Mobile Keto Allyl Systems. V.[1] Synthesis of 2-(α-Bromo-substituted benzyl)-4,4-dimethyl-1,4-dihydro-1-ketonaphthalenes and Reactions with Amines

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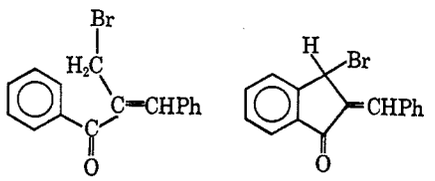
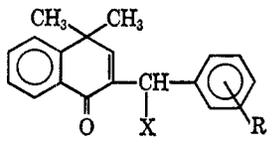
Several 2-(α-bromo-X-benzyl)-4,4-dimethyl-1,4-dihydro-1-ketonaphthalenes [X = H (**1**), *p*-NO_2 (**2**), *m*-NO_2 (**3**), *o*-NO_2 (**4**), and *p*-Cl (**5**)] have been prepared by the reaction of N-bromosuccinimide with 2-X-benzal-4,4-dimethyl-1-tetralones. Reaction of 2-(*p*-dimethylaminobenzal)-4,4-dimethyl-1-tetralone with N-bromosuccinimide gave 2-(*m*-bromo-*p*-dimethylaminobenzal)-4,4-dimethyl-1-tetralone (**6**). 2-(α-Chlorobenzyl)-1,4-dihydro-4,4-dimethyl-1-ketonaphthalene (**7**) was prepared from **1** by a halogen exchange reaction. The halo ketones **1–5** and **7** reacted with piperidine to give the corresponding 2-(α-piperidino-X-benzyl)-4,4-dimethyl-1,4-dihydronaphthalenes (**9–13**). The bromo ketone **4** reacted with morpholine to give both 2-(*o*-nitrobenzal)-morpholino-4,4-dimethyl-1-tetralone (**15**), in which the allyl system is inverted, and the direct substitution product **14**. The bromo ketones **2** and **4** each reacted with *t*-butylamine to give the corresponding direct substitution products **17** and **18**, while **1** and **5** each reacted to give both direct substitution products and the rearranged isomeric *t*-butylamino ketones. These compounds resulted from parallel courses of reaction of the bromo ketones and were not interconvertable. Possible mechanisms for these amine reactions with β-keto allyl halides are discussed.

Primary allyl halides have usually been found to react with primary and secondary amines by an SN2 reaction to yield normal substitution products,[3] but recently α-bromomethylchalcone (A) which is a β-keto allyl bromide, has been found to give the rearranged substitution product under suitable conditions.[1,4] Secondary allylic halides, on the other hand, have often been found to give some rearranged products in which the allyl system has been inverted.[3] This has been found to be the case with 3-bromo-2-benzal-1-indanone (B) (a secondary β-keto allyl bromide) on reacting with certain amines.[5,6]



A

B

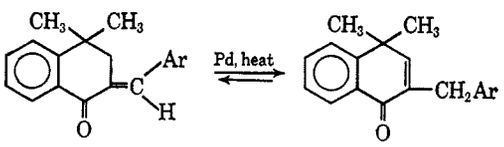


C

It was the purpose of this investigation to study the effect of varying the size of the nucleophile (amine) and the steric and electronic effects of certain substituents on the reactions of the β-keto secondary allyl halides, 2-(α-halogenobenzyl)-1,4-dihydro-1,4-dimethyl-1-ketonaphthalenes (C). It has been reported previously[7] that 2-(α-bromobenzyl)-4,4-dimethyl-1,4-dihydro-1-ketonaphthalene (**1**) reacts with the less space-demanding amines, morpholine and piperidine, to give only the substitution products in which the allyl system has not been inverted.

Results

In the earlier investigation[7] it was found that thermal dehydrohalogenation of 2-benzal-4,4-dimethyl-1-tetralone dibromide gave **1** which also resulted from the reaction of N-bromosuccinimide with 2-benzyl-4,4-dimethyl-1,4-dihydro-1-ketonaphthalene (D). It has been shown[8] that the endocyclic unsaturated ketone, E, is thermodynamically more stable than the isomeric exocyclic unsaturated ketone, D (Ar = C_6H_5). It, therefore, seemed possible that the most direct route to a series of bromo ketones of series C would be by the bromination of the readily available exocyclic α,β-unsaturated ketones (D) involving an allylic rearrangement. This has been shown to be the case.

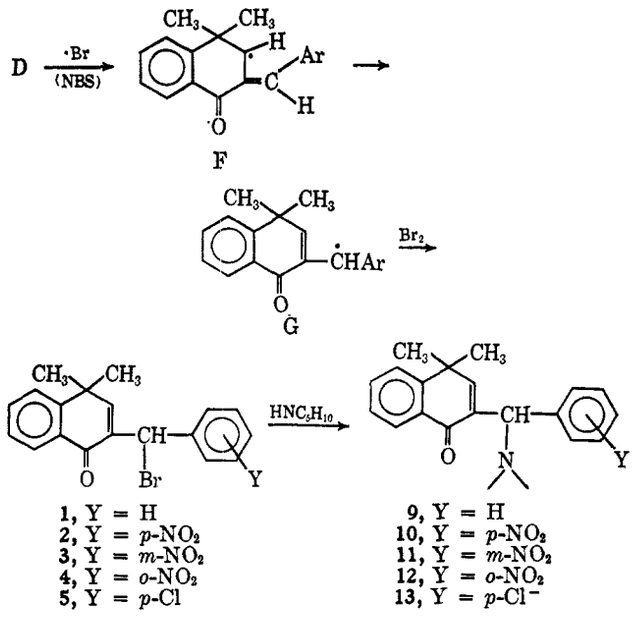


D (33%) E (67%)

Spectral studies (infrared, ultraviolet, and nmr) of the bromo ketones **1–5** clearly showed these compounds to have the endocyclic α,β-unsaturated ketone structure C. Treatment of 2-(*p*-dimethylaminobenzal)-4,4-dimethyl-1-tetralone with N-bromosuccinimide afforded 2-(*m*-bromo-*p*-dimethylaminobenzal)-4,4-dimethyl-1-tetralone (**6**).

