(s, Ar C-1), 169.33 (s, C=O); MS (*m/z*, relative intensity, chemical ionization, NH_3) 277 (MNH_4^+, 32), 260 (MH^+, 3), 249 ($MNH_4^+ - N_2$, 3), 232 ($MH^+ - N_2$, 6), 217 ($M^+ - N_3$, 80), 172 ($M^+ - N_2 -$ OAc, 100).

2-Iodo-1-isocyanato-1-phenylcyclohexane (12). The adduct **12** was prepared, following the published procedure,[6] from 1-phenyl-1-cyclohexene in 82% yield as an unstable oil: IR (neat, cm^{-1}) 2240 (N=C=O); ^1H NMR 1.60–1.98 (m, 5 H, 4- and 5-CH_2, 6-H_{eq}), 2.12 (dm, J = 15, 1 H, 3-H_{eq}), 2.35 (ddt, J = 15, 11, 4, 1 H, 3-H_{ax}), 2.71 (ddd, J = 14, 12, 5, 1 H, 6-H_{ax}), 4.68 (brt, J = 4, 1 H, CHN_3), 7.26–7.50 (m, 5 H, Ph); ^{13}C NMR 21.24 and 22.36 (t, 4-CH_2 and 5-CH_2), 32.06 (dd, 6-CH_2), 33.16 (t, 3-CH_2), 43.60 (d, J_{CH} = 154, CHI), 74.31 (s, CN=C=O), 125.33, 127.82 and 128.21 (d, Ph C-H), 128.69 (s, Ph C-1), 147.41 (s, N=C=O).

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Supplementary Material Available: ^{13}C NMR spectra for compounds **3**, **5**, **9**, and **10** (4 pages). Ordering information is given on any current masthead page.

Synthesis of Des-*N*-methylacronycine and Acronycine[1]

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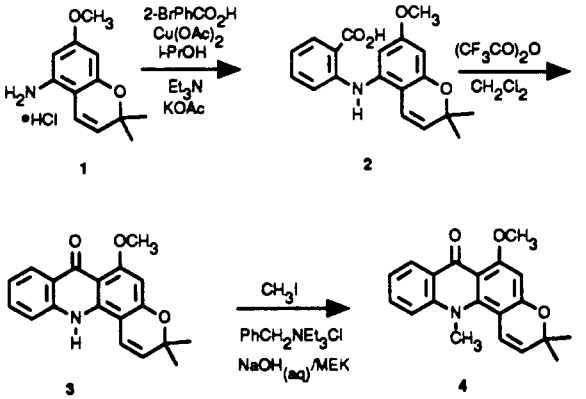
Des-*N*-methylacronycine (**3**) and acronycine (**4**) are closely related acridine alkaloids which have been isolated from a variety of plant sources.[2,3] Acronycine in particular has attracted attention because it has demonstrated antitumor activity in experimental animals[4] and has been evaluated in human patients with multiple myeloma.[5] We had interest in preparing des-*N*-methylacronycine since this compound could serve as an intermediate for the preparation of several N-substituted analogues, including acronycine itself.[6]

Des-*N*-methylacronycine has been prepared before. Adams et al.[6d] offer three related syntheses of this material. The most efficient of these three routes provides **3** in three steps from 3,5-dimethoxyphenol, but in an overall yield of less than 2%. Blechert et al.,[7] whose aim was to design a synthesis which would have the flexibility to allow preparation of acronycine metabolites, describe an eight-step synthesis of des-*N*-methylacronycine from aminochromene **1**. Since the yield of one step in this sequence is not reported, it is possible to say only that the overall yield must be less than 9%.

For the present work, a direct, two-step synthesis of des-*N*-methylacronycine from the previously described aminochromene **1**[7,8] was planned. Ullmann coupling of **1** with 2-bromobenzoic acid efficiently provided the substituted anthranilic acid **2**. A simple workup of this reaction afforded a 97% yield of crude product; then chromatography and recrystallization provided a 58% yield of analytical material. Conversion of **2** to des-*N*-methylacronycine required only an electrophilic cyclization. This turned out to be more difficult than anticipated since **2** decomposed under a variety of acid conditions (H_2SO_4, polyphosphoric acid, trifluoroacetic acid in CH_2Cl_2, $POCl_3$ followed by $HCl_{(aq)}$, or polyphosphate ester in $CHCl_3$) used to try to effect this ring closure. This problem was overcome when it was discovered that trifluoroacetic anhydride efficiently induced the desired cyclization to occur. When a recrystallized sample of **2** was allowed to stir for 3 days at room temperature with 5 equiv of trifluoroacetic anhydride in methylene chloride, workup and chromatography provided a 62% yield of an analytical sample of the desired product. Thus, this process provided des-*N*-methylacronycine in 36% yield from aminochromene **1**. Purification of the anthranilic acid **2** was not necessary to successfully achieve the preparation of **3**. In fact, a slightly higher overall conversion of aminochromene **1** to the desired **3** was achieved when the crude intermediate anthranilic acid **2** was subjected to the cyclization conditions described above. Using this procedure, des-*N*-methylacronycine was provided in 40% yield from aminochromene **1**.



