HCl. The organic layer was extracted with ether. The combined ether solutions were washed with saturated aqueous sodium chloride solution, dried over $MgSO_4$, and concentrated. Distillation of the residue gave 208 mg of a clean oil, bp 150–180 °C (bath temperature) (0.5 mm). GLC analysis showed that it consisted of 61 parts of a mixture of epimers **15** and **16** (25% yield from the bromide **11**) and 31 parts of the bifuran **17** (10% yield from the bromide **11**). The ^1H NMR spectrum indicates that the ratio of epimers **15** and **16** is nearly 1:1, by comparison of the signals due to acetyl methyl protons. Two purifications by TLC (silica gel, 19:1 hexane–ether) gave analytical samples of **15** and **16**.

Epimer 15: R_f 0.3; IR (neat) 2950, 1710, 1510, 1363, 1163, 1070, 736, 702 cm^{-1}; mass spectrum (70 eV), *m/e* (relative intensity) 234 (14, M^+), 219 (3, M – CH_3), 191 (16, M – $COCH_3$), 43 (100, $COCH_3$). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.92; H, 9.58.

Epimer 16: R_f 0.2; IR (neat) 2960, 1710, 1510, 1363, 1163, 1068, 748, 717 cm^{-1}; mass spectrum (70 eV), *m/e* (relative intensity) 234 (16, M^+), 219 (4, M – CH_3), 191 (15, M – $COCH_3$), 43 (100, $COCH_3$). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.78; H, 9.42.

3,3′-Diisopropyl-2,2′-bifuran (17): R_f 0.8; IR (neat) 2930, 1460, 1380, 1166, 1060, 889, 732 cm^{-1}; ^1H NMR (CCl_4) δ 1.18 (d, *J* = 7 Hz, 12 H, 2 $CH(CH_3)_2$), 3.28 (m, 2 H, 2 $CH(CH_3)_2$), 6.28 (d, *J* = 2 Hz, 2 H, 2β-H of furan), 7.23 (d, *J* = 2 Hz, 2 H, 2α-H of furan); mass spectrum (70 eV), *m/e* (relative intensity) 218 (39, M^+), 203 (50, M – CH_3), 175 (14, M – $CH(CH_3)_2$), 18 (100). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.30; H, 8.35.

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Registry No. (±)-1, 73803-38-0; (±)-4, 73770-50-0; 6, 16112-10-0; (±)-7, 73770-51-1; (±)-9, 73770-52-2; (±)-10, 73770-53-3; 11, 73770-54-4; 12, 53875-11-9; 13, 38071-68-0; (±)-14, 73770-55-5; (±)-15, 73803-39-1; (±)-16, 73803-40-4; 17, 73770-56-6; furan, 110-00-9; 2-bromofuran, 584-12-3; 4-isopropyl-2-furancarbaldehyde, 16015-07-9.

Thermal Rearrangement of 6-(Benzylamino)uracils to 5-Benzyl-6-aminouracils

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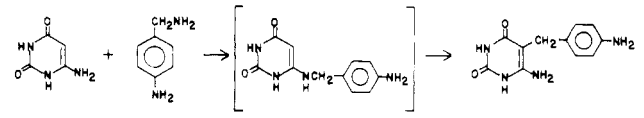
As part of our continuing interest in the chemistry of pyrimidines that are inhibitors of DNA polymerases[1,2] we have uncovered several rearrangements of N^6-substituted 6-aminouracils.[3,4] A recent attempt to prepare 6-(*p*-aminobenzylamino)uracil (1) as an inhibitor of *Bacillus subtilis* DNA polymerase III by the reaction between 6-aminouracil and *p*-aminobenzylamine led, unexpectedly, to the isolation of a compound which was isomeric with 1.[1] We report here the proof of the structure of this product and of others obtained by thermal rearrangement of 6-(benzylamino)uracils as 5-benzyl-6-aminouracils and propose a mechanism for this reaction. 5-Benzylpyrimidines and related compounds, e.g., trimethoprim, are of considerable interest as antibacterial and chemotherapeutic agents because of their ability to inhibit, selectively, dihydrofolate reductases.[5] Although many analogues bearing amino and oxo substituents in the pyrimidine ring have been synthesized,[6] 5-benzyl-6-aminouracils have not been reported. We also postulate a reason for the absence of these compounds from the literature.