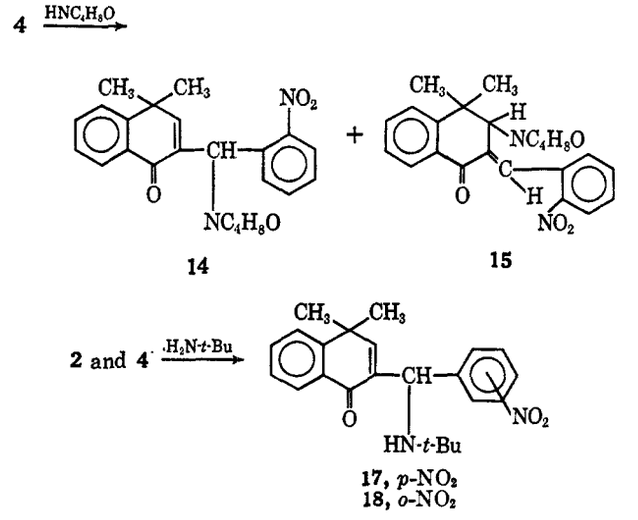
2-(α-Chlorobenzyl)-1,4-dihydro-4,4-dimethyl-1-ketonaphthalene (**7**) was obtained in low yield from the treatment of 2-bromo-2-(α-bromobenzyl)-4,4-dimethyl-1-tetralone with tetraethylammonium chloride. The major product was the dehalogenation product D (Ar = C_6H_5). Compound **7** was obtained in better yield from the reaction of tetraethylammonium chloride with 2-bromo-2-(α-chlorobenzyl)-4,4-dimethyl-1-tetralone (**8**) which was prepared by adding bromine chloride to D (Ar = C_6H_5). The best method of preparation of **7** was by a halogen ex-

(1) For paper IV in this series, see N. H. Cromwell and R. Rebman, *J. Org. Chem.*, **32**, 3830 (1967).
(2) Abstracted from the Ph.D. Thesis of E.-M. Wu, University of Nebraska, 1966.
(3) R. H. De Wolfe and W. G. Young, "The Chemistry of Alkenes," Vol. 1, S. Patai, Ed., John Wiley and Sons, Inc., New York, N. Y., 1964.
(4) R. P. Rebman and N. H. Cromwell, *Tetrahedron Lett.*, 4833 (1965).
(5) N. H. Cromwell and E.-M. Wu, *ibid*, 1499 (1966).
(6) G. Maury and N. H. Cromwell, unpublished work.
(7) A. Hassner and N. H. Cromwell, *J. Amer. Chem. Soc.*, **80**, 901 (1958).
(8) N. H. Cromwell, R. P. Ayer, and P. W. Foster, *ibid.*, **82**, 130 (1960).

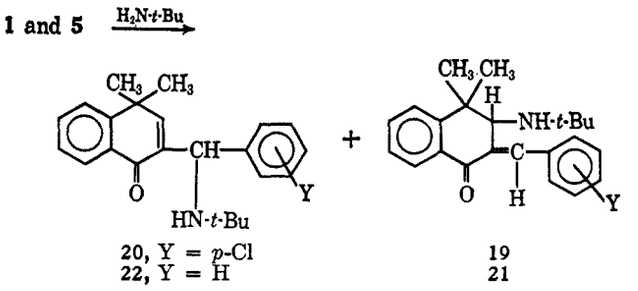


change reaction of **1** with tetraethylammonium chloride in solvent acetonitrile.

The reaction of the halogenated ketones **1–5** and **7** with excess piperidine in benzene solution at room temperature produced only the analogous piperidino ketones **9–13** in which the allyl system is not inverted. On the other hand the bromo ketone **4** reacted with morpholine to produce both the rearranged, **15** (42%), and nonrearranged, **14** (58%), morpholino ketones. Both steric and electronic factors probably are involved in causing the formation of both of these products, but this reaction was not studied in a definitive fashion. Methylamine also reacted with **1** to give only the nonrearranged amino derivative **16**.



The bromo ketones **2** and **4** were found to react with *t*-butylamine in benzene solution to give only the nonrearranged amino derivatives **17** and **18**, respectively. On the other hand the bromo ketones **1** and **5** both reacted with this space-requiring base to give mixtures of the rearranged and nonrearranged amino ketones. In the latter case the mixed product was shown to consist of 63% rearranged product, **19**, and 37% nonrearranged *t*-butylamino ketone, **20**.



The reaction of the bromo ketone **1** with *t*-butylamine was the most extensively studied. With 10 molar equiv of amine in benzene solution at 25° a mixture of 67% **21** and 33% **22** resulted, whereas at 65° the ratio of **21** to **22** was 1:1. It was shown that neither **21** nor **22** was rearranged to the other on heating at 60–65° with *t*-butylamine in benzene solution.

It was found, however, that when **21** was allowed to stand at room temperature with excess piperidine in benzene solution the rearranged amine exchange product **9**[7] resulted. The piperidino ketone **10** was unchanged after refluxing for 8 days in chloroform solution or for 7 days in benzene solution in the presence of a very large excess of piperidine.

The chloro ketone **7** was found to be unchanged after standing at room temperature for 103 hr with 2.3 molar equiv of *t*-butylamine in solvent benzene. When the reaction was repeated using 10 molar equiv of *t*-butylamine in less benzene, after 27 hr a 30% yield of mixed product shown to consist of 55% **21** and 45% **22** resulted. Following this latter procedure with piperidine, a 50% yield of the piperidino ketone **9** was obtained.

The bromo ketone **1** was shown to react with anhydrous methanol to give 2-(α-methoxybenzyl)-4,4-dimethyl-1,4-dihydro-1-ketonaphthalene (**23**).

Irradiation of *trans*-2-(*o*-nitrobenzal)-4,4-dimethyl-1-tetralone with ultraviolet light produced the *cis* isomer which was isolated and characterized by spectral methods on comparison with the previously studied[9] *cis*-2-benzal-4,4-dimethyl-1-tetralone.

Discussion

Much evidence has accumulated in recent years that peroxide-catalyzed bromination with N-bromosuccinimide proceeds through a free alkenyl or arylcarbinyl radical often involving allylic rearrangement.[10] Several investigations have developed evidence that a bromine atom chain is the most plausible mechanism for these NBS reactions[11] and, under the conditions applied, the bromine atom is the hydrogen-abstracting species.[12]

In connection with the NBS reactions of the ketones D, hydrogen abstraction from the sterically crowded 3 position on the ring might be expected to be more readily accomplished by the less space-re-

(9) D. N. Kevill, E. D. Weiler, and N. H. Cromwell, *J. Org. Chem.*, **29**, 1276 (1964).
(10) G. F. Bloomfield, *J. Chem. Soc.*, **114** (1944).
(11) (a) C. Walling, R. A. Rieger, and D. D. Tanner, *J. Amer. Chem. Soc.*, **85**, 3129 (1963); (b) G. A. Russell and K. M. Desmond, *ibid.*, **85**, 3139 (1963).
(12) R. E. Pearson and J. C. Martin, *ibid.*, **85**, 3142 (1963).

