The Chemistry of Carbanions. XXI. The Stereochemistry of Enolate Alkylation in the 1-Decalone System[1a]

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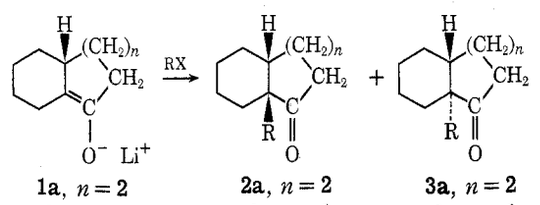
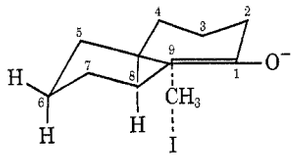
Reaction of the lithium $\Delta^{1,9}$-enolate of *syn*-6-*tert*-butyl-*trans*-1-decalone (**7**) with methyl iodide yielded the same proportion of cis (**13**, 80–86%) and trans (**14**, 14–20%) monoalkylated products as was found in the analogous reaction with the 1-decalone enolate **1a**. This result indicates that it is not necessary to postulate a transition state such as **4c** to account for the predominant formation of 9-alkyl-*cis*-1-decalones in alkylation reactions.

The bridgehead alkylation of enolate anions **1** derived from either 1-decalone or perhydro-1-indanone produces predominantly the cis-fused product **2** (Scheme I);[2] for example, the monoalkylated product

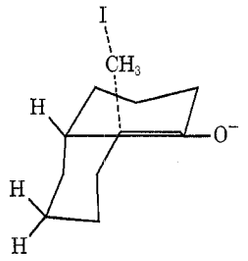
SCHEME I



1a, $n = 2$ **2a**, $n = 2$ **3a**, $n = 2$
b, $n = 1$ **b**, $n = 1$ **b**, $n = 1$



4a



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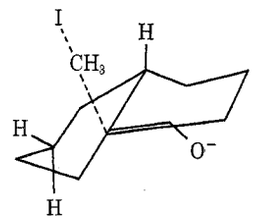
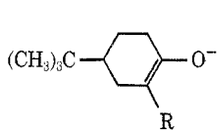


4c



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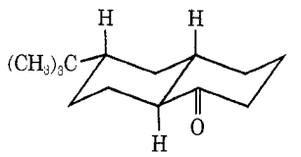

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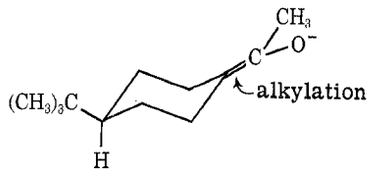

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obtained from the decalone lithium enolate **1a** and methyl iodide in 1,2-dimethoxyethane contained 78–83% of the cis product **2a** (R = CH_3) and 17–22% of the trans isomer **3a** (R = CH_3).[2a,b] The relationship of these results to those obtained with monocyclic enolates such as **5** (introduction of an equatorial alkyl group favored)[3] and **6** (substantial amounts of both epimers formed)[2d] are uncertain because both rings in the decalone enolate are conformationally mobile, so that three different enolate conformers **4** could be precursors of the cis- (**2a**) and trans- (**3a**) alkylated products. In the reactantlike transition states believed applicable[3,4] in all these alkylation reactions, reaction with conformers **4b** and **4c** would appear especially favorable to the formation of the cis product since attack by the alkylation agent from top side of these conformers (see **4b** and **4c**) is sterically less hindered than attack from the bottom. To overcome at least part of this ambiguity we have examined the corresponding methylation of the enolate **8** derived from the 6-*tert*-butyl-1-decalone **7** since the equatorial 6-*tert*-butyl substituent in this molecule precludes the existence of the corresponding enolate **8** in a conformation analogous to **4c**.

The reactions resulting in formation and alkylation of the enolate **8** are summarized in Scheme II. The stereochemistry of the alkylated products was established by the chemical correlations shown in Scheme III in which use was made of the known[5] stereoselective addition of methylcopper(I) derivatives to $\Delta^{1,9}$-octal-2-one systems (*e.g.*, **9a**) to form 9-methyl-*cis*-decalin derivatives (*e.g.*, **16** and **17**). The major monoalkylated product **13** and the major di- and trialkylated products **15** and **19** formed after relatively long reaction times were all derivatives of the 9-methyl-*cis*-1-decalone system **2a** (R = CH_3). In addition, small amounts of 9-methyl-*trans*-1-decalone **14** and other minor products were also formed. From alkylation reactions (see Table I) run for relatively short times to minimize dialkylation, the proportions of 9-methyl products were found to be 80–86% cis (**13**) and 14–20% trans (**14**), a product distribution essentially the same as that found for the methylation of the 1-decalone enolate **1a** under comparable conditions. Thus, we

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(2) (a) H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 2502 (1965); (b) H. O. House, M. Gall, and H. D. Olmstead, *ibid.*, **36**, 2361 (1971); (c) H. O. House and C. J. Blankley, *ibid.*, **32**, 1741 (1967); (d) for a review of other studies, see H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, New York, N. Y., 1972, pp 586–594.

