were irradiated in 150 ml of purified acetone in base-washed glassware from −10° to ambient temperatures. After removal of solvent *in vacuo* at approximately 0°, an ambient-temperature nmr of the photoproduct was taken in calcium carbonate treated carbon tetrachloride. Results were not reproducible but in no case were the characteristic proton absorptions [τ 5.17 (1 H, d), 6.14 (1 H, distorted t), 6.60 (1 H, m), and 7.43 (1 H, distorted t)] of a polycyclic azetidine **7c** observed. Some of the nmr spectra resembled those of fulvenes. One of the 250-mg (1.10 mmol) runs was chromatographed on Woelm activity IV basic alumina (2.3 × 33 cm column, slurry packed in 2% ether–hexane). Elution proceeded as follows: 1.0 l., 2% ether–hexane, small amount of unidentified yellow oil; 1.5 l., 5% ether–hexane, 0.134 g (0.59 mmol, 53%) of 1-*tert*-butoxycarbonylamino-1,4-dimethylmethyleneindene (16) [yellow plates, mp 97.5–98.5° (pentane–ether); ir (KBr) 2.95 (m, NH), 5.85 (s), 6.13 (s), 6.64 (s), 6.92 (m), 7.00 (m), 7.37 (m), 7.61 (m), 7.67 (m), 7.97 (m), 8.10 (s), 8.65 (s), 11.53 (m), 13.32 (s), and 13.56 μ (m); uv max (CH_3CN) 230 nm (ϵ 9530), 280 (19,100), and 324 (13,600); nmr (CCl_4) τ 2.34–2.97 (5 H, m), 3.50 (1 H, m), 7.43 (3 H, s), 7.82 (3 H, broad s), and 8.46 (9 H, s); mass spectrum *m/e* (rel intensity) 271 (18, P), 272 (4, P + 1), 51 (5), 55 (5), 56 (9), 57 (100, B), 59 (32), 77 (5), 115 (6), 127 (13), 128 (39), 129 (14), 130 (13), 153 (7), 154 (8), 155 (6), 156 (6), 170 (17), 171 (62), 172 (8), 182 (6), 197 (65), 198 (13), 215 (48), and 216 (6)].

Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.04; H, 7.76; N, 5.01.

Quantum Yield Measurements. These determinations were made in the previously described[6] two-compartment cell on magnetically stirred solutions under a nitrogen atmosphere using light from a Bausch and Lomb high-intensity grating monochrometer. The light intensity was measured immediately prior to and immediately following irradiation, and if these values differed by more than 10% the run was discarded.

Direct Irradiation of 3c. A solution of 0.50 g of carbamate in 65 ml of purified cyclohexane was irradiated at 300 nm and the analysis for formation of **5c** was made by uv analysis at 321 nm. The data below summarize the quantum yields measured at the indicated per cent conversion: Φ = 0.048 (0.26%), Φ = 0.065 (0.34%), Φ = 0.060 (0.60%), Φ = 0.057 (0.61%), Φ = 0.043 (0.85%), and Φ = 0.045 (0.91%).

Sensitized Irradiation of 3c. A solution of 0.243 g of **3c** in 65 ml of purified acetone was irradiated at 300 nm and 20.5 mg of benzalazine was added to the irradiated solution. After removal of solvent *in vacuo*, the residue was dissolved in sodium carbonate washed carbon tetrachloride for nmr analysis. The nmr spectra taken immediately after irradiation allowed calculation of the amount of **7c** formed by comparing the area of the benzalazine singlet (τ 1.48, 2 H) with the one-proton signals of the photoproduct at τ 5.17, 6.14, and 6.60. The results for two determinations were Φ = 0.95 and Φ = 0.91 at 16–17% conversion.

Registry No.—**3a**, 28035-70-3; **3c**, 5176-28-3; **4c**, 50585-27-8; **5c**, 50585-28-9; **6c**, 34813-08-6; **7c**, 34813-09-7; **8c**, 34813-10-0; **15**, 50585-34-7; **16**, 50585-35-8; 2-formylindan, 37414-44-1; *tert*-butyl 2,5-dimethylpyrrole-1-carboxylate, 50585-36-9; 2,5-dimethylpyrrole, 625-84-3; *tert*-butyl azidoformate, 1070-19-5; *o*-fluorobromobenzene, 1072-85-1.

References and Notes

(1) (a) Alfred P. Sloan Fellow, 1971–1973; Camille and Henry Dreyfus Teacher-Scholar, 1972–1977. (b) Ohio State University Undergraduate Research Scholar, 1968–1969. (c) Ohio State University Fellow, 1969–1970. (d) For a preliminary report see P. D. Rosso, J. Oberdier, and J. S. Swenton, *Tetrahedron Lett.*, 3947 (1971).

(2) (a) J. R. Edman, *J. Amer. Chem. Soc.*, **88**, 3454 (1966); **91**, 7103 (1969); (b) B. M. Trost, *J. Org. Chem.*, **34**, 3644 (1969); (c) W. Eberbach, P. Würsch, and H. Prinzbach, *Helv. Chim. Acta*, **53**, 1235 (1970); (d) J. J. Tufariello and D. W. Rowe, *J. Org. Chem.*, **36**, 2057 (1971).

(3) G. Kaupp, J. Perreten, R. Leute, and H. Prinzbach, *Chem. Ber.*, **103**, 2288 (1970).

(4) (a) J. Ipaktschi, *Chem. Ber.*, **105**, 1989 (1972). (b) See also F. Scully, J. Grutzner, and H. Morrison, *J. Amer. Chem. Soc.*, **95**, 5100 (1973).

(5) L. A. Carpino and D. E. Barr, *J. Org. Chem.*, **31**, 764 (1966).

(6) J. S. Swenton, J. A. Hyatt, T. J. Walker, and A. L. Crumrine, *J. Amer. Chem. Soc.*, **93**, 4808 (1971).

Stereochemical Course of Bromocyclizations of γ,δ-Unsaturated Alcohols. II.[1] Approaches to Various Oxaazabicyclooctane and -nonane Systems

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γ,δ-Unsaturated alcohols, *N*-methyl-2-hydroxymethyl-2-phenyl-4-pentenoic acid amide (**2**), 2-hydroxymethyl-2-phenyl-4-penten-1-ol (**6**), 3-hydroxymethyl-3-phenyl-5-hexen-1-ol (**10**), 3,3-diphenyl-1-methylamino-5-hexen-2-ol (**14d**), 1-chloro-3,3-diphenyl-5-hexen-2-ol (**14c**), and 3,3-diphenyl-1-methylamino-2-methyl-5-hexen-2-ol (**19**) were bromocyclized to the corresponding tetrahydrofurfuryl bromides (**3**, **7** and **8**, **11** and **12**, **15a**, **15c**, and **20** and **21**). The stereochemistry in each case was determined unambiguously by further intramolecular cyclization or lack of it to the corresponding oxaazabicyclooctanes (**4**, **5**, **16**, and **22**) and oxaazabicyclononane (**13**).

