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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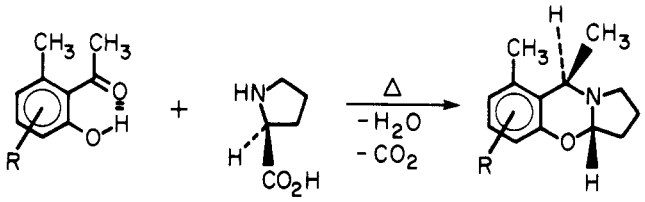
We wish to describe a novel reaction of proline discovered during the course of studies aimed at the total synthesis of optically active, naturally occurring isoprenoids.[1] Specifically, we have found that treatment of 2-hydroxy-6-methylacetophenones such as **1** with 1.5 molar equiv of (*S*)-proline (**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.

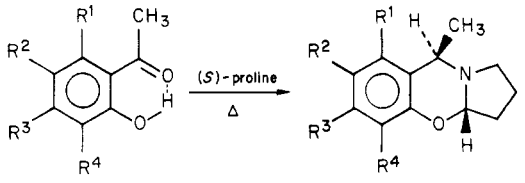
(4) For recent related heterocyclic syntheses see: (a) Vander Zwan, M. C.; Hartner, F. W.; Reamer, R. A.; Tull, R. *J. Org. Chem.* **1978**, *43*, 509–511. (b) Mohrle, H.; Miller, C. *Pharm. Acta Helv.* **1979**, *54*, 1–6.

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

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

0022-3263/79/1944-4005$01.00/0

Table I. Pyrrolo[2,1-*b*][1,3]benzoxazines



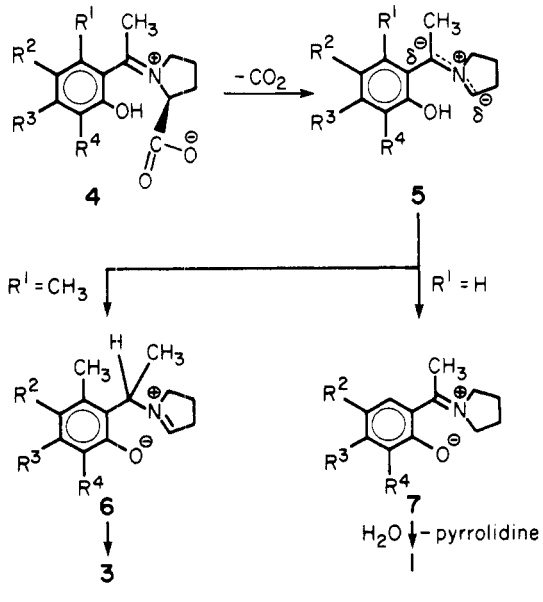
1 3

compd no.	starting material	R^1	R^2	R^3	R^4	yield,[a] %	mp, °C	crystd from	formula[b]
3a	1a[c]	CH_3	OH	CH_3	CH_3	75	139-140.5	CH_3CN	$C_{15}H_{21}NO_2$
3b	1b[d]	CH_3	H	CH_3	H	73	oil		$C_{14}H_{19}NO$
3c	1c[e]	CH_3	H	CH_3	Cl	79	74.5-76.5	hexane	$C_{14}H_{18}ClNO$
3d	1d[f]	CH_3	Br	CH_3	H	93	67-69	CH_3CN	$C_{14}H_{18}BrNO$
3e	1e[g]	CH_3	Cl	CH_3	H	73	oil		$C_{14}H_{18}ClNO$
3f	1f[h]	CH_3	OH	CH_3	H	67[o]	96.5-98	CH_3CN	$C_{14}H_{19}NO_2$
3g	1g[c]	H	OH	CH_3	CH_3	0[i]			
3h	1h[d]	H	OH	H	H	0[j]			
3i	1i[d]	H	H	H	H	0[k]			
3j	1j[m]	CH_3	OAc	-(CH=CH)-$_2$		58[n]	141-144	C_2H_5OH	$C_{19}H_{21}NO_3$

