The Reaction Product of 3,3-Dichloro-2-methylpropenal and Piperidine

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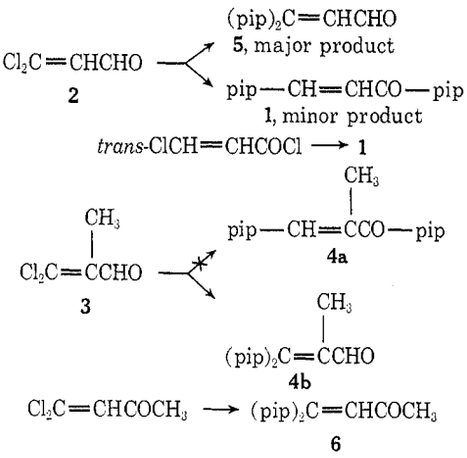
We recently attempted to prepare the vinylogous urea **1** (Chart I) by reaction of 3,3-dichloropropenal

CHART I

SUMMARY OF REACTIONS[a]



[a] pip = $C_5H_{10}N$.

(**2**) with piperidine. Our hope for success lay in the claim by Kundiger and Morris,[1] later mentioned in passing somewhat less definitely,[2] that 3,3-dichloro-2-methylpropenal (**3**) gives the 2-methyl homolog (**4a**) of **1** with piperidine. The authors[1] suggested initial attack of the amine on the carbonyl group as a mechanism. Since the aldehyde **2** is less hindered at the carbonyl than its homolog **3**, we anticipated the formation of the desired urea **1**.

We found that reaction of **2** gave a mixture of two olefins (nmr) in 70–80% crude yield. The first, **5**, 85–90% of the mixture, had absorptions at δ 4.18 (d, J = 7 Hz) and 9.03 (d, J = 7 Hz). The other, 10–15% of the mixture, absorbed at δ 4.91 (d, J = 13 Hz) and 7.14 (d, J = 13 Hz). Only the absorptions of the minor product are consistent with those of **1**. An authentic sample of **1** prepared from *trans*-3-chloropropenoyl chloride has the same absorptions (confirmed by peak enhancement) and coupling constant, and two distinct envelopes for the α-piperidino protons centered at δ 3.10 and 3.37.

The spectrum of the major product **5** is consistent with that expected for the formyl ketenaminal 3,3-bis(piperidino)propenal. The δ values and coupling constant are reasonable for =CHCHO in this compound. The α-piperidino protons are in a single envelope for this compound.[3]

We therefore duplicated the preparation of Kundiger and Morris.[1] To avoid possible loss of a minor or more soluble isomer, we initially assayed the crude material. There was no absorption near δ 7 but a singlet at δ 9.0 and one envelope for the α-piperidino protons, centered at δ 3.12. Work-up gave ~40% yield of a bright yellow solid with the properties reported by the above workers. The nmr spectrum of this purified material was the same as that of the crude, allowing for medium differences and minor impurities. Comparison of this spectrum with those of the aminal **5** and the vinylogous urea **1** strongly suggests that compound **4** is the formyl ketenaminal **4b** rather than the vinylogous urea **4a**.

Support for our structure assignment for **4** is found in the nmr spectrum of the isomeric acetyl ketenaminal **6**. This aminal **6** has α-piperidino proton absorptions in a single envelope, like **4** and **5** and unlike **1**.

We conclude therefore that the title product is in fact 3,3-bis(piperidino)-2-methylpropenal (**4b**). None of the evidence cited by the original workers[1] excludes this structure. Thus, **4b** as a *vinylidenolog*[4] of a formamide can base hydrolyze to give 2 equiv of piperidine; the other hydrolysis product, 2-formylpropionic acid, would be the same from **4a** or **4b**. The low carbonyl stretching frequency is consistent with either structure; our comparative data in dilute CCl_4 give bands at 1616 cm^{-1} for **4b**, 1627 cm^{-1} for the isomeric acetyl ketenaminal **6**, and 1640 cm^{-1} for **1**.

The small amount of **1** formed from **2** may be from initial attack at the carbonyl[1] or by the rearrangement of the possible intermediate 3-chloro-3-(piperidino)-propenal to 1-(3-chloropropenoyl)piperidine[5] and aminolysis of this vinylogous carbamyl chloride.