Des-*N*-methylacronycine is a versatile compound which can be N-alkylated to give materials related to acronycine. Conversion to acronycine (**4**) itself was achieved in 96% yield by alkylation with methyl iodide under phase-transfer conditions.[9] Thus efficient preparations of both des-*N*-methylacronycine and acronycine have been realized.

Experimental Section

Melting points are uncorrected. IR, NMR, and mass spectra of all compounds were consistent with the assigned structures. IR spectra were measured as dispersions in KBr on a Nicolet 5 PC FT infrared spectraphotometer. ^1H NMR spectra were ob-

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(8) For the present work, aminochromene **1** was obtained in 65% yield in four steps from the commercially available 2,2-dimethyl-7-methoxychromanone using minor variations of the procedures described in ref 7.

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tained in $CDCl_3$ using a Bruker WM-300 spectrometer, and the chemical shifts are reported in δ units using Me_4Si as an internal standard. Mass spectra were obtained with a MAT-311A spectrometer. Flash chromatography was performed using 230-400 mesh silica gel 60 in a 5 cm × 25 cm column.

2-[(2,2-Dimethyl-7-methoxychromen-5-yl)amino]benzoic Acid (2). A 4.83-g (20.0-mmol) sample of 5-amino-2,2-dimethyl-7-methoxychromene hydrochloride (**1**) was combined with 4.42 g (22.0 mmol) of 2-bromobenzoic acid, 4.32 g (44.0 mmol) of KOAc, 0.12 g (0.60 mmol) of $Cu(OAc)_2 \cdot H_2O$, and 3.1 mL (22 mmol) of triethylamine in 100 mL of 2-propanol, and this mixture was refluxed for 24 h. The solvent was then removed on the rotary evaporator, and the residue was partitioned between 150 mL of CH_2Cl_2 and 100 mL of 1 N $HCl_{(aq)}$. The phases were separated, and the aqueous phase was washed twice with 10-mL portions of CH_2Cl_2. The combined organic phase was dried ($MgSO_4$) and concentrated to give 6.28 g (97%) of a brown foam. This material was redissolved in CH_2Cl_2 and absorbed onto 60 g of SiO_2, which was placed at the top of a flash chromatography column. The column was eluted with hexane/acetone/acetic acid (80:20:0.5) to provide 5.05 g of material, which was crystallized from 100 mL of hexane to give 3.43 g of product, mp 131-133 °C. The mother liquor was concentrated, and the residue was dissolved in 15 mL of hot hexane. As the solution cooled, the hexane was decanted from an oily impurity which precipitated. The product that crystallized from the decanted solution was collected to give an additional 0.32 g, raising the overall yield to 58%: ^1H NMR δ 1.45 (s, 6 H), 3.77 (s, 3 H), 5.50 (d, 1 H, J = 10 Hz), 6.30 (d, 1 H, J = 2 Hz), 6.39 (d, 1 H, J = 10 Hz), 6.43 (d, 1 H, J = 2 Hz), 6.73 (ddd, 1 H, J = 8 Hz, J = 7 Hz, J = 1 Hz), 6.92 (dd, 1 H, J = 8 Hz, J = 1 Hz), 7.33 (ddd, 1 H, J = 8 Hz, J = 7 Hz, J = 2 Hz), 8.04 (dd, 1 H, J = 8 Hz, J = 2 Hz), 9.14 (bs, 1 H); IR 1662, 1615, 1568, 1240, 1150, 772 cm^{-1}; mass spectrum, m/e 325 (M^+). Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 70.17; H, 6.10; N, 4.27.

Des-*N*-methylacronycine (3). A 1.63-g (5.0-mmol) sample of anthranilic acid **2**, mp 131-133 °C, was combined with 3.5 mL (25 mmol) of trifluoroacetic anhydride in 50 mL of CH_2Cl_2, and the mixture was stirred at room temperature for 3 days. The mixture was then concentrated on the rotary evaporator. The residue was partitioned between CH_2Cl_2 and $NaHCO_{3(aq)}$, and the aqueous phase was washed with additional CH_2Cl_2. The combined CH_2Cl_2 solution was then shaken for 5 min with 10% aqueous NaOH since TLC indicated that this procedure simplified the product mixture, presumably through hydrolysis of the trifluoroacetic acid amides present. The aqueous phase was washed with additional CH_2Cl_2, and the combined organic phase was dried over $MgSO_4$ and filtered. The filtrate was added to 16 g of SiO_2, and the solvent was removed on the rotary evaporator. The SiO_2 with the product mixture absorbed onto it was placed at the top of a flash SiO_2 column which was eluted first with 80:20:0.5 hexane/acetone/acetic acid to remove acidic components. Among these was a fraction containing mostly starting material. This fraction was concentrated, redissolved in CH_2Cl_2, and washed with $NaHCO_{3(aq)}$ to remove residual acetic acid. Starting material remained in the CH_2Cl_2, which was dried and concentrated. The residue was recrystallized from hexane to provide a 50-mg sample of recovered **2**, mp 119-120 °C, identified on the basis of its ^1H NMR spectrum and elemental analysis. Subsequent elution of the column with 70:30 hexane/acetone provided product containing fractions which were concentrated to give 0.958 g (62%) of the desired product as an analytically pure, fluffy, yellow solid, mp 258-260 °C (lit.[2a] mp 268-270 °C). Recrystallization from acetone/hexane raised the mp to 273-275 °C.