2

The product of the reaction between 6-aminouracil and *p*-aminobenzylamine in boiling water had an elemental composition corresponding to an isomer of 1. Its proton NMR spectrum in dimethyl-d_6 sulfoxide showed downfield resonances typical of uracil N–H protons[7] and resonances corresponding to the benzyl group. However, the 5-H resonance was absent, and two broad resonances suggestive of amino groups were present. Reaction of this compound with acetic anhydride produced a monoacetyl derivative, **3**. On the basis of these data, two possible structures were postulated, 5-(*p*-aminobenzyl)-6-aminouracil (**2**) and the isomeric 5-[*p*-(aminomethyl)phenyl]-6-aminouracil. The two possibilities were distinguished by comparison of the proton NMR spectra of **2** and its acetyl derivative, **3**, with those of several model compounds. Phenyl proton resonances of *p*-aminobenzylacetamide (δ 6.91, 6.49) were closer to those of **2** (δ 6.87, 6.42) than to those of *p*-acetamidobenzylamine (δ 7.20, 7.49), suggesting that **2** possessed the aminophenyl rather than the (aminomethyl)phenyl structure. Further, the acetyl derivative (**3**) showed phenyl proton resonances at δ 7.10 and 7.40 similar to those of *p*-acetamidobenzylamine (see above) and *p*-acetamidobenzylacetamide (δ 7.17, 7.55); the acetamido NH and Me resonances of **3** (δ 9.74 and 2.00, respectively) were also commensurate with those derived from an aromatic amino group (δ 9.85, 2.02) rather than from an aminomethyl group (δ 8.20, 1.85).

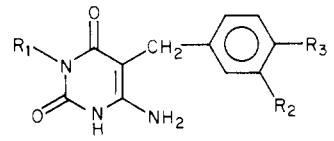
The product **2** was postulated to result from a thermal rearrangement of 1, the expected product of the reaction. Indeed, when 1 [prepared by hydrolysis of 6-(*p*-acetamidobenzylamino)uracil[1]] was heated at reflux in *N,N*-dimethylaniline, an 80% yield of a compound identical with **2** was obtained. Examination of the thermal lability of other 6-(benzylamino)uracils has now shown that his rearrangement is characteristic of such compounds.

Several 6-(benzylamino)uracils were recovered unchanged after reflux in *N,N*-dimethylaniline (bp 194 °C). However, the use of biphenyl (bp 256 °C) as solvent afforded good yields of compounds whose proton NMR spectra suggested that they were 5-benzyl-6-aminouracils. Table I lists the products obtained from the thermal rearrangement of 6-(benzylamino)uracils. Several generalizations can be made about the rearrangement. First, only compounds with electron-releasing groups in the phenyl ring undergo rearrangement in boiling biphenyl; 6-(benzylamino)uracil and 6-(*p*-nitrobenzylamino)uracil were recovered unchanged under these conditions. Second, increasing the reaction temperature by the use of *n*-decylbenzene (bp 300 °C) as solvent led to decomposition of 6-(benzylamino)uracil but to a 20% yield of 3-methyl-5-benzyl-6-aminouracil from the 3-methyl starting com-

(1) Brown, N. C.; Gambino, J.; Wright, G. E. *J. Med. Chem.* **1977**, *20*, 1186.
(2) Wright, G. E.; Brown, N. C.; Baril, E. F. *Nucleic Acids Res.* **1980**, *8*, 99.
(3) Wright, G. E. *J. Heterocycl. Chem.* **1976**, *13*, 539.
(4) Wright, G. E.; Gambino, J. *J. Heterocycl. Chem.* **1979**, *16*, 401.
(5) Hitchings, G. H.; Burchall, J. J. *Adv. Enzymol. Relat. Areas Mol. Biol.* **1965**, *27*, 417; see also (various authors) *Ann. N.Y. Acad. Sci.* **1971**, *186*.
(6) Cheng, C. C. *Prog. Med. Chem.* **1968**, *6*, 67.
(7) Wright, G. E.; Brown, N. C. *J. Med. Chem.* **1974**, *17*, 1277.