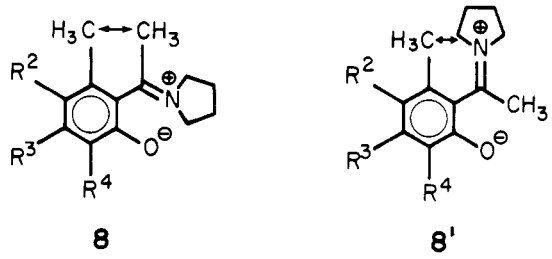
[a] Data refer to pure (TLC) products obtained by column chromatography or recrystallization. [b] All compounds were analyzed for C, H, N and gave analytical values within 0.3% of theory. Compounds 3c and 3e also gave Cl analyses within 0.3% of theory. Compound 3d gave a Br analysis within 0.3% of theory. All compounds furnished compatible IR, UV, ^1H NMR, and mass spectra. [c] Manecke, G.; Bourwieg, G. *Chem. Ber.* **1962**, *95*, 1413-1416. [d] Commercially available. [e] Mp 74-75 °C from pentane-ether. Anal. Calcd for $C_{10}H_{11}ClO_2$: C, 60.46; H, 5.58; Cl, 17.85. Found: C, 60.60; H, 5.44; Cl, 17.80. Prepared by nuclear acetylation of 2-chloro-3,5-dimethylphenol, using the procedure of Manecke and Bourwieg (footnote *c*). [f] Mp 99-103 °C from pentane-ether. Anal. Calcd for $C_{10}H_{11}BrO_2$: C, 49.41; H, 4.56; Br, 32.87. Found: C, 49.62; H, 4.79; Br, 33.24. Prepared by nuclear acetylation of 4-bromo-3,5-dimethylphenol, using the procedure of Manecke and Bourwieg (footnote *c*). [g] Sen, A. B.; Singh, S. B. *J. Indian Chem. Soc.*, **1964**, *41*, 461-464. [h] Manecke G.; Bourwieg, G. *Chem. Ber.* **1963**, *96*, 2013-2015. [i] 1g recovered in 81.4% yield. [j] 1h recovered in 98% yield. [k] Product consisted of mainly 1i along with some polar impurities. [l] *rac-cis*-9,10,11,11a-Tetrahydro-6,7-dimethyl-7*H*-naphtho[2,1-*e*]-pyrrolo[2,1-*b*][1,3]oxazin-5-ol acetate. [m] 1-(4-Acetoxy-1-hydroxy-3-methyl-2-naphthyl)ethanone: Read, G.; Ruiz, V. M. *J. Chem. Soc., Perkin Trans. 1*, **1973**, 235-243. [n] Reaction mixture heated for only 4.5 h. [o] 3f was additionally purified by partition between 1 N aqueous HCl and ether to remove some neutral impurities. The free base was regenerated from the acid solution by neutralization (pH 7) with 1 N NaOH, isolated by extraction with ethyl acetate, and chromatographed.

carboxylation pathway was operative.

These divergent results can be rationalized if one considers the fate of the resonance stabilized ylide **5** derived from decarboxylation of the initially formed zwitterionic adduct **4**. When R^1 = H, proton transfer in **5** occurs so as to generate the expected,[5] conjugated immonium species **7** in which no steric inhibition of π electron overlap involving the aromatic ring and C=N systems would be anticipated. Hydrolysis then produces pyrrolidine and regenerates the starting acetophenone ("normal" decarboxylation[5,6]). In contrast, when R^1 = CH_3, similar



proton transfer in **5** would yield a conjugated immonium phenoxide having severe steric interactions in either conformer **8** or **8'**, resulting from the presence of the *o*-



8 **8'**

methyl substituent. In order to avoid this unfavorable steric compression, proton transfer takes place leading to the alternative, nonconjugated immonium phenoxide **6** which subsequently cyclizes to give the observed products **3** ("transaminative" decarboxylation[5,7]). As can be seen in Figure 1, the presence of an sp^3-hybridized center at the benzylic position precludes steric interactions resulting from the *o*-methyl substitutent. It should be noted that this mechanistic rationale is consistent with the observed formation of racemic products.

We were somewhat disappointed to find that the scope of this heterocyclic synthesis is, apparently, quite limited. Thus piperidine-2-carboxylic acid gave only a trace quantity of the pyrido[2,1-*b*][1,3]benzoxazine homologue of **3a** when treated with acetophenone **1a**. Similarly, attempts to produce benzoxazines by exposure of **1a** to *N*-methyl-L-valine, L-thiazolidine-4-carboxylic acid, 4-hydroxy-L-proline, and D-α-phenylglycine all resulted in failure.

(7) Rizzi, G. P. *J. Org. Chem.* **1971**, *36*, 1710-1711.

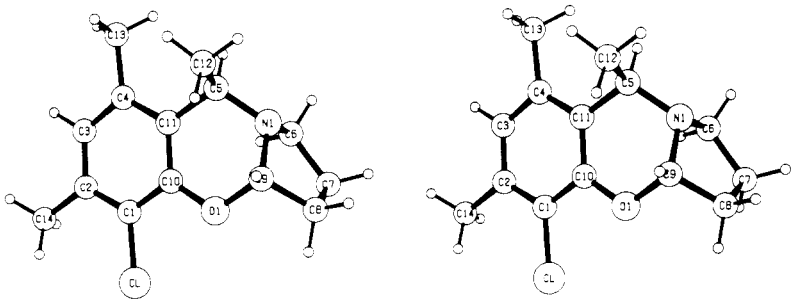


Figure 1. Stereoview of **3c**.

