Acknowledgment. A special thanks to Dr. M. F. Renard for skillful help in structure elucidation.

Registry No. 1, 91273-98-2; **2a**, 102273-62-1; **2'a**, 116531-36-3; **3a**, 108508-58-3; **3'a**, 119785-58-9; **3b**, 108508-56-1; **3'b**, 119785-59-0; **4a**, 76740-35-7; **4'a**, 76740-34-6; **4b**, 76740-36-8; **4'b**, 76334-10-6.

Superacid Cyclodehydration of Ketones in the Production of Tricyclic Antihistamines

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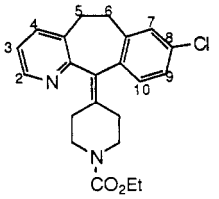
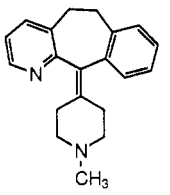
Loratadine (Sch 29851; 1) is a potent, long-acting antihistamine with a lack of central nervous system (CNS) side effects.[1] Although the compound is a derivative of azatadine (2), the presence of a chlorine in the phenyl ring causes unique problems such that the azatadine process, which requires two reduction steps, cannot be effectively used, as the chlorine is in part removed.[2] In addition, formation of the tricyclic ring structure with polyphosphoric acid results in isomers chlorinated in the 8- or 10-position. These problems were previously overcome by use of an inefficient alkylation/reduction process (yield <35%), a Friedel–Crafts acylation, and a Grignard reaction which gave greater than 30% of undesired 1,6-addition products. The overall yield for this process was ~4%.



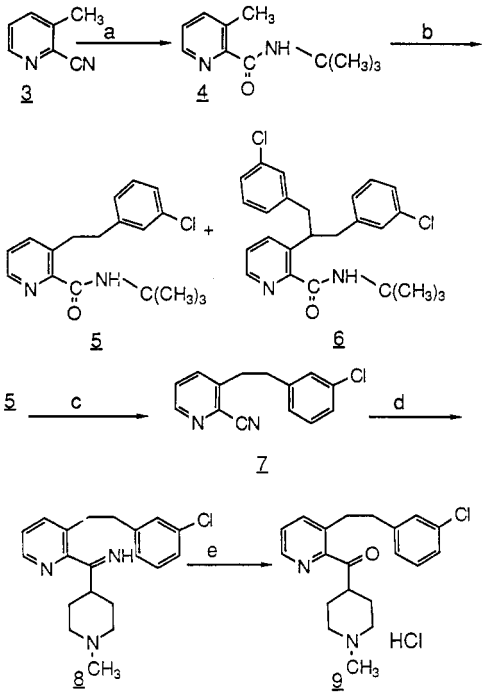
1
LORATADINE



2
AZATADINE

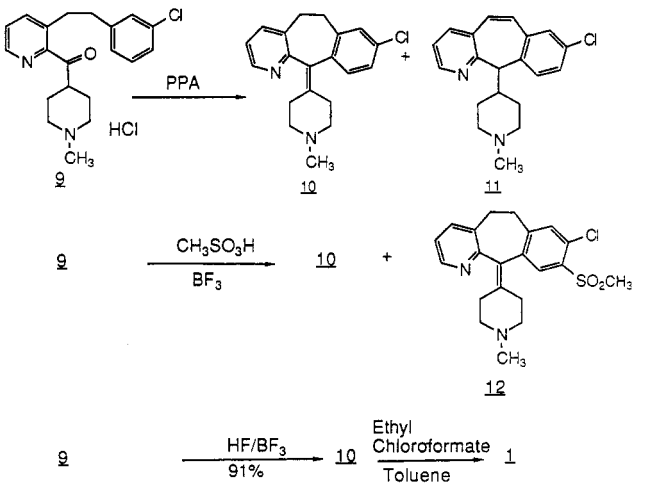
The requirement for large quantities of loratadine necessitated the practical and economical introduction of the piperidine ring as well as formation of the tricyclic ring structure. Initially, the alkylation of 2-cyano-3-methylpyridine (3) was addressed (Scheme I). Direct alkylation of 3 with *m*-chlorobenzaldehyde gave low yields due to self-condensation of the nitrile. McOmie[3] suggests that a nitrile might be protected as the *tert*-butylamide formed via a Ritter reaction.[4] Such protection proved effective, and the *tert*-butylamide 4 was formed in 97% yield with *tert*-butyl alcohol and sulfuric acid. The dianion of this amide was readily formed with *n*-butyllithium at −30 °C, the compound itself serving as an indicator for the titration of the base.[5] The dianion was alkylated with *m*-chlorobenzyl chloride to give the (chlorophenethyl)pyridine 5 in