We have previously described the synthesis of several substituted tetrahydrofurfurylamines by bromocyclizations of corresponding γ,δ-unsaturated alcohols, followed by substitution of bromine with alkylamines.[1] The interesting pharmacological properties of some of these compounds coupled with simplicity of the synthetic approach have stimulated our additional investigation in this field with the aim to extend the synthesis to various bicyclic systems.

Results

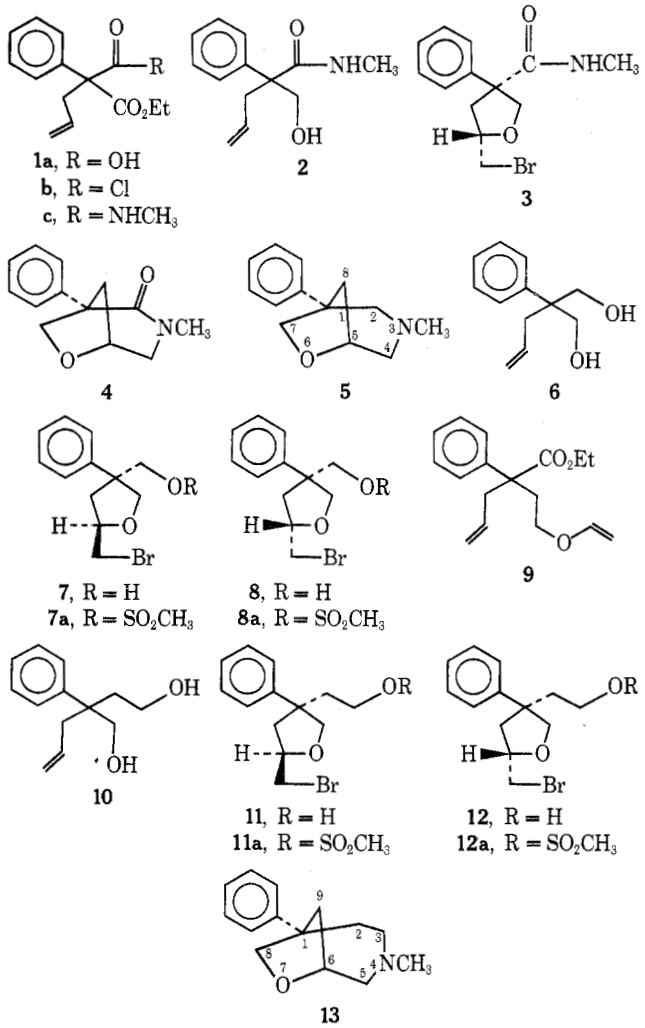
The original attempt to synthesize 3-methyl-1-phenyl-6-oxa-3-azabicyclo[3.2.1]octane (**5**) was made *via* diethyl (allyl phenyl) malonate **1** (Chart I, R = OEt) which was selectively hydrolized to the monoacid **1a**. Sequential treatment of **1a** with thionyl chloride, methylamine, and $LiAlH_4$ afforded the amido alcohol **2** *via* acid chloride **1b** and amide **1c**, respectively.

Bromocyclization of **2** afforded stereoselectively *cis*-3-*N*-methylcarboxamido-3-phenyltetrahydrofurfuryl bromide (**3**).[2] Treatment of **3** with sodium hydride in DMF afforded 3-methyl-1-phenyl-6-oxa-3-azabicyclo[3.2.1]octan-2-one (**4**). The attempted reduction of **4** to **5** with $LiAlH_4$ was not successful, resulting in either unchanged starting material or the product of ring fission.

Another approach utilizing diol **6** was more fruitful. The bromocyclization of **6** was known to give a mixture[1] of two isomers which we have now separated by column chromatography. The ratio of cis isomer **8** to trans isomer **7** was found to be very close to 1:2. The stereochemistry was assigned on a basis of successful conversion of **8** *via* mesylate **8a** to the desired **5** upon treatment with methylamine.

In a similar approach, 4-methyl-1-phenyl-7-oxa-4-azabicyclo[4.2.1]nonane (**13**) was prepared (Chart I). Successive alkylation of ethyl phenylacetate by treatment with sodium hydride and chloroethyl vinyl ether, followed by sodi-

Chart I

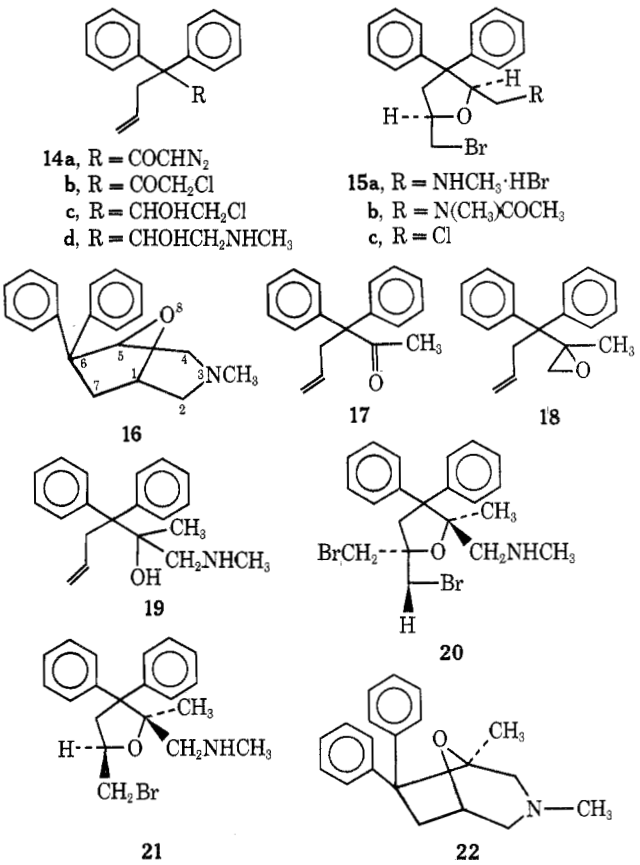


um hydride and allyl bromide, afforded ethyl 2-(2-vinyloxyethyl)-2-phenyl-4-pentenoate (**9**). Reduction of **9** with $LiAlH_4$ to the diol **10** and bromocyclization of **10** afforded a 1:1 mixture of trans and cis bromo alcohols **11** and **12**. The mixture was separated by column chromatography and **12** was converted *via* mesylate **12a** to the bicyclic base **13** upon treatment with methylamine.