In summary, proline has been found to interact efficiently with 2-hydroxy-6-methylacetophenones via a transaminative decarboxylation pathway, affording the heterocycles **3**. These results provide an additional example of unusual, sterically mediated chemistry associated with the congested nature of such acetophenones.[8]

Experimental Section

General. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Column chromatography was performed using EM Silica Gel 60 (0.063–0.2 mm). Reactions were monitored and product purities determined by thin layer chromatography (TLC), using EM Silica Gel 60 F-254 precoated plates developed with either 1:1 hexane–ether or 1:1 toluene–ethyl acetate. Spots were detected with UV light and phosphomolybdic acid spray followed by heating. ^{1}H NMR spectra were obtained in $CDCl_3$ solution. Chemical shifts are reported relative to Me_4Si as an internal standard. Infrared spectra were obtained in $CHCl_3$ solution and ultraviolet spectra in 95% C_2H_5OH.

Condensation of Proline with 1-(2-Hydroxy-6-methylphenyl)ethanones. The preparation of *rac-cis*-5-chloro-2,3,3a,9-tetrahydro-6,8,9-trimethyl-1*H*-pyrrolo[2,1-*b*][1,3]benzoxazine (**3c**) is representative. A mixture of 6.0 g (30.2 mmol) of 1-(3-chloro-2-hydroxy-4,6-dimethylphenyl)ethanone (**1c**), 5.7 g (49.6 mmol) of (*S*)-(−)-proline, and 250 mL of *N,N*-dimethylformamide was stirred and heated at 100 °C, in an argon atmosphere, for 18 h. The resulting solution was cooled, and the DMF was removed under high vacuum. The orange oily residue was treated with water, and the mixture was extracted three times with ethyl acetate. The organic extracts were combined, washed with saturated brine, dried over anhydrous $MgSO_4$, and then filtered and concentrated in vacuo. The residue (7 g) was chromatographed on 350 g of silica gel. Elution with 19:1 and 9:1 toluene–ethyl acetate afforded 6.02 g (79%) of pure **3c** as a colorless solid. The analytical specimen of **3c** was obtained by recrystallization from hexane (see Table I) and showed no optical rotation ($[\alpha]^{25}_D 0°$ (*c* 2.2, $CHCl_3$)). This sample also provided crystals suitable for X-ray analysis: UV_{max} 277 (ε 2060), 286 (2390); NMR δ 6.53 (s, 1, C_7H), 5.36 (m, 1, $C_{3a}H$), 3.93 (q, 1, *J* = 7 Hz, C_9H), 2.26, 2.16 (2 s, C_6CH_3, C_8CH_3), 1.42 (d, 3, *J* = 7 Hz, C_9CH_3); mass spectrum, *m/z* 251 (M^+). The IR spectrum exhibited no OH, NH, C=N, or C=O absorptions.

X-ray Crystallographic Analysis of 3c. Crystals of **3c** [$C_{14}H_{18}ClNO$, *M* = 251.76], obtained from hexane, are triclinic, space group $P\bar{1}$, with *a* = 7.298 (1), *b* = 8.961 (1), *c* = 10.250 (1) Å, α = 91.31 (1), β = 101.27 (1), γ = 101.42 (1)°, and d_{calcd} = 1.300 g cm^{-3} for *Z* = 2. The intensity data were measured on a Hilger–Watts diffractometer (Ni filtered Cu Kα radiation, θ–2θ scans, pulse height discrimination). The size of the crystal used for data collection was approximately 0.40 × 0.30 × 0.25 mm; the data were corrected for absorption (μ = 24.9 cm^{-1}). Of the 2621 accessible reflections for θ < 76°, 2294 were considered to be observed [$I > 2.5\sigma(I)$]. The structure was solved by a multiple solution procedure[9] and was refined by full-matrix least squares. In the final refinement, anisotropic thermal parameters were used for the heavier atoms, and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations, but their parameters were not refined. The final discrepancy indices are *R* = 0.054 and *wR* = 0.075 for the 2294 observed reflections. The final difference map has no peaks greater than ±0.2 e A^{-3}.

Acknowledgment. We are indebted to the personnel of the Physical Chemistry Department, Hoffmann-La Roche Inc., Nutley, N.J., for carrying out many of the spectral and microanalytical determinations required in this work. Helpful discussions with Dr. T. Williams and his associates must also be acknowledged. We are grateful to Dr. G. Saucy for support and encouragement during the course of this study.

Registry No. **1a**, 64794-45-2; **1b**, 16108-50-2; **1c**, 71582-56-4; **1d**, 71582-57-5; **1e**, 50343-13-0; **1f**, 71582-58-6; **1g**, 71582-59-7; **1h**, 490-78-8; **1i**, 118-93-4; **1j**, 40508-46-1; **2**, 147-85-3; **3a**, 71582-60-0; **3b**, 71582-61-1; **3c**, 71582-62-2; **3d**, 71582-63-3; **3e**, 71582-64-4; **3f**, 71582-65-5; **3j**, 71582-47-3; *N,N*-dimethylformamide, 68-12-2.

Supplementary Material Available: Tables II–V of the final atomic parameters, bond lengths, and bond angles for **3c** (3 pages). Ordering information is given on any current masthead page.

(8) Cf. Cohen, N.; Lopresti, R. J.; Williams, T. H. *J. Org. Chem.* **1978**, *43*, 3723–3726.

(9) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A* **1971**, *27*, 368–376.