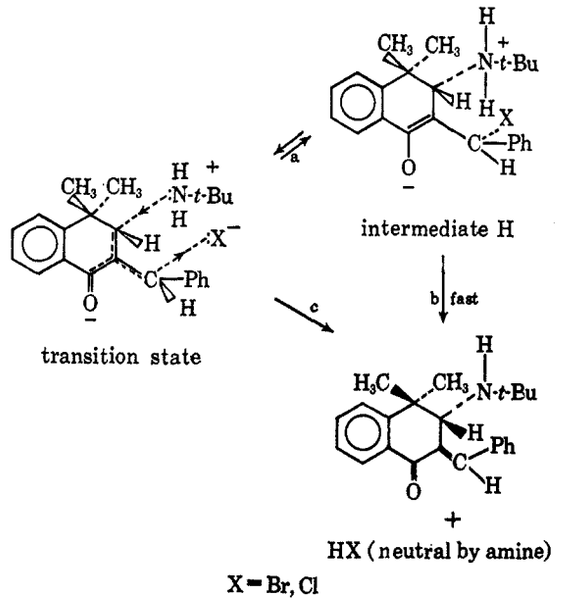
quiring bromine atom than by the succinimide radical. A transition state involving location of the unpaired electron at the exocyclic position and attack by the bromine at this position should be energetically favored.

The results from the reactions of the bromo ketones **1** and **5** with *t*-butylamine to produce mixtures of the direct replacement products **20** and **22** along with the rearranged products **19** and **21**, respectively, suggests that parallel courses of reaction, probably of an SN2 and SN2′ type, are being followed. The SN2′ type products are obviously the kinetically preferred ones as implied by the temperature variation study. That neither the rearranged product nor the direct replacement product is the precursor of the other in these reactions with *t*-butylamine was clearly demonstrated. These results with **1** and **5**, moreover, suggest that the bromo ketones **2** and **4** react with *t*-butylamine by direct replacement mechanisms, probably SN2, which are expected[3] to be enhanced by the electron-attracting power of the *p*- and *o*-nitro groups, respectively.

The quality of the leaving group in these reactions was shown to be important since the chloro ketone **7** was obviously much more sluggish in its rate of reaction with *t*-butylamine to produce the mixture of exocyclic (**19**) and endocyclic (**20**) products.

It is apparent that the reaction of the amine to give the rearranged product (exocyclic unsaturated ketone) cannot involve, in the case of bromo ketones C, a 1,4 addition[11] by the amine to the transoid α,β-unsaturated ketone system in which hydrogen is transfered to oxygen *via* a quasi-six-membered ring which could be possible with bromo ketones A and B, in which the α,β-unsaturated carbonyl system is, or may become, cisoid. Although kinetic studies have not been done with this system it is predicted that the reactions will be first order in amine and in bromo ketone as has been found to be the case with systems A[13] and B.[14] The reaction may or may not be wholly concerted (mechanism c) even though the kinetics prove to be second order over-all.

The carbonyl group would be expected to be important in sharing the developing negative charge with the leaving halogen ion in the transition state of these reactions with amines. Although 2 mol of amine are consumed in the over-all reaction the second mole is probably not kinetically important (neutralizes the released hydrogen halide in a nonrate-determining manner). Alternative to a concerted abnormal replacement, process c would be a two-step course, the first step (a) of which produces an enol anion H as a discrete intermediate in a rate-determining, over-all second-order reaction followed by a rapid first-order collapse of H (step b) to release the halide ion and produce the product in which the allyl system has been inverted. It must be emphasized that monitoring of these reactions by spectroscopic means has produced no evidence for a discrete intermediate (*i.e.* H) containing both the amino and halide groups and that quantitative results to be associated with the quality of leaving groups X have yet to be obtained.



Experimental Section[15]

2-(α-Bromo-X-benzal)-4,4-dimethyl-1,4-dihydro-1-ketonaphthalenes (C).—A solution of 0.01 mol of 2-(X-benzal)-4,4-dimethyl-1-tetralone, 0.01 mol of N-bromosuccinimide, and 0.1 g of benzoyl peroxide in 50 ml of carbon tetrachloride was refluxed for 2 hr over an infrared lamp. The reaction mixture was filtered free of succinimide and the filtrate concentrated yielding the bromo ketone. Recrystallization from carbon tetrachloride or isopropyl ether gave the pure products described below.

2-(α-Bromobenzyl)-4,4-dimethyl-1,4-dihydro-1-ketonaphthalene (1) was obtained from 2-benzal-4,4-dimethyl-1-tetraolone[7] in 78% yield: mp 115–116°, recrystallized from carbon tetrachloride and isopropyl ether; λ_{max} 252, 290, 300 mμ (ε 14,100, 3200, 2300); $\nu_{C=C}$ 1668 (90), $\nu_{C=C}$ 1685 (82), ν_{Ar} 1610 (64) cm^{-1}. The nmr spectrum showed the aromatic proton β to the carbonyl at τ 1.82 (J = 7 cps), nine protons in the range 2.38–2.78, one methine proton at 3.50, and six methyl protons as a doublet, 8.45 and 8.53. A mixture melting point with the previously prepared material showed no depression.[7]

2-(α-Bromo-*p*-nitrobenzyl)-4,4-dimethyl-1,4-dihydro-1-ketonaphthalene (2) was obtained from 2-(*p*-nitrobenzal)-4,4-dimethyl-1-tetralone[16] in 53% yield: mp 130–131°, recrystallized from carbon tetrachloride; λ_{max} 258 mμ (ε 20,100); $\nu_{C=O}$ 1668 (93), $\nu_{C=O}$ 1654 (77), ν_{Ar} 1607 (73) cm^{-1}. The nmr spectrum showed the aromatic proton β to the carbonyl at τ 1.75, eight aromatic protons in the range 1.65–2.70, a methine proton at 3.50, and the methyl protons as a soublet at 8.41 and 8.45.

Anal. Calcd for $C_{19}H_{16}NO_3Br$: C, 59.06; H, 4.15; N, 3.63; Br, 20.38. Found: C, 58.80; H, 4.26; N, 3.56; Br, 20.84.

2-(α-Bromo-*m*-nitrobenzyl)-4,4-dimethyl-1,4-dihydro-1-ketonaphthalene (3) was obtained from 2-(*m*-nitrobenzal)-4,4-dimethyl-1-tetralone[15] in 59% yield: mp 97–98°, when recrystallized from isopropyl ether and carbon tetrachloride; λ_{max} 248, 295 (sh) mμ (ε 18,400, 3600); $\nu_{C=C}$ 1666 (89), $\nu_{C=O}$ 1653 (83); ν_{Ar} 1610 (73) cm^{-1}. The nmr spectrum showed the aromatic proton β to the carbonyl at τ 1.72 (J = 7 cps), eight aromatic protons in the range 1.9–2.7, a methine proton at 3.48, and the methyl protons at 8.42.

Anal. Calcd for $C_{19}H_{16}NO_3Br$: C, 59.06; H, 4.15; N, 3.63; Br, 20.83. Found: C, 58.91; H, 4.22; N, 3.44; Br, 20.56.

2-(α-Bromo-*o*-nitrobenzyl)-4,4-dimethyl-1,4-dihydro-1-ketonaphthalene (4) was obtained from 2-(*o*-nitrobenzal)-4,4-di-

(13) E. Doomes, unpublished work, University of Nebraska, Lincoln, Neb.