A similar procedure using a 1.63-g sample of crude anthranilic acid **2**, which had been obtained in 96% yield from aminochromene **1**, provided 0.800 g (52%) of des-*N*-methylacronycine, mp 260-262 °C, and 90 mg of recovered starting material, mp 121-123 °C. Further purification of the product was necessary to obtain a correct elemental analysis: recrystallization from acetone/hexane with one reworking of the mother liquor gave a total of 0.647 g (42%). The analytically pure material had a mp of 263-265 °C: ^1H NMR δ 1.48 (s, 6 H), 3.92 (s, 3 H), 5.60 (d, 1 H, J = 10 Hz), 6.21 (s, 1 H), 6.66 (d, 1 H, J = 10 Hz), 7.21 (ddd, 1 H, J = 8 Hz, J = 7 Hz, J = 1 Hz), 7.29 (dd, 1 H, J = 9 Hz, J = 1 Hz), 7.55 (ddd, 1 H, J = 9 Hz, J = 7 Hz, J = 1 Hz), 8.25 (bs, 1 H), 8.41 (dd, 1 H, J = 8 Hz, J = 1 Hz); IR 3441, 1632 cm^{-1}; mass spectrum, m/e 307 (M^+). Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.20; H, 5.66; N, 4.53.

Acronycine (4). To a combination of 1.54 g (5.0 mmol) of des-*N*-methylacronycine, 0.341 g (1.5 mmol) of benzyltriethylammonium chloride, 25 mL of 50% $NaOH_{(aq)}$, and 25 mL of 2-butanone was added 0.47 mL (7.5 mmol) of methyl iodide, and this mixture was stirred at 60-70 °C for 3 h. The cooled reaction mixture was diluted with 100 mL of CH_2Cl_2 and a small amount of water. The aqueous phase was washed with additional CH_2Cl_2, and the combined organic phase was dried ($MgSO_4$) and concentrated. The residue was dissolved in CH_2Cl_2 and absorbed onto 15 g of SiO_2. This SiO_2 was placed at the top of a flash column, which was eluted with 75:25 hexane/acetone to provide 1.55 g (96%) of analytically pure acronycine as a light yellow solid: mp 173-175 °C (lit.[2a] mp 175-176 °C) (recrystallization from EtOAc/hexane did not raise the melting point); ^1H NMR δ 1.55 (s, 6 H), 3.83 (s, 3 H), 3.99 (s, 3 H), 5.51 (d, 1 H, J = 10 Hz), 6.32 (s, 1 H), 6.55 (d, 1 H, J = 10 Hz), 7.25 (ddd, 1 H, J = 8 Hz, J = 7 Hz, J = 1 Hz), 7.36 (dd, 1 H, J = 9 Hz, J = 1 Hz), 7.63 (ddd, 1 H, J = 9 Hz, J = 7 Hz, J = 2 Hz), 8.39 (dd, 1 H, J = 8 Hz, J = 2 Hz); IR 1622 cm^{-1}; mass spectrum, m/e 321 (M^+). Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.69; H, 5.90; N, 4.27.

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Registry No. 1·HCl, 66385-03-3; **2**, 125108-96-5; **3**, 13255-08-8; **4**, 7008-42-6; 2-$BrPhCO_2H$, 88-65-3.

A New Preparation of Difunctionalized Enamines from Thioamides Using Silver(I) Carbonate[1]

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Difunctionalized enamines are useful synthetic intermediates and have been obtained by a variety of condensation and extrusion reactions.[3] The basic reaction conditions employed in the condensation of active methylene compounds with electrophilic intermediates are often incompatible with other functional groups and can lead to racemization at sites adjacent to the electrophilic reaction center. In order to find milder conditions, we considered the use of silver carbonate. As a thiophilic reagent,[4] silver carbonate can complex with thioamide sulfur **1a** to generate thioiminium intermediate **3**, and as a base it can generate nucleophiles from active methylene compounds. In this paper, we report that the condensation of carbonucleophiles with thioiminium intermediates in the presence of silver carbonate at ambient temperature results in the formation of the corresponding enamines (Schemes I and II). This modification leads to the replacement of the amide bond by the corresponding enamine moiety, which is a useful modification of peptide backbones[5] with

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