0022-3263/80/1945-3128$01.00/0

Table I. 5-Benzyl-6-aminouracils



compd	R_1	R_2	R_3	reaction solvent[a]	yield, %	cryst solvent	mp, °C	formula[b]
2	H	H	NH_2	A	80	33% Me_2SO	360	$C_{11}H_{12}N_4O_2 \cdot H_2O$
3	H	H	NHCOMe	c	95	70% Me_2SO	318-321	$C_{13}H_{14}N_4O_3 \cdot H_2O$
4	H	H	Me	B	88	80% HOAc	328-330	$C_{13}H_{13}N_3O_2 \cdot 0.125HOAc$
5	H	H	Cl	B	78	80% HOAc	356 dec	$C_{11}H_{10}N_3O_2Cl \cdot 0.125HOAc$
6	H	H	OMe	B	55	75% HOAc	318-321	$C_{12}H_{13}N_3O_3$
7	H	OMe	OMe	B	48	50% HOAc	304-306	$C_{13}H_{15}N_3O_4 \cdot H_2O \cdot 0.125HOAc$
8	Me	H	H	C	20	H_2O	260-262	$C_{12}H_{13}N_3O_2 \cdot 0.25H_2O$
9	Me	H	Cl	B	40	60% HOAc	267-270	$C_{12}H_{12}N_3O_2Cl$
10	Me	H	OMe	B	58	50% HOAc	249-250	$C_{13}H_{15}N_3O_3$
11	Me	OMe	OMe	B	36	50% HOAc	227-229	$C_{14}H_{17}N_3O_4$
12	*n*-Bu	H	Cl	B	41	50% EtOH	255-257	$C_{15}H_{18}N_3O_2Cl$
13	*n*-Bu	OMe	OMe	B	35	40% EtOH	211-214	$C_{17}H_{23}N_3O_4$

[a] A, *N*,*N*-dimethylaniline; B, diphenyl; C, *n*-decylbenzene; see the Experimental Section for reaction conditions. [b] Satisfactory analyses (±0.4% for C, H, and N) were obtained for all compounds; NMR spectra of **4**, **5**, and **7** showed small peaks at δ 1.9 corresponding to HOAc solvates. [c] From acetylation (Ac_2O, NaOAc, H_2O) of compound **2**.

pound; 6-(*p*-nitrobenzylamino)uracil was recovered unchanged even at this temperature. Third, the products were difficult to purify, precipitated as complex solvates (Table I), and ran in diffuse streaks during thin-layer chromatography (TLC). In contrast, N^3-alkylated derivatives, obtained by heating 3-alkyl-6-(benzylamino)uracils, were crystalline compounds and ran as discrete spots during TLC.

Definitive structural proof of these products as 5-benzyl-6-aminouracils was accomplished through ring synthesis of the *p*-chloro analogue, **5**. We required the monobenzyl derivative of ethyl cyanoacetate for condensation with urea. However, the sodium ethoxide or sodium hydride catalyzed reactions of *p*-chlorobenzyl chloride with ethyl cyanoacetate invariably gave a compound characterized as ethyl bis(*p*-chlorobenzyl)cyanoacetate as the predominant product. Only the use of thallous ethoxide in *n*-heptane[8] followed by reaction of the salt with *p*-chlorobenzyl chloride gave the monobenzyl ester, although with appreciable amounts of the dibenzyl ester and the starting ester. Condensation of ethyl (*p*-chlorobenzyl)-cyanoacetate with urea in the presence of sodium ethoxide did produce a 54% yield of a compound identical with the rearrangement product, **5**. The high-resolution mass spectrum of this compound displayed a molecular ion at *m/e* 251.04367 (calcd *m/e* 251.04615) and fragments which were commensurate with the expected fragmentation pattern, e.g., a base peak at *m/e* 125.01429 (calcd for C_7H_6Cl *m/e* 125.01580).