Scheme I[a]



[a] (a) H_2SO_4, *t*-BuOH; (b) *n*-BuLi, *m*-chlorobenzyl chloride, THF; (c) $POCl_3$; (d) (*N*-methylpiperidyl)magnesium chloride, THF; (e) aqueous HCl.

Scheme II



92% yield. A small amount of dialkylated byproduct 6 was also obtained.

The amide 5 was converted to nitrile 7 with phosphorus oxychloride in 94% yield after crystallization. Formerly, ring closure was effected at this point to provide a ketone, followed by alkylation with (*N*-methylpiperidyl)magnesium chloride and dehydration with sulfuric acid. As an alternative, we investigated the addition of the Grignard reagent to the nitrile to form a ketone, followed by cyclodehydration to give 8-chloroazatadine. The nitrile was alkylated with (*N*-methylpiperidyl)magnesium chloride to give the imine 8, which could be isolated and subsequently converted to loratadine. However, we found that hydrolysis of the imine in situ with hydrochloric acid led to the convenient and efficient recovery of ketone hydrochloride 9 in 91% yield. No 1,6-addition of the Grignard reagent was observed.

The crux of this procedure is the cyclodehydration of the ketone to the penultimate azatadine derivative 10

(1) Kreutner, W.; Chapman, R. W.; Gulbenkian, A.; Siegel, M. I. *Allergy (Copenhagen)* **1987**, *42*, 57–63. Barnett, A.; Iorio, L. L.; Kreutner, W.; Tozzi, S.; Ahn, H. S.; Gulbenkian, A. *Agents Actions* **1984**, *14*, 590–597.

(2) (a) Villani, F. J. U.S. Patent 3326924, 1967. (b) Villani, F. J.; Wefer, E. A.; Mann, T. A.; Mayer, J.; Peer, L.; Levy, A. S. *J. Heterocycl. Chem.* **1972**, *9*, 1203–1207. (c) Villani, F. J.; Daniels, P. L.; Ellis, C. A.; Mann, T. A.; Wang, K.-C.; Wefer, E. A. *J. Med. Chem.* **1972**, *15*, 750–754.

(3) McOmie, J. F. W. *Protective Groups in Organic Chemistry*; Plenum Press: New York, 1973; p 409.

(4) For a review of the Ritter reaction, see: Krimen, L. I.; Cota, D. J. *Org. React. (N.Y.)* **1969**, *17*, 213–325.

(5) Compound 4 serves as an excellent indicator for organolithium reagents. An intense purple color appears immediately upon formation of the dianion.

0022-3263/89/1954-2242$01.50/0

(Scheme II). There are examples in the literature[6] of cyclodehydrations using PPA, HF, and H_2SO_4, etc.; however, we found that only PPA at 200 °C effected the desired cyclodehydration and the yield was only ~45%. In addition, a byproduct (11) was formed. (Compound 10 was converted to a 2:1 mixture of 10–11 in refluxing triflic acid.) It appeared to us that a stronger acid was required in our case, due in part to the presence of the two amines which must first be protonated.[7] Therefore, superacid systems[8] having a Hammett acidity function of less than −14 were investigated. We found that triflic acid, methanesulfonic acid/boron trifluoride, and hydrofluoric acid/boron trifluoride all gave 10 in 75–95% yield. Triflic acid proved too expensive (10 equiv was needed), and removal of the triflate salts was very tedious. Methanesulfonic acid/boron trifluoride, on scale-up, gave substantial amounts (>10%) of substitution of a methanesulfonyl group at the 9-position (12). However, hydrofluoric acid/boron trifluoride proved to be an effective and inexpensive reagent. Consequently, 9 was cyclized with HF/BF_3 for 1 h at −30 °C, giving 10 in yields in excess of 90%. Compound 10 was converted to loratadine as previously published by reaction with 3 equiv of ethyl chloroformate in toluene at 80 °C.[9]