(14) G. Maury, E.-M. Wu, and N. H. Cromwell, Abstracts, 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967, p 142s.

(15) Ultraviolet spectra were determined with a Cary Model 11-MS recording spectrophotometer using 0.001 *M* isopropyl ether solutions unless otherwise indicated. The infrared measurements were done with a Perkin-Elmer Model 21 double-beam instrument using matched 1.0-mm NaCl cells and 10-mg/ml carbon tetrachloride solution unless otherwise indicated; the results are in cm^{-1}. The nmr spectra were obtained with a Varian A-60 instrument using CCl_4 or $CDCl_3$ solutions containing a trace of tetramethylsilane (τ 10.00) as an internal reference and the results are reported as τ values with J in cps.

(16) N. H. Cromwell and R. E. Bambury, *J. Org. Chem.*, **26**, 1729 (1961).

methyl-1-tetralone[17] in 49% yield: mp 189–190°, recrystallized from carbon tetrachloride; λ_{max} 232 (sh), 245, 295 (sh) mμ, (ε, 18,000, 17,000, 4500); $\nu_{C=O}$ 1668 (79), $\nu_{C=C}$ 1654 (52), ν_{Ar} 1609 (49) cm^{-1}. The nmr spectrum showed the aromatic proton β to the carbonyl group at τ 1.84 (J = 7 cps), eight aromatic protons in the range 1.92–2.85, a methine proton at 2.92, and the methyl protons as a doublet at 8.46 and 8.50.

Anal. Calcd for $C_{19}H_{18}NO_3Br$: C, 59.06; H, 4.15; N, 3.63; Br, 20.38. Found: C, 58.75; H, 4.29; N, 3.50; Br, 20.75.

2-(α-Bromo-*p*-chlorobenzyl)-4,4-dimethyl-1,4-dihydro-1-ketonaphthalene (**5**) was obtained from 2-(*p*-chlorobenzal)-4,4-dimethyl-1-tetralone[15] in 74% yield: mp 129–131°, recrystallized from carbon tetrachloride; λ_{max} 240, 305 (sh) mμ (ε 17,600, 1300); $\nu_{C=O}$ 1668 (93), $\nu_{C=C}$ 1654 (72), ν_{Ar} 1609 (56) cm^{-1}. The nmr spectrum showed the aromatic proton β to the carbonyl at τ 1.8 (J = 7 cps), eight aromatic protons in the range 2.32–2.72, a methine proton at 3.53, and methyl protons as a doublet at 8.46 and 8.50.

Anal. Calcd for $C_{19}H_{16}OClBr$: C, 60.71; H, 4.26; Cl, 9.48; Br, 21.31. Found: C, 60.52; H, 4.42; Cl + Br, 31.13.

2-(*m*-Bromo-*p*-dimethylaminobenzal)-4,4-dimethyl-1-tetralone (**6**) was obtained from 2-(*p*-dimethylaminobenzal)-4,4-dimethyl-1-tetralone[16] in 35% yield: mp 117–119°, recrystallized from ethyl ether and carbon tetrachloride; λ_{max} 262 348 mμ (ε 19,200, 16,300); $\nu_{C=O}$ 1675 (78), ν_{Ar} 1609 (79) cm^{-1}. The nmr spectrum showed the aromatic proton β to carbonyl as a doublet (J = 8 cps) at τ 1.98, seven aromatic protons in the range 2.3–3.05, the two methylene protons as a doublet (J = 2 cps) at 7.08, the N-N-dimethyl protons at 7.16, and the six methyl protons at 8.66.

Anal. Calcd for $C_{21}H_{22}NOBr$: C, 65.38; H, 5.75; N, 3.80; Br, 20.55. Found: C, 65.63; H, 5.72; N, 3.64; Br, 20.83.

2-Bromo-2-(α-chlorobenzyl)-4,4-dimethyl-1-tetralone (**8**).—A solution of bromine chloride in glacial acetic acid containing 0.231 g of BrCl/ml of AcOH was prepared by adding 20.24 g of bromine to 125 ml of glacial acetic acid containing 9.0 g of chlorine. A solution of 5.24 g (0.2 mol) of D(Ar = C_6H_5) in 50 ml of glacial acetic acid was held at 54° while 11 ml of the bromine chloride solution was added dropwise. Evaporation of the colorless solution left a solid residue which on recrystallization from benzene and petroleum ether (bp 60–70°) gave 6.76 g (89% yield) of **8**: mp 139–142°; $\lambda_{max}^{methanol}$ 264, 298 (sh) mμ (ε 13,500, 2600); $\nu_{C=O}$ ($CHCl_3$) 1685 (s), ν_{Ar} 1606 (m) cm^{-1}. The nmr spectrum showed bands at τ 8.49 (singlet, six CH_3 protons), 7.75 (J = 16 cps) and 6.66 (J = 16 cps) (two doublets, two methylene protons), 2.3–2.7 (eight Ar protons), and 1.75 (J = 8 cps) (one Ar proton, β to carbonyl).

Anal. Calcd for $C_{19}H_{18}BrClO$: C, 60.39; H, 4.77; Br, 21.19; Cl, 9.41. Found: C, 60.24; H, 4.48; Br + Cl, 30.57.

2-(α-Chlorobenzyl)-4,4-dimethyl-1,4-dihydro-1-ketonaphthalene (**7**). **A.**—A solution of 2.1 g (0.005 mol) of 2-benzal-4,4-dimethyl-1-tetralone dibromide and 3 g (0.0175 mol) of tetraethylammonium chloride in 100 ml of acetonitrile was stirred at 25° for 47 hr under nitrogen. Addition of *n*-hexane to the reaction mixture precipitated 0.45 g of 2-benzal-4,4-dimethyl-1-tetralone, mp 107–109°. Evaporation of the solvent of the filtrate left a residue which on recrystallization from isopropyl ether gave 0.21 g of **7**: mp 107–109°; λ_{max} 250, 290 (sh), 300 (sh) mμ (ε 17,000, 3900, 3850); $\nu_{C=O}$ 1685 cm^{-1} (vs), $\nu_{C=C}$ 1654 (sh) (s), ν_{Ar} 1605 (w) cm^{-1}. The nmr spectrum showed bands at τ 8.45 and 8.49 (two methyl groups), 3.56 (J = 0.5 cps) (one benzyl proton), 1.89 (J = 7 cps) (one Ar proton β to carbonyl), and 2.45–2.84 (nine Ar protons).

Anal. Calcd for $C_{19}H_{17}ClO$: C, 76.89; H, 5.73; Cl, 11.97. Found: C, 76.76; H, 5.85; Cl, 11.75.

The yield of **7** by this method was raised to 56% by heating the reaction mixture to 105° in a sealed tube for 18 hr.