Several crossover experiments were used to determine if this reaction was intermolecular or intramolecular, the 3-alkyl groups of starting compounds providing convenient markers for this purpose. Thin-layer chromatography of the product resulting from heating **16** and **19** together in biphenyl showed spots corresponding to the four possible 5-benzyl compounds which would result if scrambling of the benzyl groups had occurred (see Experimental Section). The alternate starting compounds, **17** and **18**, gave the same results, all four products being detected by TLC. Another experiment tested if the benzyl group of a thymine analogue (**14**), which could not form a 5-benzyl product, would scramble with that of a 6-(benzylamino)-uracil. The thymine analogue itself gave unidentified decomposition products, which remained at the origin during TLC, when heated in biphenyl, but when **14** and **16** were heated together, both 5-benzyl products were detected by TLC. For the elimination of the possibility that the 5-benzyl compounds themselves would exchange benzyl groups, **9** and **13** were heated together in biphenyl: only the starting compounds were detected by TLC. These experiments clearly demonstrate that this reaction is intermolecular under the conditions used.

The rearrangement of 6-(benzylamino)uracils to 5-benzyl-6-aminouracils is a [1,3] shift of which there are but few examples in the heterocyclic literature.[9] For example, 1,3-dimethyl-5-(benzyloxy)uracil was reported to give 30% of the 5-hydroxy-6-benzyl compound after being heated in tetralin for 16 h;[10] the corresponding 5-allyloxy and 5-allylamino compounds gave the 6-allyl derivatives, although the amino derivative required higher temperature and proceeded in poorer yield.[11] *N*-Alkylanilines have been reported to rearrange thermally (Hofmann–Martius rearrangement)[12] or under Lewis acid catalysis (Reilly–Hickinbottom rearrangement)[13] to *o*- and *p*-alkylanilines; these reactions have been shown[13] to be intermolecular.

Although a radical mechanism cannot be ruled out, the influence of substituents reported above on the rearrangement of 6-(benzylamino)uracils suggested a mechanism in which ionization of the N^6–CH_2 bond would produce resonance-stabilized ions or an ion pair which could

(8) Taylor, E. C.; Hawks, G. H.; McKillop, A. *J. Am. Chem. Soc.* **1968**, *90*, 2421.

(9) In an unpublished report the reaction between 6-chlorouracil and *p*-*n*-butoxybenzylamine in refluxing decalin gave a compound characterized as 5-(*p*-*n*-butoxybenzyl)-6-aminouracil in 50% yield; the same reagents in DMF gave the expected 6-(*p*-*n*-butoxybenzylamino)uracil but in only 5% yield (Boyle, F. T. Imperial Chemical Industries, Ltd., personal communication).

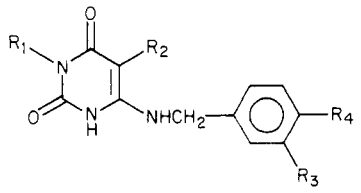
(10) Otter, B. A.; Taube, A.; Fox, J. J. *J. Org. Chem.* **1971**, *36*, 1251.

(11) The allyl rearrangements are, however, Claisen [3,3] rearrangements, as are analogous reactions of 4-(allyloxy)pyrimidines (Dinan, F. J.; Minnemeyer, H. J.; Tieckelmann, H. *J. Org. Chem.* **1963**, *28*, 1015). Interestingly, 4-(allylamino)pyrimidines did not undergo thermal rearrangement (Minnemeyer, N. J.; Clarke, P. B.; Tieckelmann, H. *Ibid.* **1966**, *31*, 400).

