 45 g of aluminum oxide (activity grade V, Merck). The column was eluted with benzene-hexane (1:4) (1000 ml; the first 75 ml were discarded), and the combined eluents were then concentrated under reduced pressure. Extraction of the residue with hot hexane gave, after evaporation of the hexane, 0.59 g (35%) of *rac*-6-methoxyruban as

a pale yellow oil. Based on tlc, the crude product was *ca.* 95% pure, containing a trace of a less polar impurity. 6-Methoxyruban formed a dipicrate as a yellow powdery solid from ethanolic dimethyl sulfoxide, mp 191–193° dec (lit.³³ mp 191–193° dec); nmr (CDCl₃) δ 1.57 (broad m's, 7), 3.15 (broad m's, 7), 3.95 (s, 3), 7.35 (m, 3), 8.09 (perturbed d, 1, J = 10 Hz), 8.74 (d, 1, J = 4.5 Hz).

Subsequent elution of the column with methylene chloride (500 ml), concentration of the combined eluents under reduced pressure, and extraction of the residue with hot hexane gave, after evaporation of the hexane, 0.29 g (17%) of the uncyclized olefin as a pale yellow oil. The olefin formed a dipicrate as a yellow powdery solid from ethanolic dimethyl sulfoxide, mp 200–202° dec (lit.³³ mp 202–203.5° dec); nmr (CDCl₃) δ 1.0–3.3 (series of broad m's, 12), 3.87 (s, 3), 6.34 (m, 1), 7.00 (d, 1, J = 16 Hz), 7.34 (m, 3), 8.05 (perturbed d, 1, J = 10 Hz), 8.71 (d, 1, J = 4.5 Hz).

erythro- (29b, 30b) and threo-6-Methoxyrubanol. Crude *rac*-6-methoxyruban (0.59 g, 2.09 mmol) was hydroxylated at C₉ in the same manner²⁰ as described above to give 0.55 g of crude product. Preparative thin layer chromatography on Merck silica gel plates (2 mm) using chloroform–triethylamine–methanol (87.5:10:2.5) gave 360 mg (58%) of *erythro*-6-methoxyrubanol as colorless plates from ethanol, mp 263–264° dec. Recrystallization of *erythro*-6-methoxyrubanol from aqueous ethanol gave the dihydrate as colorless prisms, mp 92–94° (lit.³⁵ mp 94–95°). Drying the dihydrate at 80° (1 mm) gave anhydrous *erythro*-6-methoxyrubanol, mp 171–172° (lit.³⁵ mp 172°); nmr (CDCl₃) δ 3.89 (s, 3), 5.97 (broad d, 1, J \approx 3 Hz), 7.35 (m, 2), 7.63 (d, 1, J = 4.5 Hz), 8.02 (d, 1, J = 10 Hz), 8.67 (d, 1, J = 4.5 Hz).

In addition to *erythro*-6-methoxyrubanol, 81 mg (13%) of the less polar *threo*-6-methoxyrubanol was obtained as an oil, which slowly solidified upon standing. Its nmr spectrum was consistent with this assignment.

The *erythro*/*threo* ratio of 4.5:1 is similar to that reported by Gates²¹ for the same oxidation and by Uskoković²⁰ for a similar oxidation.

Deoxyquinine and Deoxyquinidine (28c). To a stirred suspension of methyltriphenylphosphonium bromide (2.56 g, 7.18 mmol) in 50 ml of anhydrous DME under dry nitrogen at –30 to –35° was added 2.8 ml of 2.5 *N*-butyllithium in hexane; the reaction mixture was stirred for 1 hr and 4-chloro-6-methoxyquinoline (0.79 g, 4.10 mmol) in 10 ml of anhydrous DME added. The mixture was allowed to come slowly (about 1 hr) to room temperature and then refluxed for 30 hr. The reaction mixture was cooled to –50°, *N*-acetyl-3(*R*)-vinyl-4(*S*)-piperidineacetaldehyde (0.40 g, 2.05 mmol) in 10 ml of anhydrous DME added, stirring continued for 15 min, the cooling bath removed, and stirring continued for 24 hr at room temperature. The precipitated phosphonium salts were removed by suction filtration, and the filtrate was concentrated under reduced pressure. The residue was dissolved in a mixture of 10 ml of ethanol and 20 ml of 2 *N* aqueous potassium hydroxide and the mixture refluxed gently under nitrogen for 48 hr. The ethanol was evaporated under reduced pressure and the aqueous mixture extracted with ether (4 \times 25 ml). The combined ether fractions were extracted with saturated sodium chloride solution containing 10% acetic acid (4 \times 25 ml), and the combined aqueous extracts were washed with ether (4 \times 75 ml) and made alkaline with dilute sodium hydroxide solution. The resulting mixture was extracted with ether (4 \times 25 ml), and the combined ether extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 0.41 g of crude deoxyquinine–deoxyquinidine. The crude material was absorbed on 5 g of aluminum oxide (activity grade V, Merck) and chromatographed on 45 g of aluminum oxide (activity grade V, Merck), eluting first with benzene–hexane (1:4) (*ca.* 200 ml, which were discarded) and then benzene (1000 ml). Concentration of the combined benzene eluents under reduced pressure afforded 0.24 g (38%) of a mixture of deoxyquinine and deoxyquinidine as a pale yellow oil. Based on tlc, the crude product was *ca.* 95% pure, containing a trace of a less polar impurity: nmr (CDCl₃) δ 1.55 (broad m's, 6), 3.12 (broad m's, 7), 3.94 (s, 3), 5.07 (m, 2), 5.94 (m, 1), 7.33 (m, 3), 8.03 (perturbed d, 1, J = 10 Hz), 8.67 (d, 1, J = 4.5 Hz).