(3) H. O. House and T. M. Bare, *J. Org. Chem.*, **33**, 943 (1968).

(4) T. M. Bare, N. D. Hershey, H. O. House, and C. G. Swain, *ibid.*, **37**, 997 (1972).

(5) (a) R. E. Ireland, M. Dawson, J. Bordner, and R. Dickerson, *J. Amer. Chem. Soc.*, **92**, 2568 (1970); J. A. Marshall, W. I. Fanta, and H. Roebke, *J. Org. Chem.*, **31**, 1016 (1966); (b) A. J. Birch and M. Smith, *Proc. Chem. Soc.*, 356 (1962); (c) R. Church, R. E. Ireland, and D. Shridhar, *J. Org. Chem.*, **27**, 707 (1962); (d) M. Torigoe and J. Fishman, *Tetrahedron Lett.*, **No. 19**, 1251 (1963); (e) S. Boatman, T. M. Harris, and C. R. Hauser, *J. Amer. Chem. Soc.*, **87**, 82 (1965); (f) J. A. Marshall and H. Roebke, *J. Org. Chem.*, **33**, 840 (1968); (g) E. Piers and R. Keziere, *Can. J. Chem.*, **47**, 137 (1969); (h) G. Posner, *Org. React.*, **19**, 1 (1972).

