sponding 1-hydroxy-2-methoxy proaporphines in good yield, providing a convenient synthesis of (±)-glaziovine (**6**)[3] and (±)-*N*-methyloreoline (**9**).[4] The preferential O-demethylation at C-1 is presumably due to a crowding of the C-1 methyl out of plane of the aromatic ring. Thus, when synthetic[5] (±)-amuronine (**3**) was refluxed with 20% aqueous hydrochloric acid it afforded (±)-11,12-dihydroglaziovine (**4a**) in 60% yield. The IR, NMR, and mass spectra were identical with those reported in the literature.[6] Evidence that the methoxyl group in **4a** was at C-2 rather than C-1 was forthcoming from a comparison of the methoxyl signal in the NMR spectrum of the corresponding 1-methoxy-2-hydroxy isomer linearisine (**4b**).[2,7] The structure of **4a** was unequivocally established by conversion of this compound to glaziovine. Acetylation of **4a** with acetic anhydride in the presence of *N,N*-dimethyl-4-pyridineamine[8] gave (±)-1-*O*-acetyl-11,12-dihydroglaziovine (**5**), which was converted to (±)-glaziovine by bromination and dehydrobromination essentially as described by Casagrande et al.[6]

(±)-8,9,11,12-Tetrahydropronuciferine (**7**), prepared from amuronine by catalytic hydrogenation,[5] was refluxed with 20% hydrochloric acid to give (±)-8,9,11,12-tetrahydroglaziovine (**8**), mp 97 °C (ether) (Casagrande et al.[6] report mp 160–162 °C), in 55% yield. The structure of **8**, based on analytical and spectral data, was confirmed by comparison with a sample prepared by catalytic hydrogenation of **4a**. Reduction of **8** with lithium triethylborohydride followed by chromatography gave predominantly the axial alcohol, (±)-*N*-methyloreoline (**9**), identical with a sample prepared by hydrogenation of glaziovine over platinum oxide.[6]

Experimental Section[9]

(±)-11,12-Dihydroglaziovine (4a). A solution of 1.4 g (4.47 mmol) of (±)-amuronine in 50 ml of 20% HCl was refluxed for a 24-h period under a N_2 atmosphere. The resulting dark solution was cooled and concentrated under vacuum to yield a dark residue which was dissolved in 25 ml of distilled water. The acidic solution was neutralized carefully with solid $NaHCO_3$ and extracted with chloroform (3 × 25 ml). The combined extracts were dried ($MgSO_4$) and concentrated under vacuum to yield 0.9 g of a foam which crystallized from ether to yield (±)-11,12-dihydroglaziovine, mp 199–201 °C after further crystallization from ether (lit.[6] mp 199–200 °C), yield 60% (0.81 g): NMR δ_{CDCl_3} (Me_4Si) 2.4 (s, 3, *N*-methyl), 3.85 (s, 3, methoxyl), 6.09 (d, J = 10 Hz, 1, C-9 olefinic proton), 6.6 (s, 1, aromatic), 6.8 (d, J = 10 Hz, 1, C-8 olefinic proton); IR (KBr) 1681 cm^{-1} (C=O); UV λ_{max} (EtOH) 227 nm (log ϵ 4.66), 278 (3.45); MS *m/e* 299 (M^+, 100), 298 (87), 257 (19), 256 (99).