B.—A solution of 1.4 g (0.0037 mol) of **8** and 4.5 g (0.027 mol) of tetraethylammonium chloride in 20 ml of acetonitrile was heated in a sealed tube to 108° for 18 hr. Evaporation of the solvent and crystallization of the oily residue from *n*-hexane and then isopropyl ether gave 0.51 g (47% yield) of pure **7**, mp 107–109°. Also obtained from the filtrate was 0.36 g of C (Ar = C_6H_5).

C.—A 0.34 g (0.001 mol) sample of **1** and 1.0 g of tetraethylammonium chloride in 10 ml of acetonitrile was refluxed for 18 hr. Working up the reaction mixture in the usual manner produced 0.23 g (78% yield) of **7**, mp 107–108°.

(17) N. H. Cromwell and V. L. Bell, *J. Org. Chem.*, **24**, 1077 (1959).

2-[α-(Methylamino)benzyl]-4,4-dimethyl-1,4-dihydro-1-ketonaphthalene (16) Hydrochloride.—A 1.36-g (0.004 mol) sample of **1** was dissolved in 100 ml of diethyl ether. The monomethylamine gas was passed into the cold ethereal solution for 1.5 hr in a Dry Ice bath. A yellowish liquid which had two layers was obtained after removal of the solvent. The top oily layer was separated from the bottom layer. The oil was then dissolved in 70 ml of diethyl ether. Hydrogen chloride gas was bubbled into the cold ethereal solution for 1 hr; 1.15 g of white crystals (92.7% yield) were obtained and recrystallized from ethanol. The compound melted at 183–184°: $\lambda_{max}^{methanol}$ 258, 302 (sh) mμ (ε 8800, 2500); $\nu_{C=C}$ (KBr) 1668 (58), $\nu_{C=O}$ 1663 (38), ν_{Ar} 1610 (35) cm^{-1}.

Anal. Calcd for $C_{20}H_{22}NOCl$: C, 73.28; H, 6.71; N, 4.27. Found: C, 73.61; H, 6.73; N, 4.27.

2-(α-Piperidino-X-benzyl)-4,4-dimethyl-1,4-dihydro-1-ketonaphthalenes.—A solution of 0.002 mol of bromo ketone C, 0.02 mole of piperidine, and 40 ml of benzene was stored at room temperature for 20–24 hr under a nitrogen atmosphere. Piperidine hydrobromide was then removed and the amino ketones were obtained after recrystallization from aqueous ethanol.

2-(α-Piperidino-*p*-nitro-X-benzyl)-4,4-dimethyl-1,4-dihydro-1-ketonaphthalene (**10**) was obtained from **2** in 91% yield: mp 117–118°, recrystallized from 95% ethanol; λ_{max} 268 mμ (ε 19,200); $\nu_{C=O}$ 1662 (93), $\nu_{C=C}$ 1649 (66), ν_{Ar} 1609 (73) cm^{-1}. The nmr spectrum indicated one aromatic proton β to carbonyl at τ 1.82, eight aromatic protons in the range 1.95–2.94, a methine proton at 5.62, four aliphatic protons corresponding to the $-CH_2-N-CH_2-$ at 7.62, and twelve aliphatic protons corresponding to the $-CH_2-CH_2-CH_2-$ of the piperidine group combined with two methyl groups as a doublet at 8.45 and 8.58.

Anal. Calcd for $C_{24}H_{26}N_2O_3$: C, 73.82; H, 6.71; N, 7.18. Found: C, 73.72; H, 6.74; N, 7.16.

2-(α-Piperidino-*m*-nitrobenzyl)-4,4-dimethyl-1,4-dihydro-1-ketonaphthalene (**11**) was obtained from **3** in 90% yield: mp 141–142°, recrystallized from 95% ethanol; λ_{max} 255, 302 (sh) mμ (ε 17,500, 3500); $\nu_{C=C}$ 1662 (93), $\nu_{C=O}$ 1650 (58), ν_{Ar} 1610 (60) cm^{-1}. The nmr spectrum showed one aromatic proton β to carbonyl at τ 1.75 (J = 7 cps), eight aromatic protons in the range 1.95–2.90, a methine proton at 5.2, four aliphatic protons corresponding to the $-CH_2-N-CH_2-$ at 7.5, twelve protons corresponding to the $-CH_2-CH_2-CH_2-$ combined with two methyl groups as a doublet at 8.44 and 9.55.

Anal. Calcd for $C_{24}H_{26}N_2O_3$: C, 73.82; H, 6.71; N, 7.18. Found: C, 73.94; H, 6.82; N, 6.98.

2-(α-Piperidino-*o*-nitrobenzyl)-4,4-dimethyl-1,4-dihydro-1-ketonaphthalene (**12**) was obtained from **4** in 56% yield: mp 132–133°, recrystallized from ethanol; λ_{max} 262, 285 (sh), 297 (sh) mμ (ε 12,600, 5000, 3600); $\nu_{C=O}$ 1667 (89), $\nu_{C=C}$ 1650 (48), ν_{Ar} 1608 (57) cm^{-1}. The nmr spectrum showed one aromatic proton β to carbonyl as a doublet (J = 7 cps) at τ 1.84, eight aromatic protons in the range 2.02–3.35, a methlne proton at 4.58, four aliphatic protons corresponding to the $-CH_2-N-CH_2-$ of the piperidino group at 7.52, twelve protons corresponding to the $-CH_2-CH_2-CH_2-$ of the piperidino group combined with two methyl groups as a doublet at 8.52 and 8.62.

Anal. Calcd for $C_{24}H_{26}N_2O_3$: C, 73.82; H, 6.71; N, 7.18. Found: C, 73.82; H, 6.68; N, 7.35.

2-(α-Piperidino-*p*-chlorobenzyl)-4,4-dimethyl-1,4-dihydroketonaphthalene (**13**) was obtained from **5** in 89% yield: mp 135–136°, recrystallized from ethanol; λ_{max} 255, 288 (sh), 298 mμ (ε 18,000, 3400, 2200); $\nu_{C=O}$ 1663 (92), $\nu_{C=C}$ 1650 (67), ν_{Ar} 1610 (54) cm^{-1}. The nmr spectrum showed one aromatic proton β to carbonyl at τ 1.86 (J = 7 cps), eight aromatic protons in the range 2.35–2.98, a methine proton at 4.45, four aliphatic protons corresponding to $-CH_2-N-CH_2-$ of piperidino group at 7.66, and twelve protons corresponding to the $-CH_2-CH_2-CH_2-$ of piperidino group combined with two methyl groups as a doublet at 8.50 and 8.58.

Anal. Calcd for $C_{24}H_{26}NOCl$: C, 75.88; H, 6.85; N, 3.68. Found: C, 75.58; H, 6.67; N, 3.56.

