Useful Synthesis of 4-Substituted Indoles

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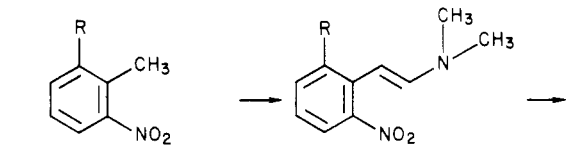
In previous communications, we have described a method for the synthesis of naphthyridinones[1] and 4- and/or 5-substituted 2-bromonicotinic acid derivatives[2] via enamine cyclization. We now wish to report on an extension of this work involving a reductive cyclization leading to the preparation of 4-substituted indoles, a class which has received only limited attention.[3,4] Such indole derivatives are of potential interest as precursors in the synthesis of ergot alkaloids and related compounds. Recently, examples of the ergoline type have aroused considerable interest for their possible role as dopaminergic agents useful in the treatment of Parkinson's disease and for the inhibition of prolactin release.[5]

Our approach was, therefore, designed to provide a convenient entry to indoles having synthetically versatile groups in the 4-position. As outlined in Scheme I, reaction of 2-methyl-3-nitrobenzoic acid (**1**)[6a] with methanolic HCl gave the ester **2**[7] in 96% yield. Treatment of **2** with 2 equiv of dimethylformamide dimethyl acetal (DMFDMA) in DMF at 110 °C for 2 days provided the enamine **3**. In our hands, these conditions were found to minimize competing reactions and to result in the complete conversion of **2** to **3** as determined by ^{1}H NMR spectra. (Initially, the enamines **3** and **6** were prepared by treating esters **2** and **5**, respectively, with a slight excess of DMFDMA and dimethylformamide diethyl acetal (DMFDEA) at 110 °C with the periodic addition of the appropriate dimethylformamide acetal reagent over 5 days. In general, these conditions proved inferior to those described above.)

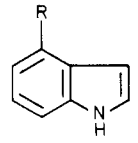
The yield of 4-carbomethoxyindole **4** by reductive cyclization of **3** was maximized through the use of Fe in AcOH–EtOH. This overall sequence of **1** to **4** represents a significant improvement in both yield (63%) and simplicity vis-à-vis previously reported syntheses of this compound.[8] On evaluating alternatives to the Fe–AcOH–EtOH method, it was found that hydrogenation with 10% palladium on carbon[3] provided only a trace amount of indole **4** as judged by TLC; $SnCl_2 \cdot 2H_2O$ reduction[9] gave esters **4** and **7** from the enamines **3** and **6** in yields ranging from 33 to 38% after a required chromatography. In one experiment, utilizing this latter procedure, the acid **8** was obtained in 45% yield when the crude ester **4** was hydrolyzed with 10% aqueous NaOH prior to isolation. None of the alternate methods approaches the Fe–AcOH–EtOH procedure in regard to ease of workup and overall yield.

Scheme I



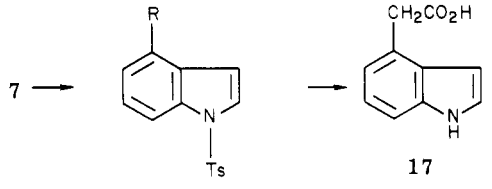
2, R = CO_2CH_3
5, R = $CO_2CH_2CH_3$
10, R = CN

3, R = CO_2CH_3
6, R = $CO_2CH_2CH_3$
11, R = CN



4, R = CO_2CH_3
7, R = $CO_2CH_2CH_3$
8, R = CO_2H
12, R = CN

Scheme II



13, R = $CO_2CH_2CH_3$
14, R = CH_2OH
15, R = CH_2Cl
16, R = CH_2CN

17

The synthesis of 4-cyanoindole (**12**) was next evaluated via direct synthesis rather than functional group manipulation of **4**. Diazotization of 2-amino-6-nitrotoluene (**9**)[6b] followed by decomposition of the diazonium salt in $KCu(CN)_2$–KCN gave the cyano derivative **10**[10] in 75% yield. The enamine **11** was obtained in quantitative yield by heating **10** with a slight excess of 1 equiv of DMFDMA for 3 h. The reduced steric requirements for the cyano group and its activating influence on the methyl substituent may account for the shorter reaction period needed for the conversion of **10** to **11**. Finally, reductive cyclization of **11** using Fe–AcOH–EtOH gave the indole **12**[8a] in 67% yield.