The starting material for 3-methyl-6,6-diphenyl-8-oxa-3-azabicyclo[3.2.1]octane (**16**) was 2,2-diphenyl-4-pentenoic acid chloride (**14**) (Chart II, R = COCl), which was treated with diazomethane to give diazo ketone **14a**. Treatment of **14a** with hydrogen chloride afforded chloro ketone **14b**, which was reduced with $LiAlH_4$ to the chlorohydrin **14c**. Treatment of **14c** with methylamine gave amino alcohol **14d**, which upon bromination afforded exclusively cis product **15a**. The alternative 2-bromomethyl-4,4-diphenyl-5-hydroxypiperidine structure for the bromocyclization product was eliminated from consideration since treatment of the free base of **15a** with acetic anhydride–pyridine gave the amide **15b** (ir 1640 cm^{-1}) rather than an ester. Heating of the free base of **15a** in DMSO at 45–50° for 20 hr afforded **16**, thus proving conclusively the cis stereochemistry of **15a**. The same result was obtained when chlorohydrin **14c** was bromocyclized and the product (**15c**) subsequently treated with methylamine.

Amino alcohol **19** was prepared in two steps from allyl diphenylacetone (**17**). Treatment of **17** with Corey's[3] reagent afforded epoxide **18**, which was opened with methylamine to give **19**. Bromocyclization of **19** afforded a 1:1 mixture of **20** and **21**. Chromatography of the mixture on an alumina column effected cyclization of **21** to 6,6-

Chart II

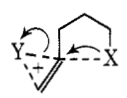


diphenyl-5-methyl-8-oxa-3-azabicyclo[3.2.1]octane (**22**), while **20** was isolated unchanged.

Discussion

It was originally postulated that addition–cyclization reactions involved intermolecular addition of an electrophile to the double bond, followed by internal nucleophilic displacement.[4]

Linstead and May[5] were first to point out that simultaneous addition and ring closure is more likely. Subsequently, this class of reactions was treated as intermolecular concerted processes involving a more or less delocalized cationic transition state[6,7] as shown below.

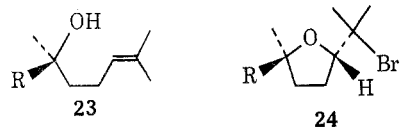


X = O, S, N
Y = Br, I, Hg^+

The stereochemistry of this class of reactions was first studied by Tanaka, *et al.*[8] They found that bromocyclization in the damarene type triterpene series (Chart III) was stereospecific and trans. Demole and Enggest[6] have attributed the stereospecific conversion of **23** to **24** to the steric interaction of the triterpene polycycle R and isopropenyl group so that the less hindered trans isomer is formed.

Similarly, the exclusive cis cyclization of alcohols **14c** and **14d** can be interpreted in terms of steric interactions between the phenyl group and bromonium ion in B (Chart IV, **14c**, R = CH_2Cl; **14d**, R = CH_2NHCH_3) in the transition state, thus favoring cyclization through the bromonium ion A. The alternative configuration C is considered to be less stable owing to steric interactions between phenyl groups and R, and consequently it is not expected to contribute appreciably to the product formation. The comparable steric effects of the methyl and methylami-

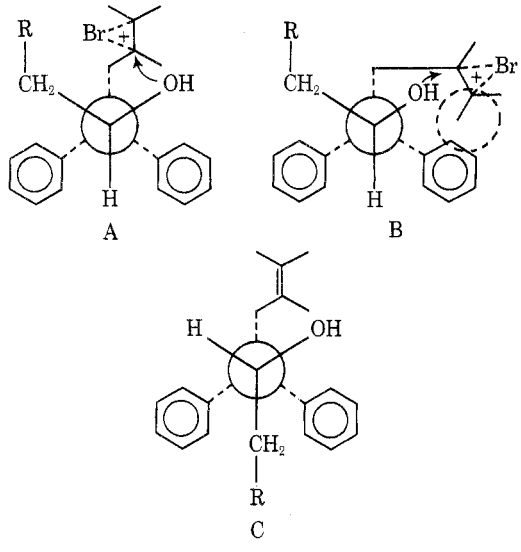
Chart III



23 24

nomethyl groups in alcohol **19** results in nonstereospecific bromocyclization and thus a 1:1 mixture of isomers is obtained.

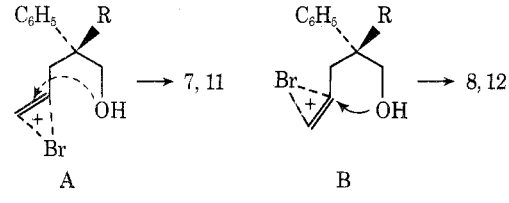
Chart IV



A B C

The stereochemical course of bromocyclization of alcohols **6** and **10** can be viewed as being governed by the relative steric effects of the phenyl group and substituent R (Chart V). When R is CH_2OH as in alcohol **6**, the transition state A is two times favored over transition state B and the 2:1 ratio of trans isomer **7** to cis isomer **8** is obtained. With the increase of the size of R as in **10** (R = CH_2CH_2OH) the steric effects of the phenyl group and R become comparable and the mixture of products converges to a 1:1 ratio.

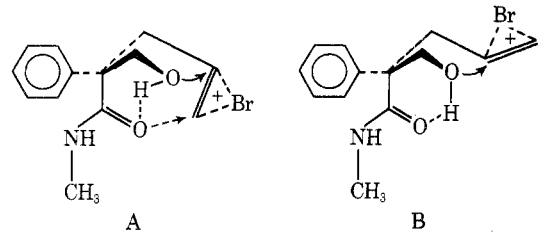
Chart V



A B

The exclusive cis cyclization of alcohol **2** is less clearly understood. A possible explanation could be arrived at if one assumes additional assistance in the process of bromocyclization by the carbonyl oxygen. This could be achieved *via* hydrogen-bonded ground-state conformation and cisoid orientation of the bromonium ion as shown in Chart VI by A. The alternative transoid bromonium ion B

Chart VI



A B

does not have the same degree of orbital overlap with the two oxygens concerned.[9]

The bromocyclizations of appropriately substituted γ,δ-unsaturated alcohols followed by further intramolecular cyclization herein described represents a useful and convenient synthetic approach to various bicyclic systems.