Experimental Section

Caution.—β-Chlorovinyl carbonyl compounds exhibit mustard gas-like vesicatory action. The aldehyde **2** and 4,4-dichloro-3-buten-2-one are cleaved by concentrated aqueous alkali to explosive chloroacetylene. All the dihalides can be safely destroyed by slow addition to excess aqueous ammonia.

General Synthetic Procedure.—Essentially the procedure of Kundiger and Morris was followed.[1] The dihalides were added dropwise with stirring at 0–5° to 6–8 molar equiv of piperidine in ether or benzene and stirred at room temperature for 1–2 days. The piperidine hydrochloride was filtered off and washed thoroughly with ether (90–100% yield), and the ether solution was stripped on a rotary evaporator [50–60° (13 mm)]. If any solid appeared and then redissolved (piperidine hydrochloride) or an amine odor remained, the material was taken up in hot methylcyclohexane, filtered, and restripped.

(1) D. G. Kundiger and G. F. Morris, *J. Amer. Chem. Soc.*, **80**, 5988 (1958). A referee has pointed out that the structure assignment for the title product **4** was corrected in the Ph.D. Thesis of G. F. Morris [Kansas State University, 1961; *Diss. Abstr.*, **21**, 3273 (1961)]. Examination of the thesis shows that Morris also prepared authentic **4a** and proved it different from the title reaction product **4b**. However, the result first alleged by Kundiger and Morris is not in general incorrect. The *tri*halopropenals reportedly give 2,3-dihalopropenamides with piperidine [C. Raulet and E. Levas, *Bull. Soc. Chim. Fr.*, 2139 (1963)].

(2) R. L. Soulen, D. G. Kundiger, S. Searles, Jr., and R. A. Sanchez, *J. Org. Chem.*, **32**, 2661 (1967).

(3) Acyl ketenaminals typically have low barriers to rotation about the carbon–carbon double bond and have their α-amino proton absorption isosynchronous or nearly so: J. Sandström and I. Wennerbeck, *Chem. Commun.*, 1088 (1971), and E. Ericsson, J. Sandström, and I. Wennerbeck, *Acta Chem. Scand.*, **24**, 3102 (1970), and references cited therein. We have found 4,4-bis(dimethylamino)-3-buten-2-one to have a single sharp absorption for all four *N*-methyls at 38° with only slight broadening at −70° in ether.

(4) Name adopted to describe the relationship between, *e.g.*, RCOX and RCOC=CX_2, as does *vinylog* for RCOC=CX, and *ethynylog* for RCOC≡CX [latter due to K. Hafner and M. Neuenschwander, *Angew. Chem., Int. Ed. Engl.*, **7**, 459 (1968)]. A referee has noted that *vinylidenolog* does not distinguish XCH=C(CHO)$_2$ from X_2C=CHCHO.

(5) M. Neuenschwander and A. Niederhauser, *Chimia*, **25**, 122 (1971).

When stored in sealed vials, compounds **1**, **4b**, and **6** discolor slowly. However, decomposition was very slow when these compounds were stored in *open* vessels over KOH|H_2SO_4| paraffin shavings in a desiccator protected from light at room temperature.

Reaction of 3,3-Dichloropropenal (2).—The starting material was prepared as reported.[6]

Following the general procedure, 2.50 g (20 mmol) of **2** in 50 ml of ether was allowed to react with 15 ml (~150 mmol) of piperidine in 100 ml of ether. Work-up afforded 3.37 g (76%) of an orange oil, which was a ~7:1 mixture of **5** and **1**: nmr (CCl_4) δ 1.62 (broad and unresolved, all 12 β- and γ-piperidino H's in both products), ~3.18 (broad and distorted multiplet, all eight α-piperidino H's in both products), 4.18 (d, J = 7 Hz, α-vinyl H in **5**), 4.91 (d, J = 13 Hz, α-vinyl H in **1**), 7.14 (d, J = 13 Hz, β-vinyl H in **1**), 9.03 (d, J = 7 Hz, formyl H in **5**). The absorptions at δ 4.91 and 7.14 were enhanced on addition of authentic **1** to the mixture.