(±)-1-*O*-Acetyl-11,12-dihydroglaziovine (5). To a solution of 0.168 g (0.56 mmol) of **4a** in 10 ml of CH_2Cl_2 stirred at room temperature under N_2 was added 0.75 ml of triethylamine, 0.07 g of *N,N*-dimethyl-4-pyridineamine, and 0.05 ml of acetic anhydride. The reaction mixture was stirred for 30 min, diluted with 20 ml of CH_2Cl_2, and washed with water (3 × 5 ml) and saturated $NaHCO_3$ solution (1 × 5 ml). The organic layer was dried ($MgSO_4$) and concentrated under vacuum to yield 0.234 g of a foam which was crystallized from ether to yield (±)-1-*O*-acetyl-11,12-dihydroglaziovine, 0.18 g (95% yield): mp 176–178 °C (lit.[6] mp 178 °C); NMR δ_{CDCl_3} (Me_4Si) 2.15 (s, 3, *O*-acetyl), 2.4 (s, 3, *N*-methyl), 3.75 (s, 3, methoxyl), 6.0 (d, J = 10 Hz, 1, C-8 olefinic proton), 6.65 (s, 1, aromatic), 6.7 (d, J = 10 Hz, 1, C-8 olefinic proton); IR (KBr) 1754, 1672 cm^{-1} (C=O); UV λ_{max} (EtOH) 223 nm (log ϵ 4.36), 283 (3.4); MS *m/e* 341 (M^+, 66), 340 (56), 298 (100), 256 (47).

(±)-8,9,11,12-Tetrahydropronuciferine (7):[5] mp 124–126 °C; NMR δ_{CDCl_3} (Me_4Si) 2.45 (s, 3, *N*-methyl), 3.85 (s, 6, methoxyls), 6.65 (s, 1, aromatic); IR (KBr) 1718 cm^{-1} (C=O); UV λ_{max} (EtOH) 285 nm (log ϵ 3.38); MS *m/e* 315 (M^+, 28), 314 (100), 272 (55).

(±)-8,9,11,12-Tetrahydroglaziovine (8) was prepared as described for **4a**, in 55% yield: mp 97 °C (ether); NMR δ_{CDCl_3} (Me_4Si) 2.45 (s, 3, *N*-methyl), 3.9 (s, 3, methoxyl), 6.55 (s, 1, aromatic), 6.45–6.9 (bd, s, 1, phenolic OH); IR (KBr) 1718 cm^{-1} (C=O); UV λ_{max} (EtOH) 285 nm (log ϵ 3.42); MS *m/e* 301 (M^+, 34), 300 (100), 259 (13), 258 (75).

(±)-*N*-Methyloreoline (9). To a stirred solution of 0.098 g (0.325 mmol) of **8** in 10 ml of THF cooled to −70° under a nitrogen atmosphere was added dropwise 0.33 ml (0.33 mmol) of a 1 M solution of lithium triethylborohydride in THF. After addition, the reaction mixture was stirred for 0.5 h, warmed to room temperature, and acidified with acetic acid–water (6:1). The resulting solution was neutralized with saturated $NaHCO_3$ and extracted with chloroform (3 × 10 ml). The combined extracts were dried ($MgSO_4$) and concentrated under vacuum to yield 0.083 g of a foam which was chromatographed on silica gel (eluted with chloroform) and crystallized from ether to give (±)-*N*-methyloreoline: mp 189–192 °C (lit.[6] mp 187–189 °C); NMR δ_{CDCl_3} (Me_4Si) 2.39 (s, 3, *N*-methyl), 3.98 (s, 3, methoxyl), 6.49 (s, 1, aromatic); UV λ_{max} (EtOH) 286 nm (log ϵ 3.37); MS *m/e* 303 (M^+, 40), 302 (100), 261 (16), 260 (85).

Registry No.—**3**, 19647-85-9; **4a**, 54274-43-0; **5**, 54169-67-4; **6**, 17127-48-9; **7**, 19647-93-9; **8**, 50300-14-6; **9**, 58166-04-4.