SCHEME II

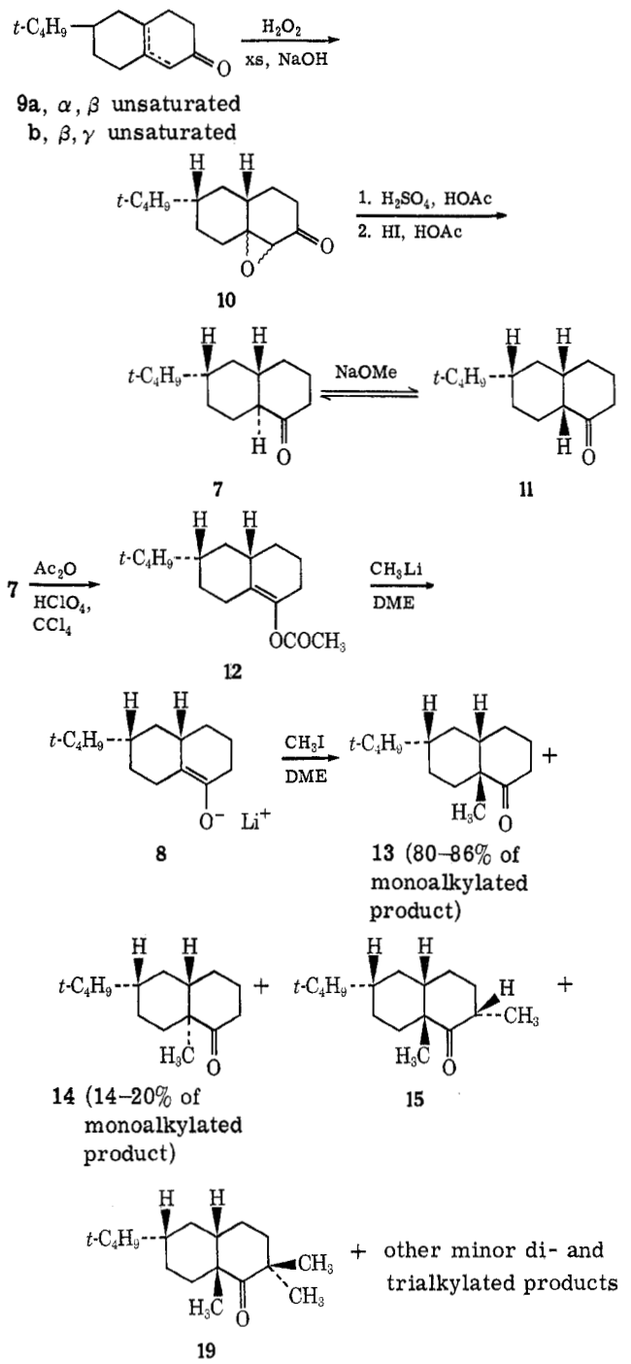


TABLE I

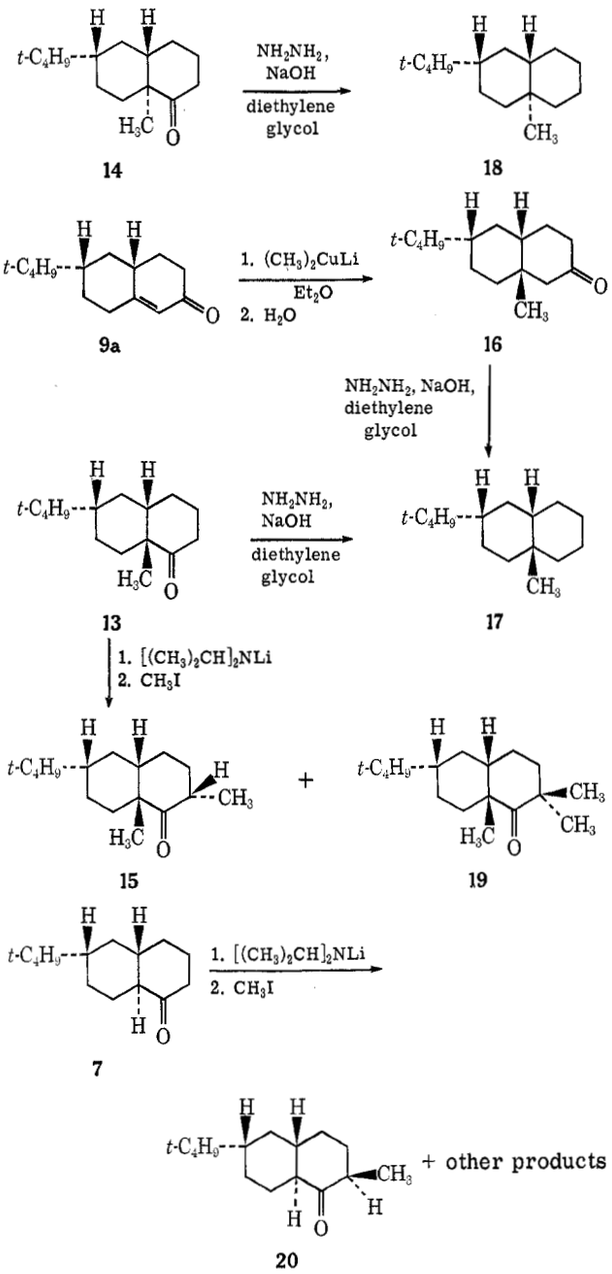
MONOALKYLATED PRODUCTS 13 AND 14 FROM REACTION OF THE ENOLATE 8 WITH MeI IN 1,2-DIMETHOXYETHANE

Time, sec	Yield of 13 +14, %	Monoalkylated —product composition— 13, %	14, %
18	30	86	14
30	51	85	15
105	49[a]	82	18
300	44[a]	81	19
1800	38[a]	80	20

[a] Substantial amounts of dialkylated ketone 15 and other polyalkylated products were present in these reaction mixtures.

conclude that alkylation of the 1-decalone enolate **1a** *via* transition states **4a** and **4b** is adequate to account for the proportion of 9-methyl-*cis*-1-decalone (**2a**, R = CH_3) formed. It is appropriate to note that both transition states **4a** and **4b** (but not **4c**) follow the same pattern as the model system **5** in that introduction of the alkyl group equatorial to the nonoxygenated cyclohexane ring is preferred by a factor of 4 or 5 to 1.

SCHEME III



Experimental Section[6]

Preparation of the Decalone 7.—A mixture of the octalones **9**, bp 115–132° (0.08–0.1 mm), $n^{23.5}$D 1.5073 [lit.[7] bp 110–115° (0.05

(6) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated, magnesium sulfate was employed as a drying agent. The infrared spectra were determined with a Perkin-Elmer Model 237 or Model 257 infrared recording spectrophotometer fitted with a grating. The ultraviolet spectra were determined with a Perkin-Elmer Model 202 recording spectrophotometer. The nmr spectra were determined at 60 MHz with a Varian Model A-60 or Model T-60 or a Perkin-Elmer Model R-20B nmr spectrometer. The chemical shifts are expressed in δ values (parts per million) relative to a tetramethylsilane internal standard. The mass spectra were obtained with an Hitachi Perkin-Elmer mass spectrometer. All reactions involving strong bases or organometallic intermediates were performed under a nitrogen atmosphere.

mm), $n^{26.5}$D 1.5100], was prepared by previously described[7] procedures. To avoid separation[7] of the isomeric octalones **9**, the mixture was treated with H_2O_2 under sufficiently alkaline conditions that interconversion of the isomers **9a** and **9b** occurred and the conjugated isomer **9a** was epoxidized. Four 35.0-g (0.17 mol) portions of the octalones were each dissolved in 820 ml of MeOH and then treated with sufficient aqueous 1 *M* NaOH to give a solution of pH 10. After each solution had been stirred at 25° for 1.8 hr it was cooled to 0° and treated with 49.5 ml (0.528 mol) of aqueous 30% H_2O_2 and a sufficient amount of aqueous 1 *M* NaOH to bring the solution to pH 10. Each solution (which warmed to 10–12°) was stirred with ice-bath cooling for 11–12 min and then diluted with 1 l. of H_2O and extracted with Et_2O. The combined ethereal extracts from the four reactions were washed with aqueous NaCl, dried, and concentrated. Recrystallization of the residual white solid from pentane afforded 97.8 g (65%) of the epoxy ketone **10** (presumably a mixture of stereoisomers) as white needles, mp 67.5–71.5°. A portion of this material was repeatedly recrystallized from pentane to separate one stereoisomer of **10**, mp 70.5–71.5° (lit.[7] mp 72–72.5°). Reaction of the epoxy ketone **10** with H_2SO_4 in HOAc as previously described[7] yielded the crude enolic α-diketone that was reduced with aqueous 57% HI in HOAc as described[7] to form the crude decalone **7**, bp 106–116° (0.2–0.4 mm), mp 59–71°. Recrystallization from MeOH separated the pure decalone **7** as white prisms, mp 74–75.5°, identified with the sample described previously[7] by comparison of ir spectra and glpc retention times.