In summary, an efficient (overall yield 57%) process for the synthesis of loratadine has been realized, and this process is being used on a multikilo scale for the production of commercial quantities of the antihistamine.[10] The key step in the synthesis is the cyclodehydration of a ketone using a superacid system.

Experimental Section

Melting points were measured on a Büchi 510 instrument and are uncorrected. ^1H NMR spectra were recorded on a Varian FT-80A, Varian XL-200, or Varian XL-400 instrument with tetramethylsilane as an internal standard. FAB mass spectra were determined on a Finnigan MAT 312 instrument and CI mass spectra on an Extranuclear ELQ-400-1 instrument.

2-[(*tert*-Butylamino)carbonyl]-3-methylpyridine (4). A suspension of 2-cyano-3-methylpyridine[11] (400 g, 3.4 mol) in 800 mL of *tert*-butyl alcohol was heated at 70 °C. Concentrated sulfuric acid (400 mL) was added over 45 min. The reaction was complete after a further 30 min at 75 °C. The reaction mixture was diluted with water (400 mL) and toluene (600 mL) and brought to pH 10 with concentrated aqueous ammonia. The temperature was kept at 50–55 °C during workup. The toluene phase was separated and the aqueous layer extracted again with toluene, and the combined toluene phases were washed with water. Removal of the toluene yielded 633 g (97%) of crystalline 4: mp 56–58 °C; NMR (200 MHz, $CDCl_3$) δ 1.52 (s, 9 H), 2.75 (s, 3 H), 7.25 (dd, 1 H, J = 7.5, 5 Hz), 7.58 (dd, 1 H, J = 7.5, 1.2 Hz) 8.08 (br s, 1 H) 8.40 (dd, 1 H, J = 5, 1.2 Hz); mass spectrum, m/e (rel intensity) 192 M^+ (12), 177 (49). Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.68; H, 8.13; N, 14.40. Found: C, 68.71; H, 8.39; N, 14.57.

3-[2-(3-Chlorophenyl)ethyl]-*N*-(1,1-dimethylethyl)-2-pyridinecarboxamide (5). To a cold (−40 °C) solution of compound 4 (31.5 g, 0.16 mol) in 600 mL of dry tetrahydrofuran was added *n*-butyllithium in hexanes (2.5 N, 131 mL) while the temperature was maintained at −40 °C. The solution turned deep red after 1 equiv was added. Sodium bromide (1.6 g) was added, and the mixture was stirred for 10 min. A solution of *m*-chlorobenzyl chloride (26.5 g, 0.174 mol) in 125 mL of dry tetrahydrofuran was added while the temperature was again maintained at −40 °C. The reaction mixture was stirred for a further 30 min, after which water was carefully added until the color dissipated. The product was isolated by extraction into ethyl acetate, which was washed with water, dried ($MgSO_4$), and concentrated to give 53.6 g (HPLC purity 89%; yield 92%) of 5 as an oil (HPLC parameters: column, Waters μBondapak; mobile phase, methanol–0.01 M aqueous dibasic potassium phosphate (7:3); flow rate, 1 mL/min; detection, 254 nm). This oil may be used directly in the next step or crystallized from hexanes to give 5 as a white solid: mp 45–46 °C; NMR (200 MHz, $CDCl_3$) δ 1.50 (s, 9 H), 2.96 (t, 2 H, J = 8 Hz), 3.40 (t, 2 H, J = 8 Hz), 7.0–7.3 (m, 5 H), 7.39 (dd, 1 H, J = 8, 2 Hz), 7.98 (br s, 1 H), 8.38 (dd, 1 H, J = 4, 1 Hz); mass spectrum, m/e (rel intensity) 316 M^+ (19). Anal. Calcd for $C_{18}H_{21}N_2OCl$: C, 68.22; H, 6.68; N, 8.88; Cl, 11.19. Found: C, 68.25; H, 6.59; N, 8.78; Cl, 11.10.