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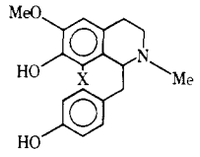

10, X = H
11, X = Br

of the alkaloid [T. Kametani, S. Shibuya, T. Nakano, and F. Fukumoto, *J. Chem. Soc. C*, 3818 (1971)]. The latter synthesis has been reinvestigated and improved (26% yield) [C. Casagrande and L. Canonica, *J. Chem. Soc., Perkin Trans. 1*, 1647 (1975)]. Recently, Casagrande et al.[6] have reported extending Bernauer's synthesis[5] of amuronine to (±)-glaziovine.
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An Improvement in the Doebner–Miller Synthesis of Quinaldines

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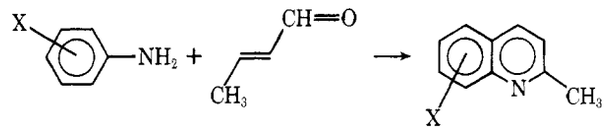
Received September 28, 1976

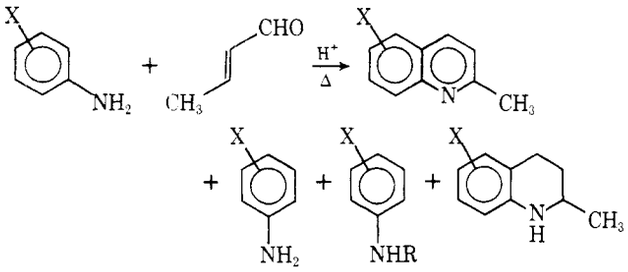
Since its discovery in 1881,[1] the Doebner–Miller reaction has found a great deal of synthetic utility for the preparation of substituted quinaldines (2-methylquinolines). Unlike the closely related Skraup synthesis of quinolines, the Doebner–Miller reaction is experimentally much simpler, and not nearly as hazardous to run.[2] However, the method does suffer from some major disadvantages. The yields reported are usually low owing to the many by-products formed in the reaction. Depending upon the particular conditions employed, a typical product mixture obtained from the reaction of an aniline with crotonaldehyde (or crotonaldehyde precursor) in strongly acidic solution consists of the desired quinaldine contami-

Table I



Aniline X	Registry No.	Quinaldine complex[n] (Q)	Registry no.	% yield	Mp, °C	Quinaldine mp, °C	Registry no.
4-F	371-40-4	6-F-Q·HCl·½ZnCl$_2$	61075-86-3	54	238–241	54–56[a]	1128-61-6
4-Cl	106-47-8	6-Cl-Q·HCl·½ZnCl$_2$	61075-87-4	53	238–241	94–95[b]	92-46-6
H	62-53-3	Q·HCl·½ZnCl$_2$·½H$_2$O	61075-88-5	55	240–243[c]	*d*	91-63-4
4-CH$_3$	106-49-0	6-CH$_3$-Q·HCl·½ZnCl$_2$	61075-89-6	52	210–212	55–58[e]	877-43-0
4-OCH$_3$	104-94-9	6-OCH$_3$-Q·HCl·½ZnCl$_2$·½H$_2$O	61075-90-9	51	198–200	65–67[f]	1078-28-0
2-Cl	95-51-2	8-Cl-Q·HCl·½ZnCl$_2$	61075-91-0	43	257–260 dec	66–68[g]	3033-82-7
2-CH$_3$	95-53-4	8-CH$_3$-Q·HCl·½ZnCl$_2$	61075-92-1	55	258–261 dec[h]	*i*	1463-17-8
2-Br	615-36-1	8-Br-Q·HCl·½ZnCl$_2$	61075-93-2	50	263–266 dec	67–68[j]	61047-43-6
2-OCH$_3$	90-04-0	8-OCH$_3$-Q·HCl·½ZnCl$_2$	61075-94-3	48	219–220 dec	124–125[k]	3033-80-5
3-Cl	108-42-9	7-Cl-Q·HCl·½ZnCl$_2$	61075-95-4	42	234–236	75–77[l]	4965-33-7
3-Br	591-19-5	7-Br-Q·HCl·½ZnCl$_2$	61075-96-5	47	250–253 dec	77–79[m]	4965-34-8