Experimental Section

All melting and boiling points are uncorrected. Infrared spectra were recorded with a Unicam Sp-200G grating ir spectrometer; nmr spectra were taken on a Varian A-60A spectrometer. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill.

Monoethyl (Allyl Phenyl) Malonate (1a). The selective hydrolysis of diethyl (allyl phenyl) malonate[1] was accomplished *via* a modified procedure of Kissinger and Ungnade.[11] To an ice-cold solution of diethyl (allyl phenyl) malonate (27.63 g, 0.1 mol) in 70 ml of absolute ethanol was added a solution of potassium hydroxide (10 g, 0.25 mol) in 200 ml of 75% ethanol. The mixture was stirred for 1 hr at 0° and left for 5 days at 5°. It was then partitioned between ice-cold water and petroleum ether (bp 30–60°). The water layer was acidified with cold dilute hydrochloric acid and extracted with ether to afford, after drying and concentration, 21.6 g (87%) of monoester **1a** as an oil: ir (neat) 1725 cm^{-1}; nmr ($CDCl_3$) δ 1.15 (3 H, t), 3.1 (2 H, d), 4.15 (2 H, q), 4.9–6.5 (3 H, m), 7.1–7.4 (5 H, m).

***N*-Methyl-2-carbethoxy-2-phenyl-4-pentenoic Acid Amide (1c).** The crude monoester **1a** (21.6 g, 87 mmol) was treated with thionyl chloride (25 ml) and a few drops of pyridine at 100° for 4 hr. The excess of thionyl chloride was removed *in vacuo*. The residual oil was dissolved in petroleum ether and the solution was washed successively with ice-cold portions of water (50 ml), 5% sodium bicarbonate (50 ml), and brine (50 ml). Then it was dried (Na_2SO_4) and concentrated *in vacuo*, and the residual oil was distilled to afford acid chloride **1b** (16.35 g, 70.5%): bp 123–125° (0.05 mm); ir (neat) 1745, 1795 cm^{-1}; nmr (CCl_4) δ 1.26 (3 H, t), 3.13 (2 H, d), 4.23 (2 H, q), 4.82–6.2 (3 H, m), 7.1–7.6 (5 H, m). The acid chloride was dissolved in anhydrous ether (200 ml) and treated with a solution of methylamine (*ca.* 125 mmol) in THF (250 ml) at 0°. The methylamine hydrochloride was removed by filtration over an alumina cake, and the filtrate was concentrated *in vacuo* to afford **1c** as an oil (12.26 g, 78%): bp 120–125° (0.02 mm); ir (neat) 1665, 1720, 3330 cm^{-1}; nmr (CCl_4) δ 1.17 (3 H, t), 2.63, 2.72 (3 H, NCH_3), 2.93, 3.17, 3.40 (2 H, td, J = 6.5 Hz, $CH_2CH{=}CH_2$), 4.16 (2 H, q) 4.8–6.1 (3 H, m), 7.0–7.4 (5 H, m).

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.93; H, 7.64; N, 5.48.

***N*-Methyl-2-hydroxymethyl-2-phenyl-4-pentenoic Acid Amide (2).** To a stirred solution of $LiAlH_4$ (1.52 g, 38 mmol) in dry ether (60 ml) was added a solution of amide **1c** (10 g, 38 mmol) in dry ether (60 ml) over a period of 30 min. Then the mixture was treated with 1 *N* NaOH (75 ml); the precipitate was removed by filtration. The filtrate was concentrated *in vacuo* to yield alcohol **2** (5.2 g, 60%) as a white solid: mp 120–121° (benzene–petroleum ether); ir ($CHCl_3$) 1645, 3440 cm^{-1}; nmr ($CDCl_3$) δ 2.78, 2.85, 2.93 (5 H, NCH_3 and $CH_2CH{=}CH_2$), 3.73–4.20 (2 H, AB q, J = 12 Hz), 5.0–6.2 (3 H, m), 7.34 (5 H, s).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 70.89; H, 7.82; N, 6.47.

5-Bromomethyl-3-phenyl-3-tetrahydrofuroic Acid *N*-Methylamide (3). To a solution of alcohol **2** (4.38 g, 20 mmol) in chloroform (50 ml) was added dropwise a 1 *M* solution of bromine in carbon tetrachloride (20 ml). After addition the mixture was washed with a 5% solution of sodium bicarbonate, dried (Na_2SO_4), and concentrated *in vacuo* to yield **3** (5.2 g, 87%) as a white solid: mp 79–81° (ether–petroleum ether); ir (Nujol) 1700, 3320 cm^{-1}; nmr ($CDCl_3$) δ 2.05–2.75 (2 H, m, C_4H_2), 3.16 (3 H, s, NCH_3), 3.67 (2 H, d, J = 5 Hz, CH_2Br), 3.74–4.16 (2 H, AB q, J = 12 Hz, C_2H_2), 4.2–4.65 (1 H, m), 7.45 (5 H, s).

Anal. Calcd for $C_{13}H_{16}BrNO_2$: C, 52.36; H, 5.49; N, 4.69. Found: C, 52.24; H, 5.51; N, 4.63.

3-Methyl-1-phenyl-6-oxa-3-azabicyclo[3.2.1]octan-2-one (4). A solution of bromo amide **3** (3.0 g, 10 mmol) in DMSO (20 ml) was added to a suspension of sodium hydride (440 mg of 55%, 10 mmol, washed with petroleum ether) in DMSO (5 ml), and the reaction mixture was stirred for 30 min. Then it was partitioned between water and benzene, and the organic layer was washed with water, dried, and concentrated to afford **4** (1.95 g, 90%): mp 125–127° (benzene–petroleum ether); ir ($CHCl_3$) 1710 cm^{-1}; nmr ($CDCl_3$) δ 2.16–2.95 (2 H, m, C_8H_2), 3.13 (3 H, s, NCH_3), 2.63

and 2.80 (2 H, dd, J = 12 Hz, C_7H_2), 3.96, 4.18, and 4.35 (2 H, td, J = 2.5 Hz, C_4H_2), 4.76 (1 H, q, $J_1 = J_2$ = 2.5 Hz, C_5H).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.49. Found: C, 71.80; H, 7.00; N, 6.50.