In addition to the functionalized indoles **4**, **7**, **8**, and **12**, a retrosynthetic analysis of the ergoline system revealed that the homologated acid **17** could also be viewed as a potential intermediate in an alternate strategic approach. With the ready availability of 4-substituted indoles, we investigated the utilization of the ester **7** as an intermediate to the homologated series by the approach outlined in Scheme II. Ester **7** was treated with *p*-toluenesulfonyl chloride and K_2CO_3 in 2-butanone[11] to give the tosylate **13** in 84% yield. Subsequent reduction of **13** with $LiAlH_4$ in cold THF provided the alcohol **14** (88%). Treatment of **14** with triphenylphosphine in CCl_4–DMF[12] gave a 92% yield of the 4-(chloromethyl)indole **15**. Displacement of Cl was accomplished (82%) using KCN in acetonitrile

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0022-3263/79/1944-4003$01.00/0

catalyzed by 18-crown-6.[13] Finally, hydrolysis of **16** with aqueous ethanolic NaOH yielded the homologated acid **17**. The synthesis of (4-indole)acetic acid (**17**) has been described previously from α-aminonaphthalene by a long, cumbersome, and impractical procedure.[14] The tosylated intermediates **13** to **16** should also be viewed as potential synthons for alkaloid construction in which deprotection would be accomplished most advantageously at a later stage in the synthesis.

In summary, this method with the ease of reaction conditions and the ready availability of starting materials offers a relatively simple and practical synthesis for 4-substituted indoles.

Experimental Section

Infrared spectra were obtained on a Perkin-Elmer Model 257 spectrophotometer. ^{1}H NMR spectra were determined in the indicated solvent on a Varian T-60 spectrometer using tetramethylsilane as an internal standard. Mass spectra were taken on an AEI MS 902 high-resolution mass spectrometer at an ionizing voltage of 70 eV and an ionizing current of 500 mA. The samples were processed by a DS50 data acquisition system. Melting points were determined on a Thomas-Hoover apparatus in open capillary tubes and are uncorrected. Liquids were distilled by short-path distillation and boiling points are uncorrected. Silica gel 60 (E. Merck, Darmstadt) and aluminum oxide 90 (E. Merck, Darmstadt) were used for column chromatography. Solutions were dried over Na_2SO_4 and concentrated to dryness using a Buchi rotary evaporator under water aspirator pressure (20 mm).

Methyl 2-Methyl-3-nitrobenzoate (2).[7] Dry HCl gas was introduced into a solution of **1**[6a] (100 g, 0.55 mol) in CH_3OH (600 mL) for 10 min. After heating at reflux for 15 h, the solution was concentrated and the residue was dissolved in CH_2Cl_2. The organic layer was washed with saturated Na_2CO_3, dried, filtered, and concentrated. The residue was triturated with C_6H_{14} and filtered to yield 103 g of **2** (96%): mp 65–66 °C (lit.[7] mp 66 °C); ^{1}H NMR ($CDCl_3$) δ 2.6 (3 H, s), 3.95 (3 H, s), 7.35 (1 H, m), 7.9 (2 H, m). The exact mass was 195.0527 (calcd 195.0531).

Ethyl 2-Methyl-3-nitrobenzoate (5). Compound **5** was prepared in a manner similar to **2** in 96% yield: bp 112–114 °C (0.3 mm); ^{1}H NMR δ 1.40 (3 H, t, J = 7 Hz), 2.6 (3 H, s), 4.4 (2 H, q, J = 7 Hz), 7.4 (1 H, m), 7.9 (2 H, m).

Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.46; H, 5.64, N, 6.66.

***N,N*-Dimethyl-2-[6-nitro-2-(carbomethoxy)phenyl]-ethenamine (3).** A mixture of **2** (30.0 g, 0.15 mol), DMF (60 mL), and DMFDMA (40 mL, 0.3 mol) was heated at 110 °C under N_2. After 2 days, the deep red solution was poured into H_2O (2 L) and extracted with Et_2O (4×). The organic layer was washed with H_2O and saturated aqueous NaCl solution, dried, filtered, and concentrated to yield 37 g of **3** as a red oil; ^{1}H NMR ($CDCl_3$) δ 2.85 (6 H, s), 3.90 (3 H, s), 5.65 (1 H, d, J = 14 Hz), 6.35 (1 H, d, J = 14 Hz), 7.0 (1 H, m), 7.7 (2 H, m). This material was used for the preparation of **4** without further purification.