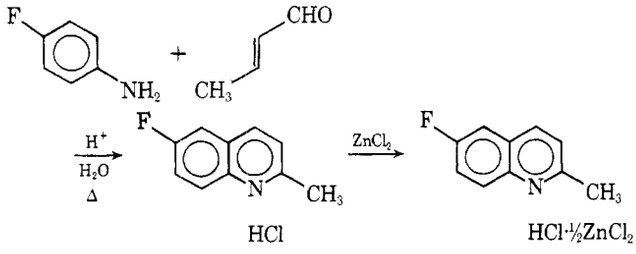
[a] Lit.[4] mp 57–59 °C. [b] Lit.[5] mp 93 °C. [c] Lit.[3] mp 240 °C. [d] Oil, IR identical with that of authentic material. [e] Lit.[6] mp 59.5 °C. [f] Lit.[6] mp 67 °C. [g] Lit.[5] mp 68 °C. [h] Lit.[3] mp 273 °C. [i] Oil, lit.[3] mp 27 °C. [j] Lit.[7] mp 69–69.5 °C. [k] Lit.[8] mp 125 °C. [l] Lit.[9] mp 76–78 °C. [m] Lit.[10] mp 77 °C. [n] Satisfactory analytical values were reported for all complexes.



nated with varying amounts of unreacted aniline, various *N*-alkylanilines, and 1,2,3,4-tetrahydroquinaldine. Isolation and purification of quinaldines from such reaction mixtures is often quite tedious, and the many manipulations involved also tend to lower the recovery of the desired product.

Since large amounts of 6-fluoroquinaldine were needed as an intermediate, we investigated the Doebner–Miller reaction as a potential method of preparation of this compound, and during the course of this work discovered an improved method of isolation of the product. Quite simply, it was found that when the reaction of *p*-fluoroaniline with crotonaldehyde under standard Doebener–Miller conditions was completed, addition of an equimolar amount of zinc chloride to the reaction mixture caused precipitation of a brown, curdy solid. Examination of the filtrate revealed that virtually all of the basic products had been removed.

When this crude, complex mixture was washed with 2-propanol, all of the impurities were dissolved and the bright yellow or gold crystalline solid which remained proved to be a pure 2:1 complex of 6-fluoroquinaldine hydrochloride and zinc chloride. The yield was consistently 50–55%.



A search of the literature revealed that only a few such complexes have been reported previously.[3,4] However, this method of purification seems to have received little attention over the years, perhaps because of a lack of experimental details and no reported yields in the earlier work.

The method was found suitable for the preparation of a number of other quinaldines. Starting with para- or ortho-substituted anilines, 6- and 8-substituted quinaldines, respectively, were obtained and isolated as their complexes. Of particular interest were results starting from meta-substituted anilines in which both 5- and 7-substituted quinaldines are formed with the 7 isomers as the major products. With only a slight variation in the workup procedure, the zinc chloride complexes of the 7 isomers could be isolated completely free of any of the 5 isomers. These results are summarized in Table I. Also included are the melting points of the free quinaldines which were recovered essentially completely from the complexes by treating an aqueous slurry with excess ammonium hydroxide.

Experimental Section

Melting points are uncorrected. Vapor phase chromatographic (VPC) analyses were performed on a Varian Aerograph 2100 instrument using a 6-ft 2% SE-30 on Chromosorb W column. Microanalyses were performed by Paul Olson and the microanalytical group of these laboratories.

Quinaldine Hydrochloride–ZnCl$_2$ Complex. General Procedure. To a solution of 0.20 mol of the aniline in 100 ml of 6 N HCl heated under reflux was added dropwise with stirring 17.3 g (0.21 mol) of 85% aqueous crotonaldehyde slowly over a 0.5–1-h period. After addition was complete, the dark solution was heated for an additional 0.5–1 h or until a VPC of a basified aliquot showed that no more aniline remained. The reaction mixture was cooled to room temperature and washed with ether to remove a small amount of tar. To the clear solution was added 27.2 g (0.20 mol) of anhydrous ZnCl$_2$ with vigorous stirring. A precipitate appeared as an oil or a solid usually in a few minutes. The mixture was stirred at room temperature for 0.5 h and then cooled to 0 °C in an ice bath. After stirring for an additional 15 min at this temperature, the brown or yellow granular solid was filtered, washed with cold 3 N HCl, and sucked reasonably dry with air. The solid was transferred to a beaker, stirred with 150–200 ml of 2-propanol, and then filtered, washed with 2-propanol until the washings were almost colorless, and washed with ether and air dried to provide the quinaldine hydrochloride–zinc chloride coimplex as a bright yellow or gold crystalline solid.