(12) Hughes, E. D.; Ingold, C. K. *Q. Rev., Chem. Soc.* **1952**, *6*, 34.

(13) Hart, H.; Kosak, J. R. *J. Org. Chem.* **1962**, *27*, 116.

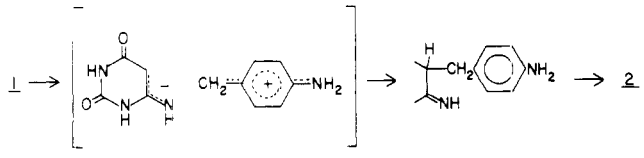
Table II. 6-(Benzylamino)uracils



compd	R_1	R_2	R_3	R_4	yield, %[a]	cryst solvent	mp, °C	formula[b]
14	H	Me	H	OMe	67	95% HOAc	272–275	$C_{13}H_{15}N_3O_3 \cdot 0.125HOAc$
15	Me	H	H	OMe	56	HOAc	284–286	$C_{13}H_{15}N_3O_3$
16	Me	H	H	Cl	65	HOAc	305–308	$C_{12}H_{12}N_3O_2Cl$
17	Me	H	OMe	OMe	70	HOAc	262–265	$C_{14}H_{17}N_3O_4$
18	*n*-Bu	H	H	Cl	75	EtOH	250–252	$C_{15}H_{18}N_3O_2Cl$
19	*n*-Bu	H	OMe	OMe	75	EtOH	237–239	$C_{17}H_{23}N_3O_4$

[a] See Experimental Section. [b] Satisfactory analyses (±0.4% for C, H, and N) were obtained for all compounds.

recombine to form the C^5–CH_2 bond. Stabilization of the anion is dependent on the presence of the 2- and 4-oxo groups on the pyrimidine ring; attempts to rearrange the analogous 2-amino-4-oxo and 2,4-diamino compounds have been unsuccessful (result not shown). For the benzyl group the driving force for ionization depends upon the stability of the benzyl carbocation, which is greatest for the *p*-amino analogue and which also occurs with other electron-releasing groups, although higher temperatures are required for the latter to rearrange.



This rearrangement proceeds in high yields with suitably substituted starting compounds and represents a convenient synthesis of 5-benzyl-6-aminouracils. Indeed, no such compounds have been reported in the literature, probably as a result of the difficulty in preparing monobenzyl cyanoacetates as precursors.[14] It would appear that the initial products of benzylation of ethyl cyanoacetate are more acidic than the starting ester, leading to exclusive formation of dibenzylated products with sodium ethoxide or sodium hydride. We have been able to obtain ethyl benzylcyanoacetates only via the thallous salt of ethyl cyanoacetate.

Preliminary results in this laboratory have indicated that 5-benzyl-6-aminouracils are weak inhibitors of DNA polymerase III from *Bacillus subtilis* and of RNA-dependent DNA polymerase (reverse transcriptase) from avian myeloblastosis virus. We are exploring both the scope and the utility of the rearrangement and the biological activity of these compounds.

Experimental Section

Melting points were determined on a Mel-temp apparatus and are uncorrected. NMR spectra in Me_2SO-d_6 were obtained at 60 MHz with a Perkin-Elmer R12B/TT7 Fourier transform instrument; chemical shifts are reported in parts per million (δ) from internal tetramethylsilane. Thin-layer chromatography employed Whatman analytical plates coated with silica gel containing a fluorescent indicator. Elemental analyses (C, H, N) were performed by Schwarzkopf Microanalytical Laboratory and agreed to ±0.4% with calculated values. 6-(Benzylamino)uracils (Table II) were prepared by published methods[1] employing 6-chlorouracil, 3-methyl-6-aminouracil, 3-*n*-butyl-6-chlorouracil, or 6-chlorothymine. Compounds 1, 3-methyl-6-(benzylamino)uracil, and 6-(*p*-nitrobenzylamino)uracil have been reported;[1] other 3*H*-6-(benzylamino)uracils, 3-*n*-butyl-6-chlorouracil, and 6-chlorothymine were identical with samples supplied by Imperial Chemical Industries, Ltd.