A solution of 215 mg (1.03 mmol) of the trans ketone **7** and 29.5 mg (0.55 mmol) of NaOMe in 5 ml of MeOH was refluxed for 14.8 hr and then partitioned between pentane and aqueous NaCl. After the pentane solution had been concentrated, analysis (glpc, Apiezon M on Chromosorb P) indicated the presence of the trans ketone **7** (retention time 14.1 min) accompanied by *ca.* 5% of a second component believed to be the cis ketone **11** (11.8 min).

Preparation of the Enol Acetate 12.—A solution of 19.0 g (91.3 mmol) of the decalone **7**, 102 g (1.0 mol) of Ac_2O, and 0.49 ml of aqueous 70% $HClO_4$ in 283 ml of CCl_4 was stirred at 23° for 1 hr and then mixed with 185 ml of cold (3–5°), saturated aqueous $NaHCO_3$ and 185 ml of pentane. Solid $NaHCO_3$ was added portionwise and with stirring until all the HOAc was neutralized. The pentane layer was separated, combined with the pentane extract of the aqueous phase, and then washed with H_2O, dried, and concentrated. Distillation separated 19.5 g (86%) of the crude product, bp 96–103.5° (0.1 mm), $n^{25.5}$D 1.4877–1.4878, which contained (glpc, Carbowax 20 M on Chromosorb P) the enol acetate **12** (retention time 26.0 min) accompanied by small amounts of the starting ketone **7** (19.8 min) and a second, unidentified component (29.8 min). Fractional distillation through a 60-cm spinning band column separated the pure enol acetate **12**: bp 101–103° (0.1 mm); $n^{25.5}$D 1.4878; ir (CCl_4) 1750 cm^{-1} (enol ester C=O); uv (95% EtOH) end absorption (ϵ 5700 at 210 mμ); nmr (CCl_4) δ 0.7–2.8 (14 H, m, aliphatic CH), 2.02 (3 H, s, CH_3CO), and 0.85 [9 H, s, $(CH_3)_3C$]; mass spectrum *m/e* (rel intensity) 250 (5, M$^+$), 208 (100), 151 (50), 133 (26), 123 (45), 110 (33), 57 (45), 55 (33), 43 (86), and 41 (61).

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 77.00 H, 10.44.

Preparation of the 9-Methyldecalin Derivatives 16 and 17.—To a cold (−10°) solution of $LiMe_2Cu$, prepared from 5.25 g (27.6 mmol) of CuI and 66 mmol of MeLi, in 45 ml of Et_2O was added, dropwise and with stirring, a solution of 5.05 g (24.5 mmol) of the octalone **9a** (purified by low-temperature crystallization[7]) in 5 ml of Et_2O. The resulting mixture was stirred for 10 min and then partitioned between Et_2O and an aqueous solution of NH_4Cl and NH_3. The organic layer was washed with aqueous $Na_2S_2O_3$, dried, and concentrated to leave a yellow liquid which was crystallized from pentane at Dry Ice temperatures. The ketone **16** separated as 3.77 g (69%) of white needles, mp 48–49°. Recrystallization gave the pure ketone **16**: mp 48.5–49.5°;[8] ir (CCl_4) 1710 cm^{-1} (C=O); uv max (95% EtOH) 282 mμ (ϵ 20); nmr (CCl_4) δ 0.9–2.7 (14 H, m, aliphatic CH) and 0.89 [12 H, s, CH_3 and $(CH_3)_3C$]; mass spectrum *m/e* (rel intensity), 222 (24, M$^+$), 166 (65), 151 (42), 124 (38), 123 (61), 110 (41), 57 (100), 55 (33), and 41 (47).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.01; H, 11.91.

A solution of 717 mg (3.2 mmol) of the ketone **16** and 917 mg (15.6 mmol) of 85% H_2NNH_2 in 6.6 ml of diethylene glycol was refluxed for 1 hr, cooled, and treated with 390 mg (9.8 mmol) of NaOH. The solution was heated to boiling, the H_2O and unchanged H_2NNH_2 were allowed to distil, and the remaining solution was refluxed for 3 hr. The reaction mixture was cooled and partitioned between Et_2O and aqueous 10% HCl. After the ethereal layer had been washed with aqueous NaCl, dried, and concentrated, distillation of the residue (1.066 g of yellow liquid) in a short-path still (0.1 mm and 60–80° bath) separated 403 mg (60%) of the pure (glpc) hydrocarbon **17** as a colorless liquid: n^{25}D 1.4792; ir (CCl_4) no OH or CO absorption in the 3- or 6-μ regions; nmr (CCl_4) δ 0.8–2.0 (multiplet, aliphatic CH) with superimposed singlets at 0.97 (CH_3) and 0.87 [$(CH_3)_3C$]; mass spectrum *m/e* (rel intensity), 208 (5, M$^+$), 152 (28), 151 (35), 150 (24), 137 (57), 109 (43), 96 (30), 95 (100), 83 (33), 81 (53), 69 (32), 67 (38), 57 (65), 56 (28), 55 (55), and 41 (68).