***N,N*-Dimethyl-2-[6-nitro-2-(carboethoxy)phenyl]-ethenamine (6).** A mixture of **5** (97.0 g, 0.46 mol), DMF (120 mL), and DMFDEA (72 g, 0.5 mol) was heated at 110 °C under N_2 with stirring for 5 days. Additional acetal was periodically added in 7-mL aliquots (total 28 mL). The deep red solution was poured into H_2O (3 L) and extracted with Et_2O (4×). The organic layer was washed with H_2O and saturated aqueous NaCl solution, dried, filtered, and concentrated to yield 124 g of a crude red oil which was 93:7 **6** and **5** by ^{1}H NMR analysis: ^{1}H NMR ($CDCl_3$) δ 1.3 (3 H, t, J = 7 Hz), 2.8 (6 H, s), 4.3 (2 H, q, J = 7 Hz), 5.55 (1 H, d, J = 14 Hz), 6.35 (1 H, d, J = 14 Hz), 7.0 (1 H, m), 7.6 (2 H, m). This material was used for the preparation of **7** without further purification.

Methyl Indole-4-carboxylate (4).[8c,d] A mixture of **3** (37.0 g), EtOH (400 mL), AcOH (400 mL), and Fe (100 g, 1.8 mol) was cautiously heated on a steam bath with mechanical stirring. After the internal temperature reached 50 °C, the source of heat was removed and the temperature was allowed to rise to 85 °C with ice bath cooling to control the exotherm. When the temperature began to fall, the mixture was again heated at reflux for 0.5 h. After cooling to 25 °C, the mixture was poured into H_2O (2 L) and filtered through Celite, and the pad was washed with Et_2O (1 L). After separating the Et_2O, the aqueous layer was further extracted with Et_2O (3×). The organic layer was washed with H_2O (3×) and saturated aqueous Na_2CO_3 solution until basic, dried, filtered, and concentrated. The crude residue was distilled at 180 °C (0.2 mm) to yield 17 g of **4** (63%): mp 67–69 °C (lit.[8c,d] mp 64 °C); ^{1}H NMR ($CDCl_3$) δ 3.9 (3 H, s), 7.5 (5 H, m), 8.76 (1 H, br s, exch). The exact mass was 175.0630 (calcd 175.0633).

Ethyl Indole-4-carboxylate (7).[8d] To an ice cooled mixture of $SnCl_2 \cdot 2H_2O$ (311 g, 1.38 mol), concentrated HCl (300 mL), and Et_2O (300 mL) was added in a steady stream with mechanical stirring a solution of **6** (124 g) in Et_2O (500 mL). The internal temperature of the reaction rose to 35 °C. After completion of the addition, the ice bath was removed and the reaction mixture was stirred at room temperature for 45 min. The mixture was then poured onto ice–H_2O (3 L) and extracted with $CHCl_3$ (3×). The organic layer was washed with H_2O (3×) and saturated aqueous Na_2CO_3 solution until basic, dried, filtered, and concentrated. The residue was chromatographed on alumina (activity grade II, 900 g) eluting with C_6H_{14}–$CHCl_3$ (1:1) to yield 33 g of **7** (38%): mp 73–74 °C (lit.[8d] mp 70–71 °C); ^{1}H NMR ($CDCl_3$) δ 1.4 (3 H, t, J = 7 Hz), 4.35 (2 H, q, J = 7 Hz), 7.3 (5 H, m), 8.4 (1 H, br s, exch). The exact mass was 189.0782 (calcd 189.0790).