Subsequent elution of the column with methylene chloride (1000 ml) gave, after evaporation of the combined eluents under reduced pressure, 0.04 g (6%) of uncyclized olefin (27c, R₃ = H). This

structural assignment is based on its nmr spectrum (presence of additional vinyl protons) and by analogy with previously described experiments; tlc indicated that a small amount of deoxyquinine–deoxyquinidine was also present. Finally, elution with 20% methanol–methylene chloride gave 0.04 g of small additional amounts of deoxyquinine–deoxyquinidine and uncyclized olefin and a trace of unidentified material.

Quinine (29c), Quinidine (30c), Epiquinine, and Epiquinidine. The crude mixture of deoxyquinine–deoxyquinidine (0.22 g, 0.71 mmol) was hydroxylated at C₉ in the manner previously described.²⁰ Preparative thin layer chromatography of the crude product mixture (0.20 g) on Merck silica gel plates (2 mm) using chloroform–triethylamine–methanol (87.5:10:2.5) as before gave 75 mg (33%) of quinine, 68 mg (30%) of quinidine, and 30 mg (10%) of a mixture of epiquinine and epiquinidine. Again, the *erythro*/*threo* ratio of 4.8:1 is similar to that reported by Gates²¹ and Uskoković²⁰ for the same oxidation.

The synthetic quinine obtained by this procedure was identical with an authentic sample (nmr, uv, mass spectrum, and tlc), mp 170–173° and mmp (with an authentic sample of quinine dihydrate, mp 173–174°) 172–174°; nmr (CDCl₃) δ 3.87 (s, 3), 4.96 (m, 2), 5.53 (d, 1, J = 4 Hz), 5.84 (m, 1), 7.27 (m, 2), 7.49 (d, 1, J = 4.5 Hz), 7.92 (d, 1, J = 10 Hz), 8.44 (d, 1, J = 4.5 Hz); exact mass, 324.183039 (calcd for C₂₀H₂₄N₂O₂, 324.183768); base peak at *m/e* 136.

The synthetic quinidine obtained by this procedure was also identical with an authentic sample (nmr, uv, mass spectrum, and tlc), mp 165–168° and mmp (with an authentic sample of quinidine monohydrate, mp 170–171°) 168–170°; nmr (CDCl₃) δ 3.85 (s, 3), 5.07 (m, 2), 5.60 (d, 1, J = 4 Hz), 6.10 (m, 1), 7.29 (m, 2), 7.51 (d, 1, J = 4.5 Hz), 7.92 (d, 1, J = 10 Hz), 8.48 (d, 1, J = 4.5 Hz); exact mass, 324.183353 (calcd for C₂₀H₂₄N₂O₂, 324.183768); base peak at *m/e* 136.

The mixture of epiquinine and epiquinidine was not fully characterized, but its nmr spectrum was consistent with this assignment.

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Stereoselective Synthesis of Sesquiterpene Lactones. Total Synthesis of (±)-Isotelekin

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Abstract: A stereoselective total synthesis of racemic isotelekin (**1**) is described. Key steps in the synthesis are the introduction of the axial allylic alcohol moiety by base-promoted opening of an epoxide (**6**); introduction of a cis-fused five-membered ring lactone by enamine alkylation of a keto ester (**8**) followed by sodium borohydride reduction of the alkylated material (**9**); and introduction of an α -methylene group onto the lactone ring by a previously developed procedure involving Mannich reaction on an α -carbomethoxylactone (**12**) followed by quaternization and cleavage-elimination to give racemic isotelekin.

Isotelekin¹ (**1**) is one of a number of known lactone bitter principles belonging to the eudesmane class of sesquiterpenes.² An important structural feature of this compound is the α -methylene- γ -butyrolactone moiety which has attracted much synthetic interest recently³ because of its occurrence in a wide variety of natural compounds having considerable biological activity as allergenic agents,⁴ growth in-

hibitors,⁵ antibacterial agents,⁶ and antitumor agents.⁷ This paper reports a stereoselective total synthesis of (±)-isotelekin.

In approaching the synthetic problems presented by isotelekin, the molecule can be viewed as consisting of two parts, A and B. The approach to part A was to involve stereoselective epoxidation of an olefin from the side opposite