Anal. Calcd for $C_{15}H_{28}$: C, 86.46 H, 13.54. Found: C, 86.65; H, 13.44.

Methylation of the Lithium Enolate 8. A. Preparation of Alkylated Products.—To a solution of 65 mmol of MeLi and several milligrams of 2,2-bipyridyl (an indicator) in 62 ml of 1,2-dimethoxyethane was added, dropwise and with stirring, 7.848 g (31.4 mmol) of the enol acetate **12**, during which time the temperature of the reaction solution rose to 60°. The resulting red (indicating excess MeLi) solution was cooled to 20–25° and then 22.2 g (156 mmol) of MeI was added. The resulting yellow reaction mixture was stirred for 1.5 min and then partitioned between pentane and aqueous $NaHCO_3$. After the pentane solution had been dried (Na_2SO_4), the volatile organic materials were fractionally distilled from the mixture and the residual liquid was distilled to separate 6.896 g of crude alkylated product, bp 80–86° (0.2 mm), n^{25}D 1.4837. Analysis (glpc, silicone fluid QF$_1$ on Chromosorb P) indicated the presence of the following components: **15** (*ca.* 30%, retention time 26.2 min); **19** (*ca.* 16%, 29.2 min); **13** (*ca.* 31%, 31.0 min); an unresolved mixture believed to contain **7**, **20**, and an unidentified dimethylated product (*ca.* 6%, 35.8 min); an unresolved mixture believed to contain an unidentified dimethylated and an unidentified trimethylated product (*ca.* 7%, 40.8 min); and **14** (*ca.* 9%, 43.2 min). On a second glpc column (ethylene glycol adipate on Chromosorb P), the same mixture was resolved into the following components: **15** and **19** (unresolved, *ca.* 45%, 16.6 min); **13** (*ca.* 31%, 17.7 min); **7** and other unidentified components (*ca.* 8%, 24.6 min); unidentified di- and/or trialkylated components (*ca.* 6%, 26.9 min); and **14** (*ca.* 9%, 29.1 min).

Partial separation of the mixture was accomplished by the selective formylation[9] of those materials with no substituents at C-2. To a cold (0–5°), stirred slurry of 1.402 g (25.9 mmol) of NaOMe in 40 ml of Et_2O was added a mixture of 4.99 g of the crude alkylated product and 1.548 g (20.8 mmol) of HCO_2Et. After the mixture had been stirred in an ice bath for 15 min and then at room temperature for 17 hr, it was partitioned between Et_2O and H_2O. The ethereal layer was washed with aqueous 1 *M* NaOH, dried (Na_2SO_4), concentrated, and distilled to separate 2.55 g of alkylated products, bp 70–75° (0.05 mm). This material contained (glpc) the following components: **15**, *ca.* 57%; **19**, *ca.* 20%; **20**, *ca.* 9%; a mixture of unidentified dimethylated and trimethylated isomers, *ca.* 23%.

The alkaline aqueous phase from the formylation procedure was mixed with 3.0 g of NaOH and refluxed for 4 hr, at which time an acidified aliquot of the mixture no longer gave a red-orange color with $FeCl_3$. After the reaction mixture had been neutralized with HCl, it was extracted with Et_2O and the ethereal extract was washed with aqueous NaCl, dried (Na_2SO_4), and concentrated. A short-path distillation (0.3–0.4 mm and 80–100° bath) of the residue separated 1.699 g of alkylated products containing (glpc) **13**, *ca.* 71%; **7**, *ca.* 7%; and **14**, *ca.* 22%.

The components of these mixtures were collected (glpc) and ir and mass spectra of each collected peak were used for tentative identification. In cases where single substances could be obtained, sufficient amounts were collected (glpc) for characterization.

(7) H. O. House, R. W. Giese, K. Kronberger, J. P. Kaplan, and J. F. Simeone, *J. Amer. Chem. Soc.*, **92**, 2800 (1970).

(8) The position of the 9-methyl signal in the nmr spectrum of the ketone **16** has been described by M. J. T. Robinson, *Tetrahedron Lett.*, **No. 22**, 1685 (1965).

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A collected sample of the *cis*-9-methyl ketone **13** was obtained as a colorless liquid: $n^{25}D$ 1.4871; ir (CCl_4) 1708 cm^{-1} (C=O); uv max (95% EtOH) 296 mμ (ε 34); nmr (CCl_4) δ 0.7–2.5 (14 H, m, aliphatic CH), 1.19 (3 H, s, CH_3), and 0.82 [9 H, s, $(CH_3)_3C$]; in benzene-d_6 the two singlets are at δ 1.00 (CH_3) and 0.82 [$(CH_3)_3C$]; mass spectrum *m/e* (rel intensity) 222 (5, M^+), 124 (100), 111 (52), 84 (24), 67 (24), 57 (52), 55 (28), and 41 (55).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.85; H, 11.86.