2-Cyano-6-nitrotoluene (10).[10] A suspension of **9**[6b] (52 g, 0.34 mol) in H_2O (750 mL) and concentrated HCl (75 mL) was heated on a steam bath with mechanical stirring until most of **9** dissolved. The mixture was then cooled to 0–4 °C and a solution of $NaNO_2$ (24.0 g, 0.35 mol) in H_2O (170 mL) was added dropwise while maintaining the temperature below 10 °C. After completion of the addition, the solution was stirred for an additional 0.5 h, added in a steady stream to a solution of CuCN (32.5 g, 0.36 mol) and KCN (105 g, 1.6 mol) in H_2O (700 mL) at 60 °C, and allowed to cool to room temperature. After standing overnight, the aqueous solution was extracted with CH_2Cl_2 (3×). The organic layer was washed with H_2O and saturated aqueous NaCl solution, dried, filtered, and concentrated. The residue was crystallized from EtOH to yield 28 g of **10**. The mother liquor was concentrated to dryness and the residue in CH_2Cl_2 was passed through a column of silica gel to yield an additional 23 g of **10**. The combined solids, 51 g, were recrystallized from EtOH–C_6H_{14} to yield 41 g of **10** (75%): mp 63–65 °C (lit.[10] mp 69.5 °C); ^{1}H NMR ($CDCl_3$) δ 2.8 (3 H, s), 7.5 (1 H, m), 7.9 (1 H, dd, J = 1 and 7 Hz), 8.1 (1 H, dd, J = 1 and 7 Hz); IR (nujol) 2220, 1560, 1340 cm^{-1}. The exact mass was 162.0429 (calcd 162.0429).

***N,N*-Dimethyl-2-(2-cyano-6-nitrophenyl)ethenamine (11).** A mixture of **10** (16.2 g, 0.1 mol), DMF (55 mL), and DMFDMA (14.5 g, 0.11 mol) was heated on a steam bath with stirring under N_2. After 3 h, the deep red solution was poured into H_2O (1 L) and extracted with Et_2O (4×). The organic layer was washed with H_2O and saturated aqueous NaCl solution, dried, filtered, and concentrated. The residue was triturated with C_6H_{14} and filtered to yield 20.2 g of **11** (93%). An analytical sample of **11** was prepared by crystallization from CH_2Cl_2–C_6H_{14}: mp 66–68 °C; ^{1}H NMR ($CDCl_3$) δ 2.95 (6 H, s), 5.45 (1 H, d, J = 13 Hz), 7.45 (1 H, d, J = 13 Hz), 7.5 (3 H, m).

Anal. Calcd for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.56; H, 5.26; N, 19.08.

4-Cyanoindole (12).[8a] A mixture of **11** (20.2 g, 0.093 mol), AcOH (300 mL), EtOH (300 mL), and Fe (30 g, 0.54 mol) was cautiously heated on a steam bath with mechanical stirring. After the internal temperature reached 50 °C, the source of heat was removed and the temperature was allowed to rise to 85 °C. An ice bath was used to control the temperature; once the exotherm had ended, the mixture was heated to reflux for 0.5 h. After cooling to 25 °C, the mixture was poured into H_2O (2 L) and filtered through Celite, and the pad was washed with Et_2O (1 L). After separating the Et_2O, the aqueous layer was further extracted with Et_2O (3×). The organic layer was washed with H_2O (3×) and saturated aqueous Na_2CO_3 solution until basic, dried, filtered, and concentrated. The residue was crystallized from H_2O to yield

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7.4 g of **12**. The aqueous mother liquor was then extracted with Et_2O (3×). The organic layer was dried, filtered, and concentrated. The residue in CH_2Cl_2 was passed through a dry column of silica gel to yield an additional 1.4 g of **12** (total yield 67%): mp 116–117 °C (lit.[8a] mp 120–121 °C);[15] ^1H NMR ($CDCl_3$) δ 6.7 (1 H, m), 7.4 (4 H, m), 8.8 (1 H, br s, exch); IR (nujol) 3300, 2220, 2200 cm^{-1}. The exact mass was 142.0532 (calcd 142.0531).

Ethyl 1-(*p*-Toluenesulfonyl)indole-4-carboxylate (13). A mixture of **7** (15 g, 0.079 mol), *p*-toluenesulfonyl chloride (30 g, 0.16 mol), K_2CO_3 (45.0 g, 0.33 mol), and 2-butanone (360 mL) was heated at reflux with stirring. After 15 h, the suspension was filtered hot and the solution was concentrated. The residue was triturated with Et_2O–C_6H_{14} and filtered to yield 22.8 g of **13** (84%). An analytical sample of **13** was prepared by crystallization from C_6H_{14}–EtOH: mp 133–134 °C; ^1H NMR ($CDCl_3$) δ 1.4 (3 H, t, J = 7 Hz), 2.3 (3 H, s), 4.3 (2 H, q, J = 7 Hz), 7.5 (9 H, m).