Compound 6 was isolated by chromatography (silica gel; ether–hexanes, 20:1) as a crystalline solid: NMR (79.5 MHz, $CDCl_3$) δ 1.44 (s, 9 H), 2.92 (d, 4 H, J = 7 Hz), 5.05 (t, 1 H, J = 7 Hz), 6.9–7.4 (m, 9 H), 7.64 (dd, 1 H, J = 8, 1.2 Hz), 8.28 (dd, 1 H, J = 5, 1.2 Hz); mass spectrum, m/e (rel intensity) 442 $(M + 2)^+$ (25), 440 M^+ (36).

3-[2-(3-Chlorophenyl)ethyl]-2-pyridinecarbonitrile (7). A solution of 5 (175 g, 0.55 mol) in 525 mL (5.6 mol) of phosphorus oxychloride was heated at reflux for 3 h. Excess phosphorus oxychloride (~300 mL) was removed by distillation, and the remaining solution was carefully poured into ice–water. The pH of the solution was adjusted to 8 with 50% aqueous sodium hydroxide while the temperature was maintained at 25–30 °C. The mixture was stirred for 2 h, during which time the pH was maintained at 8. The product was collected by filtration, washed with water, and dried in a vacuum oven at 50 °C to give 127 g (95%) of crystalline 7: mp 72–73 °C (lit.[12] mp 72–74 °C); NMR (200 MHz, $CDCl_3$) δ 2.9–3.1 (m, 2 H), 3.1–3.2 (m, 2 H), 7.0–7.1 (m, 1 H), 7.1–7.3 (m, 3 H), 7.42 (dd, 1 H, J = 7.3, 5 Hz), 7.56 (dd, 1 H, J = 7.3, 1.2 Hz) 8.58 (dd, J = 5, 1.2 Hz); mass spectrum, m/e (rel intensity) 242 M^+ (18). Anal. Calcd for $C_{14}H_{11}N_2Cl$: C, 69.28; H, 4.57; N, 11.54; Cl, 14.61. Found: C, 69.37; H, 4.48; N, 11.39; Cl, 14.48.

(1-Methyl-4-piperidinyl)[3-[2-(3-chlorophenyl)ethyl]-2-pyridinyl]methanone Hydrochloride (9). To a solution of compound 7 (118 g, 0.49 mol) in 1.2 L of dry tetrahydrofuran was added 395 mL (2.48 N, 0.59 mol) of (*N*-methylpiperidyl)magnesium chloride[13] over 0.5 h while the temperature was maintained at 40–50 °C by cooling with water as necessary. The reaction mixture was maintained at 40–50 °C for an additional 0.5 h. The reaction was quenched to below pH 2 by the addition of 2 N hydrochloric acid, and the resulting solution was stirred at 25–30 °C for 1 h. The bulk of the tetrahydrofuran was removed by distillation and the pH of the solution adjusted to 3.5 by the addition of aqueous sodium hydroxide. The mixture was cooled to 5 °C, and the product was collected by filtration, washed with cold water, and dried under vacuum at 60 °C to give 168 g (91%) of 9 as a crystalline solid: mp 183–185 °C; NMR (200 MHz, DMSO) δ 2.72 (s, 3 H), 2.8–2.9 (m, 2 H) 3.0–3.2 (m, 4 H), 3.3–3.5 (m, 3 H), 3.9–4.1 (m, 1 H), 7.2–7.3 (m, 1 H), 7.3–7.4 (m, 3 H), 7.57 (dd, 1 H, J = 6, 4 Hz), 7.84 (dd, 1 H, J = 6, 1.2 Hz), 8.59 (dd, 1 H, J = 4, 1.2 Hz), 10.95 (br s, 1 H); mass spectrum, m/e (rel intensity) 345 $(M + 1)^+$ (32), 343 M^+ (100). Anal. Calcd for $C_{20}H_{24}N_2OCl_2$: C, 63.32; H, 6.38; N, 7.39; Cl, 18.69. Found: C, 63.45; H, 6.47; N, 7.40; Cl, 18.49.