Reaction of Morpholine with 4.—A 1.06 g (0.002 mol) sample of **4** and 2.28 g (0.0025 mol) of morpholine were allowed to react in 75 ml of benzene under nitrogen. After 24 hr at 25° the reaction mixture was worked up in the usual manner to give first 0.3 g (28% yield) of **2-(*o*-nitrobenzal-3-morpholino)-4,4-dimethyl-1-tetralone** (**14**): mp 165–166°, recrystallized from 95% ethyl alcohol; λ_{max} 272, 305 (sh) mμ (ε 19,300, 8200); $\nu_{C=O}$ (CCl_4) 1671 (s), $\nu_{C=C}$ 1622 (s), ν_{Ar} 1602 (m) cm^{-1}. The nmr spectrum had bands at τ 8.35 and 8.59 (six CH_3 protons), 7.64 (center of

sextet, four CH_2–N–CH_2 protons), 6.36–6.57 (four CH_2–N–CH_2 protons), 6.36–6.57 (four CH_2OCH_2 and one methine proton), and 1.75–2.80 (nine Ar protons).

Anal. Calcd for $C_{23}H_{24}N_2O_4$: C, 70.39; H, 6.16; N, 7.14. Found: C, 70.39; H, 6.28; N, 7.00.

The filtrate from the recovery of **14** was worked up to give 0.41 g (38% yield) of **2-(α-morpholino-*o*-nitrobenzyl)-1,4-dihydro-4,4-dimethyl-1-ketonaphthalene (15)**: mp 180–181°; λ_{max} 250, 290 (sh) mμ (ε 16,500, 5400, 4100); $\nu_{C=O}$ 1665 (vs), $\nu_{C=C}$ 1650 (sh) (m), ν_{Ar} 1607 (w) cm^{-1}. The nmr spectrum showed bands at τ 8.50 and 8.58 (six methyl protons), 7.42 (center of sextet, four CH_2NCH_2 protons), 6.25 (center of triplet, four CH_2OCH_2 protons), 4.52 (one methine proton), 3.04 (J = 0.5 cps) (vinyl proton), and 1.75–2.67 (eight aromatic protons).

Anal. Calcd for $C_{23}H_{24}N_2O_4$: C, 70.39; H, 6.16; N, 7.14. Found: C, 70.69; H, 6.28; N, 7.04.

Reaction of Halo Ketones C with *t*-Butylamine.—A solution of the halo ketone C and 10 molar equiv of *t*-butylamine in benzene was allowed to react at 25 or 65° for varying times. The *t*-butylamine hydrobromide was removed by filtration and the solvent evaporated to give an oily residue which was taken up in anhydrous ether and saturated with dry hydrogen chloride gas to precipitate the amino ketone hydrochloride product.

2-[α-(*t*-Butylamino)-*p*-nitrobenzyl]-1,4-dihydro-4,4-dimethyl-1-ketonaphthalene (17) hydrochloride was obtained from 0.002 mol of **2** and 0.02 mol of *t*-butylamine in 15 ml of benzene after 22 hr at 25°: mp 240–243° (ethanol–ether); 38% yield; $\lambda_{max}^{methanol}$ 274 mμ (ε 15,300); $\nu_{C=O}$ (KBr) 1660 (vs), $\nu_{C=C}$ 1645 (s), ν_{Ar} 1605 (m) cm^{-1}.

Anal. Calcd for $C_{23}H_{27}N_2O_3Cl$: C, 66.56; H, 6.51; N, 6.75; Cl, 8.44. Found: C, 66.25; H, 6.74; N, 6.37; Cl, 8.28.

2-[α-(*t*-Butylamino)-*o*-nitrobenzyl]-1,4-dihydro-4,4-dimethyl-1-ketonaphthalene (18) hydrochloride was obtained in 49% yield (0.52 g) from 1 g of **4** in 40 ml of benzene after 7 days at 25°: mp 251–253° (methanol–ether); $\lambda_{max}^{methanol}$ 250, 268 mμ (ε 11,450, 11,300); $\nu_{C=O}$ (KBr) 1660 (vs), $\nu_{C=C}$ 1645 (s), ν_{Ar} 1605 (m) cm^{-1}. This hydrochloride was converted into the free base **18** by dissolving in ethanol and treating with 1 equiv of *t*-butylamine: mp 132–134°, recrystallized from 95% ethyl alcohol; $\lambda_{max}^{methanol}$ 243, 304 (sh) mμ (ε 14,600, 4000); $\nu_{C=O}$ 1663 (vs), ν_{Ar} 1607 (m) cm^{-1}. The nmr spectrum showed bands at τ 8.9 (ten *t*-butylamino protons), 8.56 and 8.58 (six *gem*-dimethyl protons), 4.39 (benzyl proton), and 1.9–3.3 (nine aromatic protons).

Anal. Calcd for $C_{23}H_{26}H_2O_3$: C, 72.99; H, 6.93; N, 7.40. Found: C, 72.71; H, 7.01; N, 7.18.

3-(*t*-Butylamino)-2-*p*-chlorobenzal-4,4-dimethyl-1-tetralone (19) and 2-[α-(*t*-butylamino)-*p*-chlorobenzyl]-1,4-dihydro-4,4-dimethyl-1-ketonaphthalene (20) hydrochlorides were obtained in a 60% yield from the reaction of bromo ketone **5** with *t*-butylamine after 24 hr at 25°. The mixed hydrochloride product was converted into the mixed free bases **19** and **20** by treatment with *t*-butylamine in ethanol. The mixed bases were separated by chromotography on Florisil and eluted from the column, first by a 1:1 mixture of benzene and chloroform, to give 63% of **19**, mp 120–121°, and then with ethyl acetate to give 37% of **20**, mp 96–98°. For **19** uv and ir spectral data follow: $\lambda_{max}^{methanol}$ 230, 302 mμ (ε 14,300, 16,500); $\nu_{C=O}$ 1676 (s), $\nu_{C=C}$ 1619 (m), ν_{Ar} 1604 (w) cm^{-1}. The nmr spectrum of **19** showed bands at τ 9.24 (ten *t*-butylamino protons), 8.37 and 8.61 (six *gem*-dimethyl protons), 5.74 (methine proton), and 2.02–2.57 (nine aromatic protons).

Anal. Calcd for $C_{23}H_{26}NOCl$: C, 75.09; H, 7.07; N. 3.81. Found: C, 75.19; H, 7.07; N, 3.88.

For **20** uv and ir spectral data follow: $\lambda_{max}^{methanol}$ 254 and 305 (sh) (ε 18,500, 3200); $\nu_{C=O}$ 1665 (s), $\nu_{C=C}$ 1650 (sh), ν_{Ar} 1605 (w) cm^{-1}. The nmr spectrum in CCl_4 showed bands at τ 8.92 (ten *t*-butylamino protons), 8.52 and 8.56 (six *gem*-dimethyl protons), 4.86 (benzyl proton), 2.52–2.92 (eight aromatic protons), and 1.94 (J = 7 cps) (proton β to carbonyl).