Anal. Calcd for $C_{18}H_{17}NO_4S$: C, 62.96; H, 4.99; N, 4.08. Found: C, 62.79; H, 4.86; N, 3.84.

4-(Hydroxymethyl)-1-(*p*-toluenesulfonyl)indole (14). To a mixture of $LiAlH_4$ (7.0 g, 57% oil dispersion, 0.1 mol) in THF (300 mL) cooled to 0–4 °C was added dropwise over 0.5 h and with mechanical stirring a solution of **13** (24.5 g, 0.07 mol) in THF (250 mL). After the addition was complete, the mixture was stirred at 0–4 °C for 15 min and then a solution of saturated aqueous Na_2SO_4 was added until a white suspension resulted. After filtering, the solution was concentrated. The residue was triturated with C_6H_{14} and filtered to yield 19.0 g of **14** (88%). An analytical sample of **14** was prepared by crystallization from $CHCl_3$–methylcyclohexane: mp 124–126 °C; ^1H NMR ($CDCl_3$) δ 2.35 (3 H, s), 4.85 (2 H, s), 7.5 (9 H, m).

Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.02; N, 4.65. Found: C, 63.64; H, 5.04; N, 4.56.

4-(Chloromethyl)-1-(*p*-toluenesulfonyl)indole (15). Triphenylphosphine (19 g, 0.07 mol) was added with stirring to a solution of **14** (19.0 g, 0.063 mol), DMF (100 mL), and CCl_4 (25 mL). The internal temperature of the solution rose to 55 °C and then gradually returned to 25 °C. After 15 h, the solution was poured into H_2O (500 mL) and extracted with EtOAc (3×). The organic layer was washed with H_2O and saturated aqueous NaCl solution, dried, filtered, and concentrated. The residue was chromatographed on silica gel and the product was eluted with CH_2Cl_2 to yield 18.4 g (92%) of **15**. An analytical sample of **15** was prepared by crystallization from EtOAc–ligroin: mp 139–141 °C; ^1H NMR ($CDCl_3$) δ 2.35 (3 H, s), 4.7 (2 H, s), 7.45 (9 H, m).

Anal. Calcd for $C_{16}H_{14}ClNO_2S$: C, 60.09; H, 4.41; N, 4.38. Found: C, 60.26; H, 4.33; N, 4.11.

4-(Cyanomethyl)-1-(*p*-toluenesulfonyl)indole (16). A mixture of KCN (1.3 g, 0.02 mol), H_3CCN (30 mL), 18-crown-6 (0.5 g), and **15** (3.2 g, 0.01 mol) was stirred at 25 °C for 4 h. The mixture was then poured into H_2O and extracted with CH_2Cl_2 (3×). The organic layer was dried, filtered, and concentrated. The residue was crystallized from CH_2Cl_2–ligroin to yield 2.55 g of **16** (82%): mp 148–150 °C; ^1H NMR ($CDCl_3$) δ 2.30 (3 H, s), 3.85 (2 H, s), 7.45 (9 H, m); IR (nujol) 2240 cm^{-1}.

Anal. Calcd for $C_{17}H_{14}N_2O_2S$: C, 65.79; H, 4.55; N, 9.02. Found: C, 65.40; H, 4.45; N, 8.64.

(4-Indole)acetic Acid (17). A solution of **16** (0.9 g, 0.0029 mol), EtOH (20 mL), and 20% aqueous NaOH (20 mL) was heated at reflux for 15 h. After concentrating off the EtOH, the aqueous layer was extracted with Et_2O (1×) and then acidified with concentrated HCl. The solid was collected and dried to yield 0.4 g (80%) of **17**: mp 205–206 °C (lit.[14] mp 205 °C); ^1H NMR (Me_2SO-d_6) δ 3.75 (2 H, s), 6.45 (1 H, m), 7.1 (4 H, m), 11.0 (1 H, br s, exch), 12.0 (1 H, br s, exch). The exact mass was 175.0632 (calcd. 175.0633).

Acknowledgment. The authors are grateful to Drs. Ralph Hirschmann and E. L. Engelhardt for their interest and encouragement throughout this work. Technical assistance was provided by Mr. K. B. Streeter and Ms. J. Stranick for analytical determinations and by Mr. R. E. Rhodes for mass spectra.