1-[3-(Piperidino)propenoyl]piperidine (1).—Distillation of 48.0 g (450 mmol) of *trans*-3-chloropropenoic acid[7a] with 82 ml (710 mmol) of benzoyl chloride through a 30-cm Vigreux column keeping the head temperature below 116°[7b] afforded 32.6 g (58%) of *trans*-3-chloropropenoyl chloride: bp 107–116° (748 mm) [lit.[7a] bp 115–115.5° (1 atm)]; nmr (neat) δ 6.22 (d, 1, J = 13 Hz, α-H), 7.32 (d, 1, J = 13 Hz, β-H). This material contained some dissolved HCl and a little benzoyl chloride but was not further purified.

Following the general procedure, 12.5 g (100 mmol) of the acid chloride in 30 ml of ether was allowed to react with 60 ml (600 mmol) of piperidine in 350 ml of ether. Work-up gave 19.3 g (87%) of crude yellow product. Two recrystallizations from ethyl acetate afforded slightly stained material, mp 98.5–99.5°. Two further recrystallizations gave near-white needles: mp 99–100°; ir (CCl_4) 1640 (s, C=O), 1572 cm^{-1} (s, C=C); nmr (CCl_4) δ 1.57 (broad, 12, β- and γ-piperidino H's), 3.10 and 3.37 (two distorted multiplets cleanly separated, 4 each, α-piperidino H's), 4.89 (d, 1, J = 13 Hz, α-vinyl H), 7.11 (d, 1, J = 13 Hz, β-vinyl H).

Anal. Calcd for $C_{13}H_{22}N_2O$: C, 70.23; H, 9.97; N, 12.60. Found: C, 70.06; H, 10.01; N, 12.44.

3,3-Bis(piperidino)-2-methylpropenal (4b).—In 40 ml of ether 7.0 g (50 mmol) of the aldehyde **3**[1] was allowed to react with 35 ml (350 mmol) of piperidine in 200 ml of ether in the usual way to give 8.71 g (74%) of crude yellow-orange solid. The reported work-up[1] and repeated recrystallization from ethyl acetate and cyclohexane gave yellow needles of **4b**: mp 127–129° (lit.[1] mp 129–131°); nmr (CCl_4) δ 1.47 (s, CH_3), 1.59 (broad, β- and γ-piperidino H's, base overlaps δ 1.47, total both 15), 3.12 (distorted poorly resolved multiplet but one envelope, 8, α-piperidino H's), 8.97 (s, 1, CHO); ir (CCl_4) 2853 (m), 2819 (m, sh), 2727 (w, sh) (possibly formyl CH),[8] 1616 (s, C=O), 1541 cm^{-1} (vs, C=C); ir (Nujol) 1604, 1535–1520 cm^{-1} (lit., 1608, 1527 cm^{-1}).

4,4-Bis(piperidino)-3-buten-2-one (6).—4,4-Dichloro-3-buten-2-one was prepared as previously described (Darzens–Friedel–Crafts acetylation of 1,1-dichloroethene)[9a,b] except that substitution of dichloromethane for carbon tetrachloride as solvent facilitates stirring.

The general procedure, using 13.9 g (100 mmol) of the dichlorovinyl ketone in 25 ml of benzene and 65 ml (650 mmol) of amine in 180 ml of the same solvent, gave 21.8 g (92%) of crude yellowish product.[10] Two recrystallizations from ethyl acetate gave 14.5 g (61%) of near-white crystals: mp 79.5–80.5° (lit.[11] mp 80–81°) [rework of the mother liquors ultimately gave a total of 19.3 g (82%) of material of mp >78°]; ir (CCl_4) 1627 (s, C=O), 1501 cm^{-1} (s, C=C); ir (Nujol) 1617, 1508 cm^{-1} (lit.[11] 1623, 1517 cm^{-1}); nmr (CCl_4) δ 1.56 (broad, 12, β- and γ-piperidino H's), 1.80 (s, 3, methyl), 3.07 (broad and distorted but one envelope, 8, α-piperidino H's), 4.23 (s, 1, vinyl H); nmr ($CDCl_3$) δ 1.60, 1.96, 3.17, 4.40 (lit.[11] δ 1.60, 1.98, 3.19, 4.41). This compound has an anise odor not abolished when stored for several months as described above.