7-Chloroquinaldine Hydrochloride–ZnCl$_2$ Complex. The Doebner–Miller reaction with *m*-chloroaniline was run exactly as above. Addition of ZnCl$_2$ caused precipitation of a dark oil and the whole mixture was heated to reflux to give a clear brown solution. Upon cooling to room temperature with stirring, a tacky brown solid was obtained. Purification in the usual manner with 2-propanol gave the 7-chloroquinaldine hydrochloride–ZnCl$_2$ complex as a pale yellow solid. The free base was pure by VPC.

7-Bromoquinaldine Hydrochloride–ZnCl$_2$ Complex. The complex obtained starting from *m*-bromoaniline in the usual manner proved to be a thick gum which was insoluble in boiling 6 M HCl. Addition of more acid and water had no effect, and the mixture was cooled to room temperature. Treatment of the brown gum even with

boiling 2-propanol failed to dissolve the impurities. The product was successfully purified by triturating with boiling anhydrous ethanol, cooling to room temperature, filtering, and washing with ethanol, then ether, then air drying to give the pure complex as a pale yellow solid.

Isolation of Quinaldines. Each complex from above was placed in a separatory funnel and shaken with ~150 ml of cold water. To this slurry was added ~50 ml of concentrated ammonium hydroxide and the slurry was shaken again. The resulting oil or solid was extracted into ether (two or three times), dried ($MgSO_4$), filtered, and evaporated to dryness. Except in the cases of quinaldine and 8-methylquinaldine (yellow-brown oils), the products were obtained as yellow or white crystalline solids which were >98% pure by VPC. The yields were approximately quantitative. To obtain the melting points listed in Table I, the quinaldines were transferred to a filter funnel with cold hexane and air dried.

Acknowledgment. The author wishes to express his sincere appreciation to Mr. David L. Anderson for his competent technical assistance.

Registry No.—Crotonaldehyde, 4170-30-3; $ZnCl_2$, 7646-85-7.

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Carbohydrate Thio Ortho Esters. 3.[1] Transformation to Thioglycosides with Deactivated Raney Nickel

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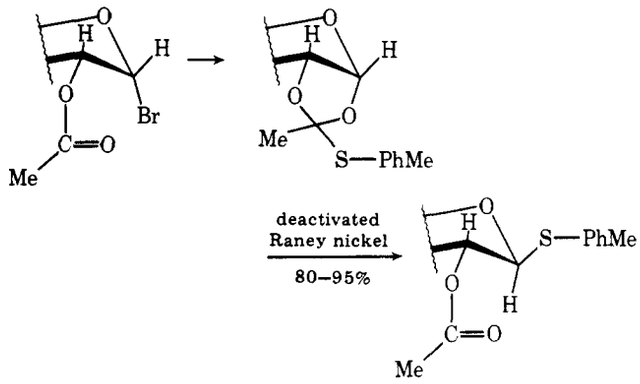
Received August 18, 1976

Phenyl 1-thioglycosides have been used inter alia for affinity chromatography (linked by a *p*-amino group substituent and a spacer to an insoluble matrix such as Sepharose) of glycosidases,[2] for stereoselective Hg^{2+}-mediated solvolysis to *O*-glycosides[3] and for synthesis of glycosyl benzoates and halides.