Anal. Found: C, 74.84; H, 7.25; N, 4.33.

3-(*t*-Butylamino)-2-benzal-4,4-dimethyl-1-tetralone (21) and 2-[α-(*t*-butylamino)benzyl]-1,4-dihydro-4,4-dimethyl-1-ketonaphthalene (22) hydrochlorides were obtained after reaction of 2.2 g (0.03 mol) of *t*-butylamine with 1.03 g (0.003 mol) of **1** in 10 ml of benzene for 72 hr at 25°. The mixed hydrochlorides were converted into the free bases (0.667 g, 67% yield) on treatment with sodium carbonate in 95% ethyl alcohol. Analysis of the oily product by nmr indicated that it consisted of 67% of **21** and 33% of **22**. Chromatography on Florisil using first benzene as the eluting agent gave 0.4 g of **21** as an oil: $\lambda_{max}^{methanol}$ 270 (sh), 298 mμ (ε 19,100, 22,800); $\nu_{C=O}$, 1672 (m) cm^{-1}. The nmr spectrum showed bands at τ 1.92 (J = 8 cps) (Ar proton β to carbonyl), 2.50–3.00 (eight Ar protons), 5.78 (doublet J = 0.5 cps) (one methine proton), 8.39 and 8.55 (two bands, *gem*-dimethyl protons), and 9.25 (ten protons *t*-butylamino group).

Anal. Calcd for $C_{23}H_{27}NO$: C, 82.84; H, 8.16; N, 4.20. Found: C, 82.55; H, 8.15; N, 4.28.

Further elution with ethyl acetate gave 0.2 g of **22**, mp 74–76°; $\lambda_{max}^{methanol}$ 255, 298 (sh) mμ (ε 11,070, 3300); $\nu_{C=O}$ 1662 (vs), $\nu_{C=C}$ 1648 (sh), ν_{Ar} 1605 (w) cm^{-1}. The nmr spectrum showed bands at τ 1.91 (one Ar proton, β to carbonyl), 2.52–2.98 (eight Ar protons), 4.84 (one benzyl proton), and 8.53 and 8.55 (two bands, *gem*-dimethyl protons).

Anal. Found: C, 82.60; H, 8.01; N, 4.46.

Repeating this reaction at 65° for 15 hr, an over-all yield of 75% of **21** and **22** in a 1:1 ratio resulted.

The amino ketone **21** (0.21 g, 0.0006 mol) was heated at 60° for 22 hr with 0.21 g (0.03 mol) of *t*-butylamine in 1.5 ml of benzene. An nmr examination of the reaction mixture gave no indication of the presence of isomeric amino ketone **22**. When 0.15 g (0.0004 mol) of **22** and 0.31 g (0.004 mol) of *t*-butylamine and a trace of *t*-butylamine hydrobromide in 1.5 ml of benzene were heated at 65° for 17 hr, an nmr examination of the recovered material showed no change had taken place.

Amine Exchange Reaction of 21 with Piperidine to Give 9.—A 0.355-g (0.001 mol) sample of **21** and 0.85 g (0.01 mol) of piperidine in 2.5 ml of benzene were allowed to stand at room temperature for 42 hr. An nmr examination of the oily product showed that it consisted of 71.5% of **21** and 28.5% of the rearranged piperidino ketone **9**.[7] The ratio of the two amino ketones **21** and **9** was readily determined from the intensities of the methine protons.

When the amino ketone **10** (0.25 g), 10 ml of piperidine, and 5 ml of benzene were refluxed for 7 days, only the starting material could be recovered.

Reaction of the Chloro Ketone 7 with *t*-Butylamine.—When a solution of 0.3 g (0.001 mol) of **7** and 0.17 g (0.0023 mol) of *t*-butylamine in 20 ml of benzene stood at 25° for 103 hr no change took place. The experiment was repeated with 0.3 g (0.001 mol) of **7** and 0.69 g (0.01 mol) of *t*-butylamine in 1 ml of benzene. After 27 hr at 25° an over-all yield of 30% of the mixed product resulted which nmr analysis showed consisted of 55% **21** and 45% **22**.

Reaction of the Chloro Ketone 7 with Piperidine.—A mixture of 0.24 g (0.008 mol) of **7** and 0.16 g (0.0018 mol) of piperidine in 16 ml of benzene gave 0.15 g (50% yield) of the amino ketone **9**, mp 100–101°.[7] The nmr spectrum showed bands at τ 1.92 (J = 6 cps) (one as a proton β to carbonyl), 2.40–2.95 (nine Ar protons), 5.22 (one benzyl proton), 7.54 (four CH_2–NCH_2 protons), and 8.48 and 8.58 (two bands for two *gem*-dimethyl groups and three piperidino CH_2 groups).

2-(α-Methoxybenzyl)-1,4-dihydro-4,4-dimethyl-1-ketonaphthalene (23).—A 0.33-g sample of **1** in 10 ml of anhydrous methanol was heated under reflux for 4 hr. Evaporation of the solvent left 0.284 g of an oil which slowly crystallized on standing at room temperature for 2 months: mp 66–67°; $\lambda_{max}^{methanol}$ 253, 302 (sh) mμ (ε 11,500, 2500); $\nu_{C=O}$ 1665 (vs), $\nu_{C=C}$ 1650 (sh), ν_{Ar} 1605 (m) cm^{-1}. The nmr spectrum showed bands at 1.88 (J = 8 cps) (one as a proton β to carbonyl), 2.50–2.86 (eight Ar protons), 3.0 (J = 0.5 cps) (one vinyl proton), 4.58 (one methine proton), 6.70 (methoxy protons), and 8.48 and 8.56 (two bands for *gem*-dimethyls).

Anal. Calcd for $C_{20}H_{20}O_2$: C, 82.15; H, 6.89. Found: C, 81.88; H, 7.17.

Irradiation of *trans*-2-(*o*-Nitrobenzal)-4,4-dimethyl-1-tetralone.—A solution of 1 g of a pure *trans* sample in 220 ml of methanol was irradiated in a Pyrex flask for 70 hr by means of a B-100 A Blakray source. A brown oil was obtained after evaporation of solvent. The product was chromatographed on aluminum oxide using benzene as eluent. In this way pure *cis* isomer, mp 108–110°, was obtained. The nmr spectrum indicated nine aromatic protons in the range τ 2.96–1.85, one aromatic proton β to the carbonyl group at 1.95 (J = 7 cps), methylene protons at 7.27, and six methyl protons at 8.58; $\lambda_{max}^{methanol}$ 274, 312 mμ (ε 13,800, 5500); $\nu_{C=O}$ 1676 (76), $\nu_{C=C}$ 1634 (57), ν_{Ar} 1607 (67) cm^{-1}.

Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.08; H, 5.62; N, 4.62.