8-Chloro-6,11-dihydro-11-(1-methyl-4-piperidylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (10).[2c] To a solution of 9 (59.0 g, 0.15 mol) in 120 mL (120 g, 6.0 mol) of hydrofluoric acid at −35 °C was added boron trifluoride (44.3 g, 0.66 mol) over 1 h. The reaction was quenched by using ice water and potassium hydroxide to a final pH of 10. The product was extracted into toluene, which was washed with water and brine. The toluene solution was concentrated to a residue, which was triturated with hot hexanes. Insoluble salts were removed by filtration, and the

(6) Olah, G. A. *Friedel-Crafts and Related Reactions*; Interscience Publishers: New York, 1964; Vol. 2, Part II, pp 859–927.
(7) In support of this theory, the cyclization of the N-protected ketone was also carried out. Although a superacid was still required, the desired conversion to loratadine proceeded under milder conditions.
(8) Olah, G. A.; Prakash, G. K. S.; Sommer, J. *Superacids*; John Wiley & Sons: New York, 1985; pp 33–61.
(9) Villani, F. J.; Magatti, C. V.; Vashi, D. B.; Wong, J.; Popper, T. L. *Arzneim.-Forsch./Drug Res.* **1986**, *36*, 1311–1314.
(10) Schumacher, D. P.; Murphy, B. L.; Clark, J. E. U.S. Patent 4731447, 1988.
(11) Available from Reilly Tar & Chemical.
(12) Villani, F. J.; Danield, P. J. L.; Ellis, C. A.; Mann, T. A.; Wang, K.-C. *J. Heterocycl. Chem.* **1971**, *8*, 73–81.
(13) Engelhardt, E. L.; Zell, H. C.; Saari, W. S.; Christy, M. E.; Colton, C. D.; Stone, C. A.; Stavorski, J. M.; Wenger, H. C.; Ludden, C. T. *J. Med. Chem.* **1965**, *8*, 829.

filtrate was concentrated to give 45.7 g (HPLC purity 96%; yield 91%) (HPLC parameters: column, Waters μBondapak; mobile phase, MeOH–0.05 M aqueous monobasic potassium phosphate (6:4); flow rate, 1 mL/min; detection, 254 nm) of **10** as an off-white solid: mp 116–119 °C; NMR (400 MHz, CD_3OD) δ 2.0–2.2 (m, 2 H), 2.27 (s, 3 H), 2.3–2.6 (m, 4 H), 2.6–3.0 (m, 4 H) 3.3–3.6 (m, 2 H), 7.11 (d, 1 H, J = 8.17 Hz, H_{10}), 7.16 (dd, 1 H, J = 8.14, 2.07 Hz, H_9), 7.21 (d, 1 H, J = 2.07 Hz, H_7), 7.24 (dd, 1 H, J = 7.70, 4.92 Hz, H_3), 7.64 (dd, 1 H, J = 7.70, 1.55 Hz, H_4), 8.31 (dd, 1 H, J = 4.95, 1.55 Hz, H_2); mass spectrum, m/e (rel intensity) 327 $(M + 3)^+$ (28), 325 $(M + 1)^+$ (100). Anal. Calcd for $C_{20}H_{21}N_2Cl$: C, 73.94; H, 6.52; N, 8.63; Cl, 10.92. Found: C, 73.88; H, 6.48; N, 8.69; Cl, 10.80.