Thermal Rearrangement of 6-(Benzylamino)uracils. The compound (1 g) was placed in 15 mL of solvent and heated at reflux for 2–4 h. The reaction mixture was diluted with hot benzene, allowed to stand at room temperature, and the product was filtered with suction, washed with benzene, and crystallized from the solvents indicated in Table I.

Ethyl (*p*-Chlorobenzyl)cyanoacetate. Thallous ethoxide (11.0 g, 0.044 mol) was added to a solution of ethyl cyanoacetate (5.0 g, 0.044 mol) in *n*-heptane (50 mL) at room temperature. The colorless precipitate which formed was filtered and added to *p*-chlorobenzyl chloride (7.0 g, 0.044 mol). The resulting suspension was stirred at room temperature for 0.5 h, mixed with benzene (70 mL), and filtered. The solvent was evaporated, leaving 9.2 g of oil. Vacuum distillation (1.5 mm) produced several fractions: (1) bp 70–100 °C (1.9 g), (2) bp 170–195 °C (1.3 g), (3) bp 195–220 °C (0.5 g), (4) bp 225–250 °C (1.9 g). Fraction 1 was primarily ethyl cyanoacetate, fractions 2 and 3 contained the desired product with a small amount of ethyl bis(*p*-chlorobenzyl)cyanoacetate in the latter, and fraction 4 consisted of nearly pure disubstituted ester. Combined fractions 2 and 3 from several reactions (4.9 g) were distilled, giving 2.5 g of ethyl (*p*-chlorobenzyl)cyanoacetate: bp 195–215 °C (1.5 mm); NMR ($CDCl_3$) δ 7.26 (s, 4 H, Ar H), 4.24 (q, 2 H, OCH_2), 3.65 (t, 1 H, CH), 3.12 (d, 2 H, $CHCH_2$), 1.27 (t, 3 H, CH_3). Anal. Calcd for $C_{12}H_{12}NO_2Cl$: C, 60.64; H, 5.09; N, 5.89. Found: C, 60.81; H, 5.29; N, 6.12. The higher boiling material corresponded to ethyl bis(*p*-chlorobenzyl)cyanoacetate: NMR ($CDCl_3$) δ 7.25 (s, 8 H, Ar H), 4.00 (q, 2 H, CH_2), 3.10 (AB q, 4 H, CH_2), 0.96 (t, 3 H, CH_3).

5-(*p*-Chlorobenzyl)-6-aminouracil (5) by Ring Synthesis. Ethyl (*p*-chlorobenzyl)cyanoacetate (1.0 g, 0.0042 mol) was added to a solution of sodium (0.2 g, 0.0084 mol) in super dry EtOH (10 mL). Urea (0.3 g, 0.0042 mol) was added, and the solution was heated at reflux for 7 h. The resulting suspension was chilled and filtered, and the solid material was washed with water to give 0.6 g (54%) of **5** (from 80% HOAc): mp 357 °C dec; mixture melting point with **5** derived from the thermal rearrangement was 355–356 °C dec; NMR (Me_2SO-d_6) δ 10.22 (3-H), 9.90 (1-H), 7.24 (Ar H), 6.00 (6-NH_2), 3.48 (CH_2) (identical with NMR of **5** derived from rearrangement).