A 306-mg (1.4 mmol) sample of this ketone **13** was subjected to the previously described Wolff–Kishner reduction procedure employing 471 mg (8.0 mmol) of 85% H_2NNH_2, 190 mg (4.8 mmol) of NaOH, and 3.1 ml of diethylene glycol. The crude product, 178 mg (62%) of yellow liquid, contained (glpc) one major component, the hydrocarbon **17**. A collected (glpc) sample of this hydrocarbon was identified with the previously described sample by comparison of glpc retention times and ir and mass spectra.

A collected (glpc) sample of the *trans*-9-methyl ketone **14** was obtained as a colorless liquid: $n^{25}D$ 1.4879; ir (CCl_4) 1705 cm^{-1} (C=O); uv max (95% EtOH) 288 mμ (ε 34); nmr (CCl_4) δ 0.8–2.8 (14 H, m, aliphatic CH), 1.03 (3 H, s, CH_3), and 0.89 [9 H, s, $(CH_3)_3C$]; in benzene-d_6 the two singlets are superimposed at δ 0.80; mass spectrum *m/e* (rel intensity) 222 (17, M^+), 147 (34), 111 (29), 109 (21), 95 (30), 81 (47), 68 (21), 67 (40), 57 (100), 55 (51), 53 (21), 43 (23), 41 (96), and 39 (22).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.92; H, 11.61.

The previously described Wolff–Kishner reduction procedure was followed with 68.7 mg (0.309 mmol) of the trans ketone **14**, 110 mg (3.4 mmol) of 95% H_2NNH_2, 68.5 mg (1.7 mmol) of NaOH, and 0.7 ml of diethylene glycol. The crude neutral reaction product contained (glpc) a single major component, the hydrocarbon **18**. A collected (glpc) sample of the product **18** was obtained as a colorless liquid with ir (CCl_4), nmr, and mass spectra clearly different from those of the hydrocarbon **17**. The trans hydrocarbon **18** has an nmr (CCl_4) multiplet at δ 0.4–1.9 with superimposed singlets at δ 0.78 (*ca.* 3 H, CH_3) and 0.85 [*ca.* 9 H, $(CH_3)_3C$]; mass spectrum *m/e* (rel intensity) 208 (12, M^+), 152 (65), 151 (27), 137 (39), 109 (41), 96 (37), 95 (100), 83 (36), 81 (51), 69 (34), 67 (42), 57 (83), 55 (60), and 41 (77).

Anal. Calcd for $C_{15}H_{28}$: C, 86.46 H, 13.54. Found: C, 86.74; H, 13.29.

A collected (glpc) sample of the dimethylated ketone **15** was obtained as a colorless liquid: $n^{25}D$ 1.4800; ir (CCl_4) 1705 cm^{-1} (C=O); uv max (95% EtOH) 297 mμ (ε 37); nmr (CCl_4) δ 0.7–2.8 (13 H, m, aliphatic CH), 1.20 (3 H, s, CH_3 at C-9), 0.93 (3 H, d, J = 6.5 Hz, CH_3 at C-2), and 0.83 [9 H, s, $(CH_3)_3C$]; in benzene-d_6 the nmr peaks are found at δ 1.03 (CH_3 at C-9), 0.97 (doublet, CH_3 at C-2), and 0.80 [$(CH_3)_3C$]; mass spectrum *m/e* (rel intensity) 236 (9, M^+), 138 (24), 125 (44), 109 (35), 95 (37), 81 (40), 79 (20), 69 (22), 68 (23), 67 (41), 57 (63), 55 (48), 53 (20), 43 (35), 41 (100), and 39 (21).

Anal. Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 81.30; H, 11.97.

A collected (glpc) sample of the starting ketone **7** present among the alkylated products was identified with an authentic sample by comparison of glpc retention times and ir spectra. A collected (glpc) sample of the trimethylated ketone **19** exhibited the following spectral properties: ir (CCl_4) 1695 cm^{-1} (C=O); nmr (CCl_4) δ 0.6–2.7 (12 H, m, aliphatic CH), 1.10 (6 H, s, two CH_3 groups), 0.98 (3 H, s, CH_3), and 0.78 [9 H, s, $(CH_3)_3C$]; in benzene-d_6 the nmr singlets are found at δ 1.11 (3 H, CH_3), 1.07 (6 H, two CH_3 groups), and 0.79 [9 H, $(CH_3)_3C$]; mass spectrum *m/e* (rel intensity) 250 (10, M^+), 193 (20), 152 (62), 110 (22), 109 (65), 95 (46), 81 (36), 69 (32), 68 (20), 67 (38), 57 (100), 55 (47), 43 (37), and 41 (75).

To establish the presence of a cis ring fusion in the major dimethylated product **15** and the major trimethylated product **19**, the cis monomethyl ketone **13** was alkylated by the following procedure.