(15) Compound **12** was identical in all respects with material prepared according to the procedure described by Uhle.[8a]

Registry No. **1**, 1975-50-4; **2**, 59382-59-1; **3**, 71516-33-1; **4**, 39830-66-5; **5**, 59382-60-4; **6**, 71516-34-2; **7**, 50614-84-1; **8**, 2124-55-2; **9**, 603-83-8; **10**, 71516-35-3; **11**, 71516-36-4; **12**, 16136-52-0; **13**, 71516-37-5; **14**, 71516-38-6; **15**, 71516-39-7; **16**, 71516-40-0; **17**, 16176-74-2; DMF, 68-12-2; *p*-toluenesulfonyl chloride, 98-59-9.

A Novel Sterically Mediated Transformation of Proline

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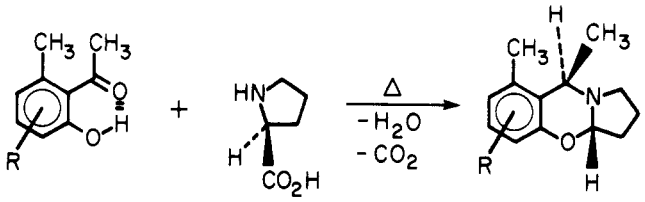
We wish to describe a novel reaction of proline discovered during the course of studies aimed at the total synthesis of optically active, naturally occurring isoprenoids.[1] Specifically, we have found that treatment of 2-hydroxy-6-methylacetophenones such as **1** with 1.5 molar equiv of (*S*)-proline (**2**) in *N*,*N*-dimethylformamide, at 100 °C, leads to the racemic[2] pyrrolo[2,1-*b*][1,3]benzoxazines **3**,[3] in good to excellent yields.[4] Our results are summarized in Table I.



1 **2 (S)** **3 (±)**

The structures of heterocycles **3** were assigned on the basis of the spectral and microanalytical data which these substances provided. In addition, a single crystal X-ray analysis was carried out on **3c**. A view of the molecule is shown in Figure 1. This result not only confirms the gross structure of these molecules but also establishes the relative configuration of the two asymmetric centers.

It is most intriguing to note that the formation of **3** in these reactions is, apparently, a result of steric factors associated with the starting acetophenone. Thus compounds **1g–i**, which lack the *o*-methyl substituent, failed to provide the corresponding heterocycles **3g–i**. In these examples, the products consisted, predominantly, of starting acetophenone and pyrrolidine indicating that the known[5,6] ketone (or aldehyde) induced amino acid de-

(1) The use of (*S*)-proline and other amino acids as catalysts or reagents for effecting highly enantiospecific intramolecular aldol cyclizations leading to steroid intermediates has been reported: (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615–1621 (West German Patent 2102623 (Hoffmann-La Roche), priority date Jan. 21, 1970: *Chem. Abstr.*, **1971** *75*, 129414r. (b) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496–497. (c) Cohen, N. *Acc. Chem. Res.* **1976**, *9*, 412–417, and references cited therein.

(2) Compounds **3** are depicted for convenience as only one enantiomer in order to describe the relative stereochemistry of the two asymmetric centers.

(3) Relatively few examples of compounds having this ring system have been reported, all possessing a carbonyl function at position 9. See: (a) Böhme, H.; Böing, H. *Arch. Pharm.* **1961**, *294*, 556–562. (b) Aeberli, P.; Houlihan, W. J. *J. Org. Chem.* **1968**, *33*, 2402–2407. (c) Shkrob, A. M.; Krylova, Yu. I.; Antonov, V. K.; Shemyakin, M. M. *Zh. Obshch. Khim.* **1968**, *38*, 2030–2046.

(4) For recent related heterocyclic syntheses see: (a) Vander Zwan, M. C.; Hartner, F. W.; Reamer, R. A.; Tull, R. *J. Org. Chem.* **1978**, *43*, 509–511. (b) Mohrle, H.; Miller, C. *Pharm. Acta Helv.* **1979**, *54*, 1–6.

(5) Chatelus, G. *Bull. Soc. Chim. Fr.* **1964**, 2523–2532.

(6) Takano, S.; Nishimura, T.; Ogasawara, K. *Heterocycles* **1977**, *6*, 1167–1171.

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