***cis*- and *trans*-4-Hydroxymethyl-4-phenyltetrahydrofurfuryl Bromides (8 and 7).** A mixture of isomers (8 g), prepared according to the procedure previously given,[1] was separated by column chromatography (silica gel, 1200 g). Elution of the column with a mixture of benzene–ether (1:1) afforded cis isomer **8** (2.5 g, 31.3%): bp 126–130° (0.02 mm); nmr ($CDCl_3$) δ 1.88–2.65 (2 H, m, C_3H_2), 3.45 (2 H, d, J = 6 Hz, CH_2Br), 3.6 (2 H, s, $-CH_2OH$), 3.87–4.34 (2 H, AB q, J = 9 Hz, C_5H_2), 4.21 (1 H, m), 7.1–7.5 (5 H, m). Further elution of the column afforded trans isomer **7** (4.2 g, 52.6%): bp 126–130° (0.02 mm); nmr ($CDCl_3$) δ 1.85, 2.05, 2.51, 2.72 (2 H, ABX qd, J = 13 Hz, C_3H_2), 3.3 (2 H, d, J = 6 Hz, outer peak split into doublets, J = 1.5 Hz, CH_2Br), 3.62 (2 H, s, CH_2OH), 3.85–4.15 (2 H, AB q, J = 8 Hz, C_5H_2), 4.1–4.7 (1 H, m), 7.0–7.5 (5 H, m).

***cis*-4-Methanesulfonyloxymethyl-4-phenyltetrahydrofurfuryl Bromide (8a).** The cis alcohol **8** (1.355 g, 5 mmol) in benzene (20 ml) was treated with methanesulfonyl chloride (0.81 g, 7 mmol) and triethylamine (0.71 g, 7 mmol) for 4 hr at room temperature. Then the mixture was washed with water, dried, and concentrated to afford ester **8a** (1.74 g, 100%) as an oil: nmr ($CDCl_3$) δ 2.0, 2.15, 2.42, 2.56 (2 H, ABX qd, J = 13 Hz, C_3H_2), 2.65 (3 H, s, SO_2CH_3), 3.52 (2 H, d, J = 6 Hz, CH_2Br), 3.96–4.40 (2 H, AB q, J = 9 Hz, C_5H_2), 4.05–4.5 (1 H, m), 4.35 (2 H, s, $CH_2OSO_2CH_3$), 7.0–7.5 (5 H, m).

Anal. Calcd for $C_{13}H_{17}BrO_4S$: C, 44.72; H, 4.90. Found: C, 44.93; H, 4.93.

***trans*-4-Methanesulfonyloxymethyl-4-phenyltetrahydrofurfuryl Bromide (7a).** The trans ester **7a** was obtained in quantitative yield from **7**, as described for **8a**.

Anal. Calcd for $C_{13}H_{17}BrO_4S$: C, 44.72; H, 4.90. Found: C, 44.91; H, 5.14.

3-Methyl-1-phenyl-6-oxa-3-azabicyclo[3.2.1]octane (5). A solution of cis mesylate **8a** (500 mg, 1.4 mmol) in DMSO (5 ml) was saturated with methylamine gas and heated in a pressure bomb for 2 hr at 100°. After cooling, the mixture was partitioned between water and benzene. The organic layer was washed with water, dried, and concentrated *in vacuo* to afford bicyclic base **5** (250 mg, 86%) as an oil: nmr ($CDCl_3$) δ 1.6–2.1 (2 H, AB q, C_8H_2), 2.4 (3 H, s, NCH_3), 2.5–3.0 (4 H, m, C_4H_2 and C_2H_2), 3.8–4.3 (2 H, AB q, C_7H_2), 4.3–4.6 (1 H, m, C_5H), 7.1–7.5 (5 H, m). The hydrochloride salt of **5** was crystallized from methanol–ether, mp 270–272°.

Anal. Calcd for $C_{13}H_{17}NO\cdot HCl$: C, 65.13; H, 7.10; N, 5.84. Found: C, 64.87; H, 7.09; N, 5.85.

2-Phenyl-2-(2-vinyloxyethyl)-4-pentenoic Acid Ethyl Ester (9). The ethyl phenylacetate (49.26 g, 0.3 mol) was added dropwise to a cooled (ice water) and stirred suspension of sodium hydride (13.64 g of 55%, 0.3 mol, freed from carrier with petroleum ether) in DMF (500 ml) followed by 2-chloroethyl vinyl ether (31.96 g, 0.3 mol). After standing at room temperature for 16 hr the mixture was added to a stirred suspension of sodium hydride (13.64 g, 0.3 mol). Then to it was added allyl bromide (36.3 g, 0.3 mol), and the mixture was left at room temperature for 6 hr. Then it was partitioned between water and benzene. The organic layer was washed with water, dried, and concentrated *in vacuo*. The residual oil was distilled and the fraction boiling at 92–95° (0.02 mm) was collected to afford ester **9** (56.3 g, 68.5%): ir (neat) 1730 cm^{-1}; nmr ($CDCl_3$) δ 1.17 (3 H, t, CH_3CH_2O), 2.4 (2 H, t, J = 6 Hz, CH_2CH_2O–), 2.84 (2 H, d, J = 6 Hz, $CH_2CH{=}CH_2$), 3.63 (2 H, dt, J_1 = 6, J_2 = 2 Hz, CH_2CH_2O–), 4.9–6.0 (3 H, $CH_2CH{=}CH_2$), 6.38 (1 H, symmetrical q, J = 7 Hz, $OCH{=}CH_2$), 7.3 (5 H, s).

Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.73; H, 8.17.

3-Hydroxymethyl-3-phenyl-5-hexen-1-ol (10). The ester **9** (27.5 g, 0.1 mol) in dry ether (50 ml) was added dropwise to a solution of $LiAlH_4$ (2.3 g, 60 mmol) in ether (150 ml). The mixture was heated to reflux for 45 min, the excess of hydride was decomposed in NaOH (11.5 ml), the mixture was filtered, and filtrate was concentrated *in vacuo*. The residual oil was dissolved in methanol (100 ml) and 6 *N* hydrochloric acid (20 ml) and the mixture was heated at 30–35° for 15 min. It was then diluted with water (50 ml), heated at 35–40° for another 15 min, and concentrated *in vacuo* to *ca.* 50 ml. After cooling, a solid was removed by filtration to yield diol **10** (14.4 g, 70%), mp 76–79°. A sample recrystallized from benzene melted at 82–83°: ir (Nujol) 3240 cm^{-1}; nmr ($CDCl_3$) δ 1.8–2.2 (2 H, m, CH_2CH_2OH), 2.46 (2 H, d, J = 6 Hz, $CH_2CH{=}CH_2$), 3.4–3.7 (2 H, m, CH_2CH_2OH), 3.52–3.88 (2 H, AB q, J = 12 Hz, CH_2OH), 4.8–6.0 (3 H, m, $-CH{=}CH_2$), 7.4 (5 H, s).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.89; H, 8.80. Found: C, 76.20; H, 8.89.