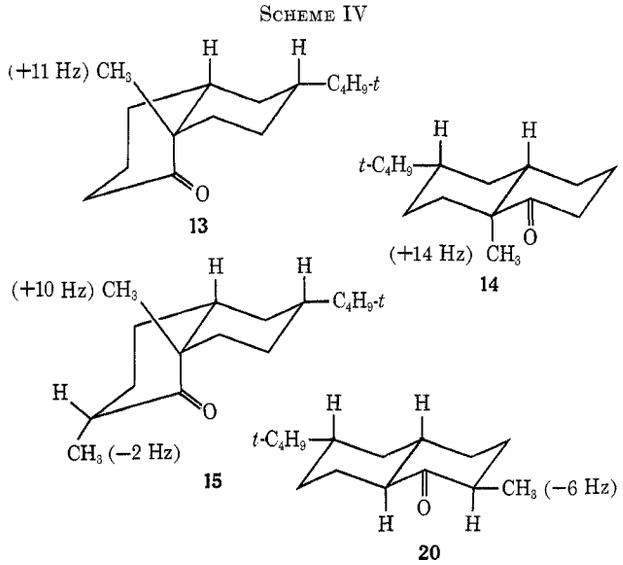
To a cold (0°) solution of $(Me_2CH)_2NLi$ [from 1.39 mmol of MeLi and 158 mg (1.56 mmol) of $(Me_2CH)_2NH$] in 3.7 ml of 1,2-dimethoxyethane containing several milligrams of 2,2-bipyridyl (as an indicator) was added 265.5 mg (1.20 mmol) of the ketone **13**. The resulting solution was warmed to 28°, treated with 744 mg (5.23 mmol) of MeI, stirred at 28–32° for 6.8 min, and then partitioned between pentane and aqueous $NaHCO_3$. The organic layer was washed successively with aqueous 1 *M* HCl and aqueous $NaHCO_3$ and then dried and concentrated to leave a liquid product containing (glpc) ketones **13**, **15**, and **19**. A collected (glpc) sample of the dimethyl ketone **15** was identified with the previously described sample by comparison of glpc retention times and ir spectra. A solution of the remaining reaction product mixture (106 mg) in 1 ml of 1,2-dimethoxyethane was added to 0.55 mmol of $(Me_2CH)_2NLi$ in 1 ml of 1,2-dimethoxyethane and then 191 mg (1.95 mmol) of MeI was added and the mixture was stirred at 25–35° for 23.5 hr. Use of the previously described isolation procedure afforded a crude liquid containing (glpc) primarily the trimethyl ketone **19**. A collected (glpc) sample of **19** was identified with the previously described sample by comparison of ir spectra and glpc retention times.

To obtain an authentic sample of the 2-methyl ketone **20**, the same alkylation procedure was followed with 5.96 mmol of $(Me_2CH)_2NLi$, 1.179 g (5.68 mmol) of the ketone **7**, and 1.77 g (12.5 mmol) of MeI in 13 ml of 1,2-dimethoxyethane. After a reaction period of 6.3 min at 30°, the usual isolation procedure followed by short-path distillation separated 992.4 mg (*ca.* 79%) of crude alkylated product. Reaction of this product with 406 mg (5.5 mmol) of HCO_2Et and 251 mg (4.7 mmol) of NaOMe in 8.6 ml of Et_2O, as previously described, followed by separation of the unformylated material and short-path distillation, separated 423 mg of material containing (glpc, silicone fluid QF_1 on Chromosorb P) the 2-methyl ketone **20** (retention time 49.2 min) accompanied by at least three minor components (33.6, 39.9, and 54.5 min), some of which are believed to be the less stable stereoisomers of ketone **20**. A collected (glpc) sample of ketone **20** has the following properties: ir (CCl_4) 1715 cm^{-1} (C=O); nmr (CCl_4) δ 0.86 [9 H, s, $(CH_3)_3C$], 0.90 (3 H, d, J = 6 Hz, CH_3), and 0.8–2.5 (14 H, m, aliphatic CH); in benzene-d_6 the resolved peaks are at δ 0.82 [$(CH_3)_3C$] and 1.00 (d, J = 5.7 Hz, CH_3); mass spectrum *m/e* (rel intensity) 222 (M^+, 32), 166 (41), 165 (24), 124 (28), 81 (24), 67 (25), 57 (100), 55 (24), and 41 (55).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.94; H, 11.68.

The stereochemical assignments made for ketones **13**, **14**, **15**, and **20** are all consistent with the generalization[10] that the nmr signal for α-methyl groups axial to a cyclohexanone ring will be shifted upfield significantly by changing the solvent from CCl_4 to C_6D_6 whereas the corresponding equatorial methyl groups will exhibit a slight downfield shift with the same solvent change. The solvent-shift values, $\delta_{CCl_4} - \delta_{C_6D_6}$, for these ketones are summarized in Scheme IV.

SCHEME IV



B. Determination of the Proportions of Monoalkylated Ketones 13 and 14.—Employing glpc equipment calibrated with known mixtures of the ketones **13** and **14** and an internal standard

(10) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 159–182.