8-Chloro-11-(1-methyl-4-piperidinyl)-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (11). A solution of **9** (6.04 g) in 120 g of polyphosphoric acid was heated at 190 °C for 8 h. The reaction mixture was poured into ice–water and adjusted to pH 9 with 50% aqueous sodium hydroxide. The aqueous solution was extracted with ethyl acetate, and the combined organic extracts were washed with brine and concentrated to a residue. Column chromatography (silica gel; toluene–CH_2Cl_2–MeOH–MeOH saturated with gaseous ammonia, 16:4:0.75:0.25) yielded 2.52 g of **10** (44%) and 0.85 g of **11**: mp 151–153 °C; NMR (200 MHz, $CDCl_3$) δ 0.8–0.9 (m, 1 H), 1.0–1.1 (m, 1 H), 1.1–1.4 (m, 2 H), 1.66 (m, 2 H) 1.8–2.0 (m, 1 H), 2.18 (s, 3 H), 2.6–2.8 (m, 2 H), 4.11 (d, 1 H, J = 8 Hz), 6.90 (dd, 2 H, J = 19, 12 Hz), 7.2–7.4 (m, 4 H), 7.67 (dd, 1 H, J = 7, 2 Hz), 8.55 (dd, 1 H, J = 5, 2 Hz); mass spectrum, m/e (rel intensity) 325 $(M + 1)^+$ (19). Anal. Calcd for $C_{20}H_{21}N_2Cl$: C, 73.94; H, 6.52; N, 8.63; Cl, 10.92. Found: C, 74.62; H, 6.53; N, 8.33; Cl, 10.51.

8-Chloro-7-(methylsulfonyl)-5-(4′-*N*-methylpiperidylidene)-4-aza-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (12). Boron trifluoride (118 g, 1.74 mol) was added over 15 min to a solution of 40.0 g (0.117 mol) of **9** in 250 mL of methanesulfonic acid at 0–5 °C in a Teflon pressure reaction vessel. This was then sealed, and the reaction mixture was heated at 120 °C for 4 h. The reaction mixture was cooled, and the solution was poured into ice–water and adjusted to pH 10 with 50% aqueous sodium hydroxide. The product was extracted into methylene chloride, which was concentrated to a residue. The residue was triturated with hot hexanes and clarified by filtration. The filtrate was concentrated to afford 32.6 g of a crude mixture of products. Purification by chromatography (silica gel; 16:4:0.75:0.25 toluene–methylene chloride–methanol saturated with gaseous ammonia) gave 20 g of **10** and 0.3 g of **12**. NMR (200 MHz, $CDCl_3$): δ 2.2–2.6 (m, 6 H); 2.33 (s, 3 H), 2.7–3.0 (m, 4 H), 3.22 (s, 3 H), 3.4–3.6 (m, 2 H), 7.13 (dd, 1 H, J = 7, 5 Hz), 7.3–7.4 (m, 1 H), 7.49 (d, 1 H, J = 9 Hz), 8.02 (s, 1 H), 8.44 (d, 1 H, J = 5 Hz). Mass spectrum: m/e (rel intensity) 403 $(M + 1)^+$ (11).