4-(2-Hydroxyethyl)-4-phenyltetrahydrofurfuryl Bromides (11 and 12). To a stirred and cooled (ice water) solution of diol **10** (7.23 g, 35 mmol) and pyridine (2.8 g, 35 mmol) in dichloromethane (30 ml) was added dropwise a solution of bromine in carbon tetrachloride (35 ml, 1 *M*). The mixture was then washed with water, dried, and concentrated *in vacuo*. The residual oil was distilled and the fraction boiling at 115–117° (0.02 mm) was collected to afford mixture of **11** and **12** (9.4 g, 94%), ir (neat) 3420 cm^{-1}.

Anal. Calcd for $C_{13}H_{17}BrO_2$: C, 54.73; H, 6.01. Found: C, 54.78; H, 6.12.

The mixture was separated by column chromatography (1.2 kg of silica gel, dry packed). Elution with ether afforded cis isomer **12** (3.1 g): nmr ($CDCl_3$) δ 1.89, 2.02, 2.50, 2.61 (2 H, ABX qd, J = 13 Hz, C_3H_2), 1.9–2.2 (2 H, m, CH_2CH_2OH), 3.20–3.50 (4 H, m, CH_2Br and CH_2CH_2OH), 3.8–4.3 (1 H, m), 3.90–4.37 (2 H, AB q, J = 9 Hz, C_5H_2), 7.3 (5 H, s).

Further elution of the column afforded an unresolved mixture (0.6 g) followed by trans isomer **11** (3.2 g): nmr ($CDCl_3$) δ 1.98–2.75 (4 H, m, C_3H_2 and CH_2CH_2OH, 3.25–3.55 (4 H, m, CH_2Br and $-CH_2OH$), 3.9–4.25 (2 H, Ab q, J = 8 Hz, C_5H_2), 4.2–4.65 (1 H, m), 7.1–7.3 (5 H, m).

***cis*-4-(2-Methanesulfonylethyl)-4-phenyltetrahydrofurfuryl Bromide (12a).** The alcohol **12** (2.0 g, 7 mmol) in dry benzene (15 ml) was treated with triethylamine (1.0 g, 10 mmol) and methanesulfonyl chloride (1.016 g, 10 mmol) at room temperature for 4 hr. The mixture was then washed with water, dried, and concentrated to afford **12a** as an oil (2.5 g, 98%): nmr ($CDCl_3$) δ 1.83–2.80 (4 H, m), 2.83 (3 H, s), 3.5–4.45 (7 H, m), 7.45 (5 H, s).

Anal. Calcd for $C_{14}H_{19}BrO_4S$: C, 46.26; H, 5.27. Found: C, 46.29; H, 5.50.

***trans*-4-(2-Methanesulfonylethyl)-4-phenyltetrahydrofurfuryl Bromide (11a).** In a similar procedure, the trans ester **11a** was obtained in quantitative yield from **11**.

Anal. Calcd for $C_{14}H_{19}BrO_4S$: C, 46.26; H, 5.27. Found: C, 46.25; H, 5.49.

4-Methyl-1-phenyl-7-oxa-4-azabicyclo[4.2.1]nonane (13). A solution of mesylate **12a** (0.50 g, 1.38 mmol) and methylamine (*ca.* 1.0 g) in DMSO (5 ml) was heated in a pressure bomb on a steam bath for 1 hr. After cooling, the mixture was partitioned between water and ether. The ether layer was extracted with dilute hydrochloric acid and the acidic extract was basified with ammonium hydroxide. The free base was extracted with benzene, dried, and concentrated to afford **13** (252 mg, 84%): mp 75–77° (petroleum ether); nmr ($CDCl_3$) δ 1.7–2.4 (4 H, m, C_2H_2 and C_9H_2), 2.4 (3 H, s, NCH_3), 2.54–3.07 (4 H, m, C_3H_2 and C_5H_2), 3.85–4.28 (2 H, AB q, J = 7 Hz, outer doublet split, J = 1.5 Hz, C_8H_2), 4.42–4.67 (1 H, m, C_6H), 7.1–7.5 (5 H, m).

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.65; H, 8.97; N, 6.41.

1-Diazo-3,3-diphenyl-5-hexen-2-one (14a). A mixture of the 2,2-diphenyl-4-pentenoic acid (20 g, 79.3 mmol) and thionyl chloride (30 ml) was heated to reflux for 1 hr. The excess of thionyl chloride was then distilled *in vacuo*, and the traces were removed azeotropically with benzene. The residual oil was distilled and the fraction boiling at 112–115° (0.02 mm) was collected to yield acid chloride (16 g, 73.5%) as colorless oil, ir (neat) 1780 cm^{-1}. It was dissolved in ether (50 ml) and added to an excess of diazomethane solution in ether (800 ml), prepared from EXR-101 (28 g). The mixture was fitted with an efficient condenser and left at room temperature for 24 hr. The ether was then removed *in vacuo* to afford diazo ketone **14a** (17 g) as a yellow oil: ir (neat) 1635, 2120 cm^{-1}; nmr δ 5.05 (1 H, $COCHN_2$).

Anal. Calcd for $C_{18}H_{16}N_2O$: C, 78.23; H, 5.84; N, 10.14. Found: C, 78.18; H, 5.94; N, 9.65.

1-Chloro-3,3-diphenyl-5-hexen-2-one (14b). The solution of diazo ketone **14a** (17 g, 61.5 mmol) in ether (150 ml) was saturated with hydrogen chloride gas and left at room temperature for 1 hr. The ether was then removed *in vacuo* and the residue was crystallized from petroleum ether (bp 35–60°) to afford slightly yellow chloro ketone **14b** (13.6 g, 78%): mp 53–55°; ir (Nujol) 1625 cm^{-1}; nmr (CCl_4) δ 3.06 (2 H, d, J = 7, Hz), 3.94 (2 H, s) 4.75–5.90 (3 H, m), 7.3 (10 H, s).

Anal. Calcd for $C_{18}H_{17}ClO$: C, 75.91; H, 6.00. Found: C, 76.12; H, 6.11.