(n-$C_{16}H_{34}$), the yields of alkylated products obtained after various reaction times (see Table I) at 2–7° were determined. The reaction solutions contained the enolate **8** (from 1.030 g or 4.12 mmol of enol acetate **12** and 8.3 mmol of MeLi), and 2.676 g (18.8 mmol) of MeI in 7.8 ml of 1,2-dimethoxyethane.

Registry No.—**7**, 28435-46-3; **8**, 35096-20-9; **12**, 35096-21-0; **13**, 35096-22-1; **14**, 35096-23-2; **15**, 35096-24-3; **16**, 2530-19-0; **17**, 35096-26-5; **18**, 35096-27-6; **19**, 35096-28-7; **20**, 35096-29-8.

Stereoselective Syntheses of Isoquinuclidones. I[1,2]

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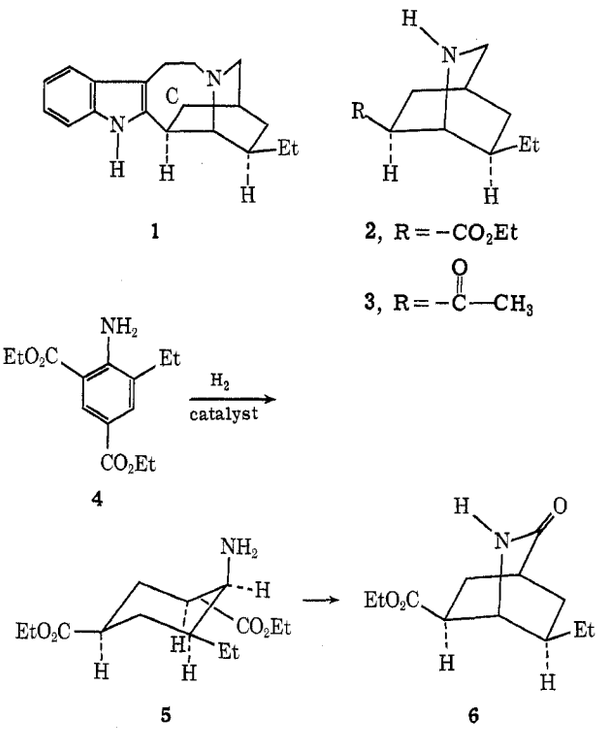
Catalytic hydrogenation of 2,4,6-trisubstituted anilines over a ruthenium catalyst occurs in all cis fashion with concomitant lactam formation to give the corresponding isoquinuclidone derivatives. The 6-acetyl-7-ethyl derivative **23** and the 6-carbethoxy-7-ethyl derivative **6**, prepared in this way, have interest as precursors for the synthesis of iboga and related alkaloids.

The first synthesis of ibogamine (**1**) was reported by Büchi, *et al.*, in 1965.[3] Since then, alternate and stereoselective syntheses of ibogamine have been reported by a number of different groups,[4] as well as partial syntheses[5,6] and alternate approaches.[7] Prior to the synthesis by Büchi, *et al.*,[3] we had undertaken an approach to the synthesis of ibogamine involving a stereoselective synthesis of the isoquinuclidine moiety of the molecule.[2] Since our work has not been duplicated in the intervening period[7] and since the methods employed may be useful to others, the present report and its companion paper[8] are presented to summarize our findings.

Through chemical studies and X-ray crystallographic analysis[9] the configuration of ibogamine has been shown to be as given by structure **1**. Thus, the isoquinuclidine moiety has both substituents cis to the nitrogen bridge. For an eventual synthesis of **1** it appeared desirable to synthesize an isoquinculidine moiety where R is carbethoxy (**2**) or acetyl (**3**). The key to our approach was the expectation that catalytic hydrogenation of a 2,4,6-trisubstituted aniline such as **4** could be accomplished in an all cis fashion to give **5** which, either spontaneously or on heating, would cyclize to the corresponding isoquinuclidone **6**. To test this idea, then, it was necessary to develop convenient syntheses of 2,4,6-trisubstituted anilines.

As starting material, *o*-ethylaniline was converted to 7-ethylisatin (**7**) in good yield following the general procedure of Marvel and Hiers.[10] This was readily brominated in high yield to the 5-bromo derivative **8** which, on treatment with hydrogen peroxide and base, gave the anthranilic acid derivative **9** in quantitative yield. A von Braun reaction between cuprous cyanide and the corresponding ester **10** proceeded in 83% yield to the cyano derivative **11**. Treatment of **11** with ethanolic hydrogen chloride then gave the desired diester **4** in 83% yield. Although, as summarized in Scheme I, five steps are involved in the formation of **4**, they all proceed in high yield and are convenient to carry out.

Although a number of catalysts and different procedures were investigated for the reduction of **4**, the best conditions found were those using ruthenium oxide as catalyst in absolute ethanol under 2200 psi of hydrogen at 125.° Under these circumstances spontaneous cyclization occurred and the desired isoquinuclidone **6** was isolated in 41% yield, accompanied by the cor-



(1) We thank the Public Health Service, National Heart Institute Grant No. 5-ROI-HE 09813, for financial support of this investigation.

(2) Abstracted from the doctoral dissertation of V. A. Snieckus, University of Oregon, 1965.

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