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Registry No.—**1**, 6162-62-5; **2**, 2648-51-3; **3**, 1561-34-8; **4b**, 40428-93-1; **5**, 40428-94-2; **6**, 10099-09-9; piperidine, 110-89-4; *trans*-3-chloropropenoic acid, 2345-61-1; *trans*-3-chloropropenoyl chloride, 3721-36-6; 4,4-dichloro-3-buten-2-one, 5780-61-0.

(6) M. Levas, *Ann. Chim. (Paris)*, [12] **7**, 719 (1952).

(7) (a) E. Gryszkiewicz-Trochimowski, W. Schmidt, and O. Gryszkewicz-Trochimowski, *Bull. Soc. Chim. Fr.* 593 (1948); (b) H. C. Brown, *J. Amer. Chem. Soc.*, **60**, 1325 (1938). This method was chosen for its convenience rather than yield.

(8) L. J. Bellamy, "The Infra-Red Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1958, p 157.

(9) (a) S. Searles, Jr., R. A. Sanchez, R. L. Soulen, and D. G. Kundiger, *J. Org. Chem.*, **32**, 2655 (1967); (b) J. B. Ellern and H. B. Gray, *J. Org. Chem.*, **37**, 4485 (1972).

(10) The acetylene, 4-(piperidino)-3-butyn-2-one is an intermediate (ir). Use of too little piperidine permits this intermediate to decompose to red-brown polymeric material. If diethylamine is substituted for piperidine, addition of excess amine to the corresponding acetylene is so slow that it can be isolated in >75% yield. These results will be presented in detail in a future article.

(11) W. E. Truce, D. J. Abraham, and P. Son, *J. Org. Chem.*, **32**, 990 (1967).

Synthesis of DL-3-(3,4-Dihydroxyphenyl)alanine Methyl Ester and Related Compounds

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Successful results with L-3-(3,4-dihydroxyphenyl)-alanine (L-dopa) in the treatment of Parkinson's disease[2] have stimulated efforts in both the synthesis and resolution of DL-dopa. Ring-hydroxylated α-amino acids have usually been prepared[3] by condensation of an appropriate aromatic aldehyde with an active methylene compound, such as an azlactone in the Erlenmeyer synthesis. Low to moderate yields (30–60%) of DL-dopa have been reported by these methods.

We wish to report the synthesis of DL-3-(3,4-dihydroxyphenyl)alanine methyl ester, which was carried out *via* a single-vessel process in 83% yield. Methyl isocyanoacetate[4] (**1**), a material known[5] to undergo a wide variety of carbanion condensation reactions, was used as a starting material.[6] The isocyano group, in addition to activating the α-carbon atom for proton abstraction, affords an ideal protective group for a primary amine easily regenerated by acid hydrolysis. Condensation of **1** with 3,4-dibenzyldioxybenzaldehyde (**2**) in methyl alcohol with potassium *tert*-butoxide as the catalyst yielded the alkoxide

(1) Summer Research Associate, Procter & Gamble.

(2) A. Barbeau, *Can. Med. Ass. J.*, **101** (13), 59 (1959); D. B. Calne and M. Sandler, *Nature (London)*, **226**, 21 (1970); J. D. Parkes, K. J. Zilka, D. M. Calver, and R. P. Knill-Jones, *Lancet*, **1**, 259 (1970).

(3) J. P. Greenstein and M. Winitz, Ed., "Chemistry of the Amino Acids," Wiley, New York, N. Y., 1961, pp 2713–2723.

(4) We have used methyl isocyanoacetate to prepare several amino acids; U. S. patent application filed December 19, 1969, serial no. 886,748.

(5) U. Schoellkopf, *Angew. Chem., Int. Ed. Engl.*, **9**, 763 (1970), and references cited therein.

(6) Recently, Schoellkopf and coworkers and Suzuki, *et al.*, have used isocyano and isocyanopropionic esters to prepare alkyl amino acids and α-methyl-dopa by alkylation of the isocyano ester carbanions: U. Schoellkopf, D. Hoppe, and R. Jentsch, *Angew. Chem., Int. Ed. Engl.*, **10**, 331 (1971); M. Suzuki, K. Matsumoto, T. Iwasaki, and K. Okumura, *Chem. Ind. (London)*, 687 (1972).