1-Chloro-3,3-diphenyl-5-hexen-2-ol (14c). To a solution of chloro ketone **15b** (30 g) in ether (300 ml) was added in few por-

tions $LiAlH_4$ (3 g) and the mixture was heated to reflux for 30 min. After cooling and decomposition of excess hydride with water, the mixture was treated with 1 *N* hydrochloric acid (400 ml) and ether (300 ml). The ether layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residual oil was distilled to afford chlorohydrin **14c** (25.1 g, 83%), bp 120–125° (0.02). The analytical sample was purified by chromatography (silica gel, eluent petroleum ether and benzene), to remove small amount of corresponding epoxide: ir (neat) 3560 cm^{-1}; nmr (CCl_4) δ 2.52–3.45 (3 H, m), 3.75 (1 H, dd, J_1 = 10, J_2 = 1.5 Hz), 4.45–4.50 (1 H, m), 4.75–5.6 (3 H, m), 7.2 (2 H, d, J = 2 Hz).

Anal. Calcd for $C_{18}H_{19}ClO$: C, 75.38; H, 6.68. Found: C, 75.41; H, 6.47.

3,3-Diphenyl-1-methylamino-5-hexen-2-ol (14d). A cold solution of chlorohydrin **14c** (4.1 g, 14.3 mmol) in DMSO (8 ml) was saturated with methylamine gas and the mixture was heated for 20 hr in a pressure bomb at 48–52°. Then it was partitioned between water and benzene. The organic layer was washed with water and extracted with dilute hydrochloric acid. The acid extract was basified with ammonium hydroxide and the free base was again extracted with benzene. The extract was dried and concentrated *in vacuo*, and the residue was crystallized from benzene–petroleum ether to afford **14d** (2.7 g, 67%): mp 74–75°; nmr (CCl_4) δ 1.9–3.3 (5 H, m), 2.3 (3 H, s), 4.5 (1 H, dd, J_1 = 9, J_2 = 3 Hz), 4.85–5.7 (3 H, m), 7.4 (10 H, s).

Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.08; H, 8.64; N, 4.77.

***N*-Methyl-5-bromomethyl-3,3-diphenyltetrahydrofurfurylamine Hydrobromide (15a).** To the stirred solution of amino alcohol **14d** (5.63 g, 20 mmol) in dichloromethane (50 ml) was added a 1 *M* solution of bromine in carbon tetrachloride (20 ml) over a period of 10 min. The mixture was then treated with dry ether (160 ml) and cooled for 2 hr. Then the solid was removed by filtration to afford **15a** (6.9 g, 78%): mp 173–175°; ir (Nujol) 2420, 2710 cm^{-1}; nmr (free base, $CDCl_3$) δ 2.2–3.4 (4 H, m), 2.73 (3 H, s, NCH_3), 3.8 (2 H, d, J = 5 Hz, CH_2Br), 4.0–4.50 (1 H, m, C_5 H), 5.57 (1 H, t, J = 7 Hz, C_2 H), 7.33 (10 H, s).

Anal. Calcd for $C_{19}H_{22}BrNO \cdot HBr$: C, 51.72; H, 5.25; N, 3.18. Found: C, 51.97; H, 5.24; N, 3.13.

***N*-Acetyl-*N*-methyl-5-bromomethyl-3,3-diphenyltetrahydrofurfuryl Amine (15b).** The free base of **15a** (4.5 mmol, obtained by treatment of 2.0 g of hydrobromide salt in dichloromethane with aqueous ammonia) was treated with acetic anhydride (500 mg) and triethylamine at room temperature to yield **15b** (1.65 g, 93%): mp 130° (dichloromethane–petroleum ether); ir (Nujol) 1645 cm^{-1}; nmr ($CDCl_3$) δ 2.1 (3 H, s) 2.4–3.4 (5 H, m), 3.1 (3 H, s), 3.65 (2 H, d, J = 6 Hz), 3.95–4.35 (1 H, m), 5.0–5.3 (1 H, m), 7.2–7.5 (10 H, m).

Anal. Calcd for $C_{21}H_{24}BrNO_2$: C, 62.69; H, 6.01; N, 3.48. Found: C, 62.19; H, 6.01; N, 3.63.

3-Methyl-6,6-diphenyl-8-oxa-3-azabicyclo[3.2.1]octane (16). The salt **15a** (3.08 g, 7.0 mmol) in dichloromethane (20 ml) was shaken with ammonium hydroxide, dried, and concentrated *in vacuo*. The residue was dissolved in DMSO (20 ml) and heated for 20 hr at 45–50°. The mixture was then partitioned between dilute ammonium hydroxide and benzene, and the organic layer was washed with water, dried, and concentrated *in vacuo*. The residual oil was purified by chromatography (alumina, eluent dichloromethane) to afford crystalline **16** (1.44 g, 74%): mp 93–94° (from petroleum ether); nmr ($CDCl_3$) δ 1.93 (3 H, s), 2.1–2.7 (5 H, m), 3.15 (1 H, d, J = 12 Hz), 4.45 (1 H, d, J = 7 Hz), 4.75 (1 H, t, $J_1 = J_2$ = 2 Hz), 7.1–7.3 (10 H, m).

Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.94; H, 7.63; N, 5.04.

Alternatively, **16** was obtained in 65% overall yield when chlorohydrin **14c** was treated with 1 equiv of bromine in carbon tetrachloride and the product **15c** (an oil), without purification, was treated with methylamine in DMSO at 50–55° for 24 hr.

1,2-Epoxy-3,3-diphenyl-2-methyl-5-hexene (18). Sodium hydride (5.585 g of a 55% suspension, 0.128 mol) was washed free of the carrier with petroleum ether and covered with dry DMSO (20 ml). To this was added with stirring a solution of trimethylsulfonium iodide (24.684 g, 0.121 mol) in dry DMSO (150 ml) followed by 25.0 g (0.1 mol) of ketone **17** in DMSO (60 ml). The inner temperature throughout addition was maintained at 22–25° by cooling with an ice–water bath. The mixture was stirred for 22 hr at room temperature and then it was partitioned between water and ether–petroleum ether (1:1). The organic layer was washed with water, dried (Na_2SO_4), and concentrated *in vacuo* to afford crude **18** (25.7 g, 97%): bp 105° (0.05 mm); nmr ($CDCl_3$) δ 1.23 (3 H, s), 2.75–3.0 (2 H, m), 4.7–5.9 (3 H, m), 7.1–7.3 (10 H, m).