Crossover Experiments. The two test compounds (25 mg each) were heated at reflux in 0.5 mL of biphenyl for 4 h. Hot benzene (2 mL) was added to the warm suspension and, after the mixture had been allowed to stand at room temperature for 0.5 h, the solid material was filtered and washed with benzene. Solutions of reaction products, standard compounds, and physical

(14) 5-Benzylpyrimidine precursors have normally been made by formylation of substituted ethyl hydrocinnamates (Roth, B.; Falco, E. A.; Hitchings, G. H.; Bushby, S. R. M. *J. Med. Pharm. Chem.* **1962**, *5*, 1103). Alkylation of ethyl cyanoacetate and malononitrile with *higher* phenylalkyl halides gave good yields of intermediates in the preparation of 5-(phenylalkyl)pyrimidines (Baker, B. R.; Santi, D. V. *J. Pharm. Sci.* **1965**, *54*, 1252).

mixtures in EtOH were spotted on silica gel TLC plates, and the plates were developed in 10% EtOH in $CHCl_3$ (a, b, c) or 5% EtOH in $CHCl_3$ (d). R_f values for standards in 10% EtOH in $CHCl_3$ were 0.63 (**13**), 0.61 (**12**), 0.57 (**11**), 0.51 (**9**), and 0.55 (**10**).

(a) 19 and 16. Spots were observed at R_f 0.62, 0.61, 0.56, and 0.51, corresponding to all four possible products (**13**, **12**, **11**, and **9**). Addition of each pure component showed a selective increase in fluorescence intensity of the corresponding spot in the mixture.

(b) 18 and 17. Spots were observed at R_f 0.63, 0.61, 0.57, and 0.51, corresponding to all four possible products as in a above.

(c) 9 and 13. Spots corresponding only to the two starting materials were observed at R_f 0.51 and 0.63, respectively.

(d) 16 and 14. Spots were observed at R_f 0.36 and 0.41, corresponding to a physical mixture of **10** (R_f 0.36) and **9** (R_f 0.42), respectively. Heating of **14** alone gave unidentifiable products which remained at the origin on TLC plates; **14** itself had R_f 0.26.

Note Added in Proof. It was recently reported that several ethyl benzylcyanoacetates were prepared from benzyl chlorides and ethyl cyanoacetate (in large excess) in the presence of sodium methoxide in methanol (Calas, M.; Pages, C.; Pastor, G.; Giral, L.; Despaux, E. *Eur. J. Med. Chem.* **1979**, *14*, 529).

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Registry No. **1**, 64054-68-8; **2**, 73926-10-0; **3**, 73908-06-2; **4**, 73908-07-3; **5**, 73908-08-4; **6**, 73908-09-5; **7**, 73908-10-8; **8**, 22305-88-0; **9**, 73908-11-9; **10**, 73908-12-0; **11**, 73908-13-1; **12**, 73908-14-2; **13**, 73908-15-3; **14**, 73908-16-4; **15**, 73908-17-5; **16**, 73908-18-6; **17**, 73908-19-7; **18**, 73908-20-0; **19**, 73908-21-1.

Isourea-Mediated Preparation of Dehydro Amino Acids

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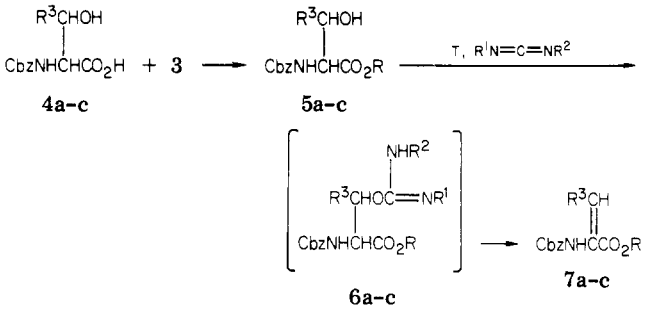
α,β-Dehydro amino acids are constituents of many recently discovered peptides including several fungal metabolites which possess antibiotic activity.[1] Dehydroalanine residues have also been implicated at the active sites of some enzymes.[2] In addition, the chemical reactivity of dehydroalanine generated from serine has been utilized for the site-specific cleavage of proteins.[3]