The phenyl 1-thioglycoside grouping has been synthesized by a number of different routes, for instance, nucleophilic substitution of the bromine in acetobromo sugars by sodium or potassium thiolates,[4] reduction of dithioacetals,[5] and thermal decomposition of arylazothioglycosides.[6] I now wish to report an improved, rapid, and efficient high-yield synthesis of peracetylated *p*-methylphenyl 1,2-*trans*-1-thioglycopyranosides using the route shown in Scheme I.

As mentioned in a previous report,[1] treatment of *p*-methylphenyl thio ortho esters in ethanol or 2-propanol with active Raney nickel gave the corresponding ethyl and isopropyl ortho esters in high yield instead of the expected 1,2-ethylidene acetals. An attempt to make cyclohexyl ortho esters by this method in toluene with azeotropically dried Raney nickel, gave a mixture of products, many of which still contained sulfur. Obviously the Raney nickel was deactivated by the toluene distillation so that desulfurization could not occur. Analysis of the reaction mixture revealed that the main

Scheme I



product formed was the *p*-methylphenyl 1,2-*trans*-1-thioglycoside. After testing different reaction conditions, a preparatively useful method was found for the synthesis of these compounds. Thioglycosides with the D-gluco, D-galacto, D-xylo, D-lacto, and D-glucurono configurations have been prepared in 80–95% yield.

The procedure is simple and consists of stirring the appropriate thio ortho ester[7] (mixture of exo and endo diastereomers) with deactivated Raney nickel (see Experimental Section) and a trace of *p*-methylthiophenol in toluene for ca. 10 min followed by filtration and evaporation. The residue (a colorless oil) was pure (TLC, NMR) 1-thioglycoside that crystallized on addition of a few drops of ethanol (except for the lacto derivative). The starting thio ortho esters were prepared from the appropriate acetobromo sugars and *p*-methylthiophenol.[7] The only detectable by-products in the preparation of the thio ortho esters are the corresponding thioglycoside and di-*p*-methylphenyl disulfide but these can easily be removed by chromatography if desired (cf. below).

A trial preparation of the thioglucoside, without purification of the thio ortho ester by chromatography, was made using a two-step sequence from acetobromoglucose. Treatment of the crude product with deactivated Raney nickel and a trace amount of *p*-methylthiophenol gave the *p*-methylphenyl 1-thio-β-D-glucopyranoside in ca. 80% overall yield. The only contaminant that could be detected was di-*p*-methylphenyl disulfide.

To give some idea of the mechanism of the present Raney nickel reaction, a test was made omitting the *p*-methylthiophenol. The reaction time had to be increased ca. tenfold to allow all the thio ortho ester to react and several by-products were found. It thus seems as if the reaction does *not* proceed via a fully developed acetoxonium ion that is stabilized only by the solvent but rather via a close ion pair with the *p*-methylthiophenoxy anion reversibly adsorbed to the nickel surface. Free *p*-methylthiophenol (which is regenerated in the reaction) can then make a nucleophilic attack at the anomeric center giving the thioglycoside. Evidence for ion-pair formation in thio ortho esters was also found when using active Raney nickel in ethanol[1] (see above).

Experimental Section

Melting points are uncorrected. IR spectra were run as KBr pellets. ^1H NMR spectra were run in $CDCl_3$ (Me_4Si) on a JEOL PMX-60 spectrometer and mass spectra on a Varian MAT 311 spectrometer. Deactivated Raney nickel was prepared as follows. Raney nickel in water (Merck hydrogenation catalyst) was washed with five portions of absolute ethanol and five portions of toluene (centrifugation). The catalyst was heated (toluene reflux) for 1 h and then dried by azeotropic distillation of the toluene. The resulting catalyst could be stored (in toluene) at room temperature without any noticeable decrease in reactivity.

General Procedure for Preparation of the Thioglycosides. The appropriate peracetylated thio ortho ester[7] (200 mg, mixture of exo and endo diastereomers) and *p*-methylthiophenol (<1 mg) were