Anal. Calcd for $C_{19}H_{20}O$: C, 86.32; H, 7.63. Found: C, 86.99; H, 7.78.

3,3-Diphenyl-1-methylamino-2-methyl-5-hexen-2-ol (19). A solution of crude epoxide **18** (12.0 g, 45.5 mmol) in DMSO (15 ml) was saturated with methylamine gas at 0° and heated for 6 days at 48–52° in a pressure bomb. The reaction mixture was then partitioned between water and ether, and the basic fraction was isolated by acid–base treatment to afford **19** (4.25 g, 20.6%) as an oil: nmr ($CDCl_3$) δ 1.2 (3 H, s), 2.24–2.95 (2 H, AB q, J = 12 Hz), 2.35 (3 H, s), 3.18 (2 H, d, J = 7 Hz), 4.75–5.9 (3 H, m), 7.0–7.4 (10 H, m). The oxalate salt was crystallized from methanol, mp 194–196°.

Anal. Calcd for $C_{20}H_{25}NO \cdot C_2H_2O_4$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.90; H, 7.14; N, 3.61.

3,5-Dimethyl-6,6-diphenyl-8-oxa-3-azobicyclo[3.2.1]octane (22) and *trans*-5-Bromomethyl-3,3-diphenyl-2-methyl-*N*-methyltetrahydrofurfurylamine (20). The amino alcohol **19** (4.13 g, 14 mmol) in carbon tetrachloride (50 ml) was stirred and treated with 1 *M* bromine in carbon tetrachloride (14 ml). The solid precipitate (5.0 g of a mixture of **20** and **21**) was filtered off and treated with ammonium hydroxide and ether. Drying and evaporation of the ether afforded an oil (3.7 g) which was chromatographed on basic alumina. Elution with chloroform afforded bicyclic base **22** (1.45 g, 37%) as an oil: nmr ($CDCl_3$) δ 1.07 (3 H, s), 1.91 (3 H, s), 2.1–3.25 (6 H, m), 4.5 (1 H, dd, J_1 = 7, J_2 = 1.5 Hz), 7.05 (5 H, s), 7.3 (5 H, s). The hydrochloride salt was crystallized from methanol–ether, mp 234–236°.

Anal. Calcd for $C_{20}H_{23}NO \cdot HCl$: C, 69.05; H, 7.53; N, 4.02. Found: C, 68.74; H, 7.15; N, 4.01.

Further elution of alumina with 20% methanolic chloroform afforded trans amino bromide **20** (1.75 g, 34%) as an oil, which was relatively stable, and upon repeated chromatography did not yield any more of **22**: nmr ($CDCl_3$) δ 1.27 (3 H, s), 2.38 (3 H, s), 2.65–3.8 (6 H, m), 4.2–4.7 (1 H, m), 7.1–7.3 (10 H). The hydrochloride salt was recrystallized from MeOH–ether, mp 218–222°.

Anal. Calcd for $C_{20}H_{24}BrNO \cdot HCl$: C, 58.48; H, 6.13; N, 3.41. Found: C, 58.52; H, 6.38; N, 3.18.

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Registry No.—**1a**, 50790-06-2; **1b**, 50790-07-3; **1c**, 50790-08-4; **2**, 50790-09-5; **3**, 50789-91-8; **4**, 50790-10-8; **5**, 50790-11-9; **5** hydrochloride, 50790-12-0; **7**, 50789-92-9; **7a**, 50789-93-0; **8**, 50789-94-1; **8a**, 50789-95-2; **9**, 50790-13-1; **10**, 50790-14-2; **11**, 50789-99-6; **11a**, 50789-96-3; **12**, 50789-97-4; **12a**, 50789-98-5; **13**, 50790-15-3; **14a**, 50790-16-4; **14b**, 50790-17-5; **14c**, 50790-18-6; **14d**, 50790-19-7; **15a**, 50790-00-6; **15a** free base, 50790-01-7; **15b**, 50790-02-8; **16**, 50790-20-0; **17**, 41921-51-1; **18**, 50790-21-1; **19**, 50790-22-2; **19** oxalate, 50790-23-3; **20**, 50790-03-9; **20** hydrochloride, 50790-04-0; **21**, 50790-05-1; **22**, 50790-24-4; **22** hydrochloride, 50790-25-5; diethyl (allyl phenyl) malonate, 50790-26-6; methanesulfonyl chloride, 124-63-0; ethyl phenylacetate, 101-97-3; 2-chloroethyl vinyl ether, 110-75-8; allyl bromide, 106-95-6; 2,2-diphenyl-4-pentenoic acid, 6966-03-6; 2,2-diphenyl-4-pentenoic acid chloride, 50790-27-7.

References and Notes

(1) Paper I: I. Monkovic, Y. G. Perron, R. Martel, W. J. Simpson, and J. A. Gylys, *J. Med. Chem.*, **16**, 403 (1973).
(2) The stereochemistry of tetrahydrofurfuryl bromides throughout this paper is defined with respect to the functionalized substituents such as $-CH_2Br$ and $-C(=O)NHCH_3$.
(3) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1353 (1965).
(4) R. Fittig and E. Hjelt, *Justus Liebigs Ann. Chem.*, **216**, 672 (1883).
(5) R. D. Linstead and C. J. May, *J. Chem. Soc.*, 2567 (1927).
(6) V. I. Staninets and E. A. Shilov, *Russ. Chem. Rev.*, **46**, 272 (1971).
(7) E. Demole and P. Enggist, *Helv. Chim. Acta*, **54**, 456 (1971).
(8) O. Tanaka, N. Tanaka, T. Oshawa, Y. Iitaka, and S. Shibata, *Tetrahedron Lett.*, 4235 (1968).
(9) A referee brought up the question concerning the lack of participation of nitrogen and carbonyl oxygen in alcohols (**14d** and **2**, respectively. Perhaps the hydrogen bonding in both instances significantly contributes to the nucleophilicity of the hydroxylic oxygen. Thus an indirect participation of nitrogen in **14d** and carbonyl oxygen in **2**, acting as proton acceptors, may be postulated. However, in the case of **14d** the known preference[6,10] for formation of five-membered rings to six-membered ones should also be a significant factor.
(10) D. L. H. Williams, E. Bienvenue Goetz, and J. E. Dubois, *J. Chem. Soc. B*, 517 (1969).
(11) L. W. Kissinger and H. E. Ungnade, *J. Org. Chem.*, **23**, 1340 (1958).