8-Chloro-6,11-dihydro-11-[1-(ethoxycarbonyl)-4-piperidylidene]-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (1). Ethyl chloroformate (40.4 mL, 45.9 g, 0.423 mol) was added slowly to a hot (~80 °C) solution of **10** (45.7 g, 0.141 mol) in 320 mL of toluene. Following complete addition, the temperature was maintained at 80 °C for 1 h. The reaction mixture was cooled to ambient temperature and the toluene solution washed with water which was adjusted to pH 10 with aqueous sodium hydroxide. The organic layer was concentrated to a residue, which was dissolved in hot acetonitrile and decolorized with charcoal. The solution was concentrated to a crystalline slurry, which was cooled (5 °C). Product **1** was isolated by filtration, yielding 42.4 g: mp 134.5–136 °C (lit.[9] mp 134–136 °C); NMR (400 MHz, CD_3OD) δ 1.25 (t, 3 H, J = 8 Hz), 2.3–2.4 (m, 3 H), 2.4–2.5 (m, 1 H), 2.7–2.9 (m, 2 H), 3.1–3.2 (m, 2 H), 3.3–3.4 (m, 2 H), 3.81 (br s, 2 H), 4.13 (q, 2 H, J = 8 Hz), 7.12 (d, 1 H, J = 8.11 Hz, H_{10}), 7.17 (dd, 1 H, J = 8.11, 2.17 Hz, H_9), 7.23 (d, 1 H, J = 2.13 Hz, H_7), 2.26 (dd, 1 H, J = 7.71, 4.90, H_4), 7.65 (dd, 1 H, J = 7.73, 1.65 H_4), 8.32 (dd, 1 H, J = 4.88, 1.15 Hz, H_2); mass spectrum, m/e (rel intensity) 385 $(M + 3)^+$ (35), 383 $(M + 1)^+$ (100). Anal. Calcd for $C_{22}H_{23}N_2ClO_2$: C, 69.00; H, 6.05; N, 7.32; Cl, 9.26. Found: C, 69.37; H, 6.09; N, 7.35; Cl, 9.37.

Acknowledgment. We thank the staff of the Physical–Analytical Departments for spectra and microanalyses and Professor Ronald Breslow for helpful discussions.

Registry No. **1**, 79794-75-5; **4**, 32998-95-1; **5**, 107285-30-3; **6**, 119770-59-1; **7**, 31255-57-9; **9**, 119770-60-4; **10**, 38092-89-6; **11**, 119770-61-5; **12**, 119770-62-6; 2-cyano-3-methylpyridine, 20970-75-6; *m*-chlorobenzyl chloride, 620-20-2; (*N*-methylpiperidyl)-magnesium chloride, 63463-36-5.

Benzylidene Isophorone Dimer and Its Photoproduct

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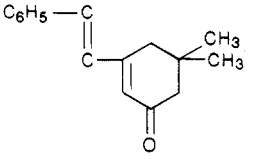
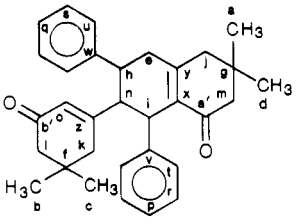
Received November 1, 1988

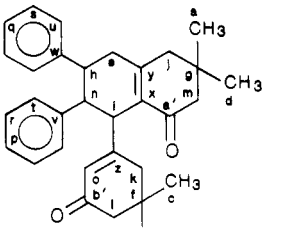
Condensation of benzaldehyde with isophorone by aqueous sodium hydroxide gives benzylidene isophorone,



mp 73.5 °C, and its dimer, mp 198–9 °C. On the basis of IR, UV, mass, and NMR spectra, Kabas[1] postulated either structure **1** or structure **2** for the dimer. We irradiated

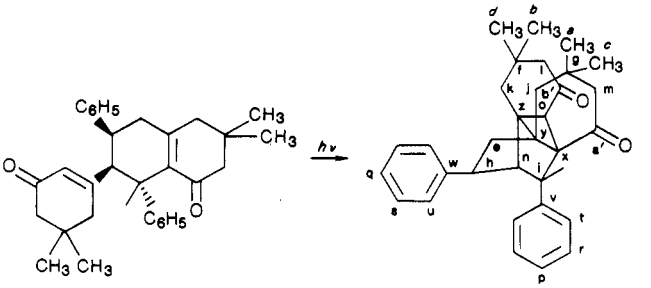


1



2

the dimer in acetone and produced a new compound mp 239–41 °C. 2D NMR and crystal structure analysis showed that the dimer had structure **1**, and the photoproduct structure **3**, derived from **1** by intramolecular 2 + 2 cycloaddition.



Although crystals of **3** tended to fall apart, appeared to be composed of several layers, and diffracted only moderately well, the data collected were sufficient to determine

(1) Kabas, G. *Tetrahedron* **1966**, *22*, 1213.

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