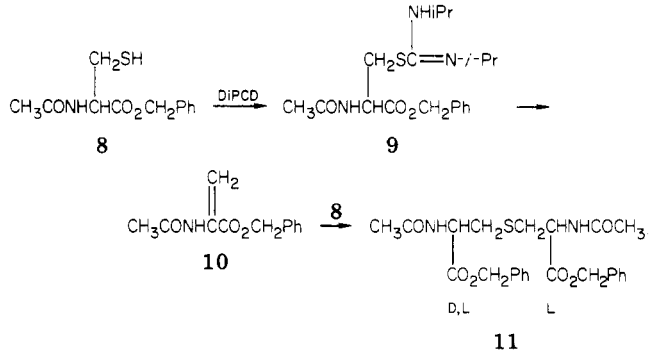
Of the many methods available for the synthesis of dehydro amino acids, β-elimination, the process which mimics the apparent biosynthetic process,[4] is most attractive since the elimination reaction can be performed as the final step on previously incorporated serine, cysteine, or threonine derivatives. Several methods for the preparation of dehydro amino acids by β-elimination processes have been described.[1,5,6] However, these methods often

Scheme I



a, R^3 = H, R = CH_3; b, R^3 = H, R = CH_2Ph; c, R^3 = CH_3, R = CH_3

Scheme II



are low yielding, multistep, require tedious purification steps to remove reagent side products, or incorporate unusual, difficultly obtained amino acid intermediates. Described here is a mild, efficient, and experimentally simple, isourea-mediated β-elimination process for the synthesis of dehydro amino acid derivatives from serine, cysteine, and threonine.

O-Alkylisoureas (**3**) have received increased attention as alkylating agents.[7] These reagents are conveniently prepared by the CuCl-catalyzed reaction of the corresponding alcohol **1** with a carbodiimide (**2**) (eq 1). How-

$$\underset{\mathbf{1}}{ROH} + \underset{\mathbf{2}}{R^1N{=}C{=}NR^2} \xrightarrow{CuCl} \underset{\mathbf{3}}{ROC(NHR^2){=}NR^1} \quad (1)$$

ever, attempts to isolate the isoureas (**6**) from the reactions of various carbodiimides and the hydroxyl group of serine and threonine derivatives **5** gave only the elimination products **7** (Scheme I).[8] Thus treatment of Cbz serine methyl ester **5a** with diisopropylcarbodiimide in the presence of 30 mol % (0.3 equiv) CuCl gave an 82% yield of the corresponding dehydroalanine **7a** after filtration, evaporation, and chromatography to remove the diisopropylurea. The results of other trials are given in Table I.

Several additional points are noteworthy. The use of a water-soluble carbodiimide [WSC, 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate] eliminated the need for chromatographic separation of the resulting urea. Peroxide-free solvents were required for both the reaction and workup since the unsaturated amino acid derivatives were found to polymerize rapidly in the

(1) For a recent review of dehydro amino acids see: Schmidt, U.; Häusler, J.; Öhler, E.; Poisel, H. In *Prog. Chem. Org. Nat. Prod.* **1979**, *37*, 251-327.
(2) Givot, J. L.; Smith, T. A.; Abeles, R. H. *J. Biol. Chem.* **1969**, *244*, 6341.
(3) Sokolovsky, M.; Sadek, T., Patchornik, A. *J. Am. Chem. Soc.* **1964**, *86*, 1212.
(4) Pearce, C. J.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.*, **1979**, *101* 5069.
(5) Srinivasan, A.; Stephenson, R. W.; Olsen, R. K. *J. Org. Chem.* **1977**, *42*, 2253; *J. Org. Chem.* **1977**, *42*, 2256.
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(7) For a recent review see: Mathias, L. J. *Synthesis* **1979**, 561-576.
(8) Similar results have been observed in the dehydration of β-hydroxy ketones: Corey, E. J.; Andersen, N. H.; Carlson, R. M.; Paust, J.; Vedejs, E.; Vlattas, I.; Winter, R. E. K. *J. Am. Chem. Soc.* **1968**, *90*, 3245. Alexandre, C.; Rouessac, F. *Bull Soc. Chim. Fr.* **1971**, 1837.

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