Further elution of the column with methylene chloride gave the pure *trans* isomer: mp 185–187°; $\lambda_{max}^{methano}$ 274, 318 (sh) mμ (ε 27,800, 7300); $\nu_{C=O}$ 1677 (s), $\nu_{C=C}$ 1630 (m), ν_{Ar} 1610 (s)

cm^{-1}. The nmr spectrum showed bands at τ 1.85 (aromatic proton β to the carbonyl), 2.3–2.8 (nine aromatic protons), 7.35 (J = 2 cps) (methylene protons), and 8.72 (*gem*-dimethyl protons).

Registry No.—2, 15982-09-9; **3**, 15982-10-2; **4**, 15982-11-3; **5**, 15982-12-4; **6**, 15982-13-5; **7**, 15982-14-6; **8**, 15982-41-9; **10**, 15982-42-0; **11**, 15982-43-1; **12**, 15982-44-2; **13**, 15982-45-3; **14**, 15982-46-4; **15**, 15982-47-5; **16** HCl, 15982-48-6; **17** HCl, 15982-49-7; **18** HCl, 15982-50-0; **19** HCl, 15982-51-1; **20** HCl, 15982-52-2; **21**, 15982-53-3; **22**, 15982-54-4; **23**, 15982-55-5; *cis*-2-(*o*-nitrobenzal)-4,4-dimethyl-1-tetralone, 15982-56-6; *trans*-2-(*o*-nitrobenzal)-4,4-dimethyl-1-tetralone, 15982-57-7.

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Mobile Keto Allyl Systems. VI.[1a] Reaction of 3-Bromo-2-benzal-1-indanone with Amines

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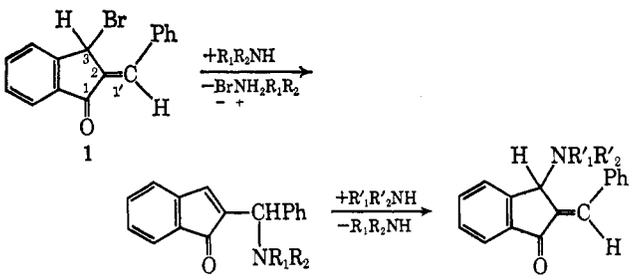
The reaction of 3-bromo-2-benzal-1-indanone (**1**) with primary and secondary amines proceeds in two steps, giving initially 2-[α-(X-amino)benzyl]-1-indenones (**2**) as the kinetically favored products, and then 3-(X-amino)-2-benzal-1-indanones (**3**) as the thermodynamically stable isomers. With diisopropylamine, only the aminoindenone **2b** is isolated, and the reaction of **1** → **2b** has been found to be first order with respect to the bromoindanone and the amine; the rate is equal to the rate of consumption of the amine and to the rate of appearance of the bromide ion. These data are accommodated by a variant of an SN2′ mechanism in which the entry of the amino group and the departure of the bromide ion are nearly synchronous, but the carbon to nitrogen bond making is running slightly ahead of the carbon to halogen bond breaking.

In a previous paper[2] Cromwell and coworkers reported that 3-bromo-2-benzal-1-indanone (**1**) reacted with piperidine, morpholine, and cyclohexylamine, in the absence of solvent, to give the direct substitution products 3-(X-amino)-2-benzal-1-indanones, **3**. It was suspected, although not proved, that the reaction might proceed by an abnormal allylic substitution followed by rearrangement. Such a mechanism has recently been reported for the reaction of *t*-butylamine with *trans*-α-(bromomethyl)chalcone.[3] Therefore, it seemed desirable to reexamine the substitution of **1** by primary and secondary amines, particularly since this substrate has a fixed conformation and may involve the resonances of either the 2-benzal-1-indanone- or 2-benzyl-1-indenone systems in the reaction transition state.



2a, R_1 = H; R_2 = *t*-butyl
b, R_1 = R_2 = isopropyl
c, R_1 = R_2 = morpholino
d, R_1 = H; R_2 = cyclohexyl
e, R_1 = H; R_2 = *n*-butyl
f, R_1 = H; R_2 = phenyl
g, R_1 = methyl; R_2 = phenyl
h, R_1 = R_2 = piperidino
j, R_1 = R_2 = pyrrolidino
k, R_1 = H; R_2 = methyl

3a, R_1 = H; R_2 = *t*-butyl
b, R_1 = R_2 = isopropyl
c, R_1 = R_2 = morpholino
d, R_1 = H; R_2 = cyclohexyl
e, R_1 = H; R_2 = *n*-butyl
f, R_1 = H; R_2 = phenyl
g, R_1 = methyl; R_2 = phenyl
h, R_1 = R_2 = piperidino
j, R_1 = R_2 = pyrrolidino
k, R_1 = H; R_2 = methyl

Results

I. Thermodynamically Favored Products.—A series of experiments was first carried out to study the over-all course of the reaction. The bromo ketone **1** was allowed to react, for approximately 24 hr, with a number of amines including *t*-butylamine, diisopropylamine, *n*-butylamine, piperidine, morpholine, and cyclohexylamine in an apolar medium at room temperature. Under these conditions, it was observed that the nature of the isolated product depended upon the nature of the reacting amine. If the amine was bulky (*t*-butylamine, diisopropylamine) the compounds **2** or **3** were isolated. *t*-Butylamine (2 equiv) was treated with **1** in benzene solution to give 2-[α-(*t*-butylamino)benzyl]-1-indenone (**2a**). If 10 equiv of amine was used, 3-(*t*-butylamino)-2-benzal-1-indanone (**3a**) was formed; compound **2a** seemed to be an intermediate in this reaction since it reacted with *t*-butylamine to give the isomeric aminoindanone **3a**.[4] Spectroscopic evidence supported the structure of **2a**. The uv absorption (mainly at 238 and 244 mμ in *n*-hexane) was almost identical with that of 2-ethyl-1-indenone[2,5] but differed appreciably from that of 2-benzal-1-indanone and derivatives.[2] Further support for the indenone structure was provided by the ir carbonyl absorption at 1715 cm^{-1} in carbon tetrachloride.[6]

(1) (a) For paper V in this series, see N. H. Cromwell and E.-M. Wu, *J. Org. Chem.*, **33**, 1895 (1968). (b) The author to whom all correspondence concerning this article should be addressed.

(2) B. D. Pearson, R. P. Ayer, and N. H. Cromwell, *ibid.*, **27**, 3038 (1962).

(3) R. P. Rebman and N. H. Cromwell, *Tetrahedron Lett.*, 4833 (1962).

(4) N. H. Cromwell and E.-M. Wu, *ibid.*, 1499 (1966).

(5) N. H. Cromwell and R. P. Ayer, *J. Amer. Chem. Soc.*, **82**, 133 (1960).

(6) C. S. Marvel and C. W. Hinman, *ibid.*, **76**, 5435 (1954).