The Stereochemistry of β-Keto Ester and β-Keto Nitrile Alkylations

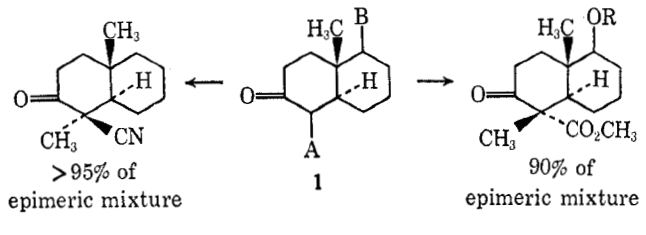
Martin E. Kuehne

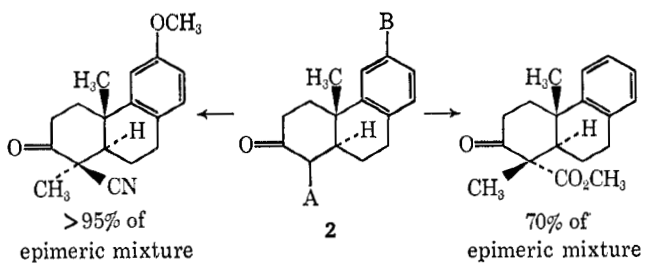
Department of Chemistry, University of Vermont, College of Technology, Burlington, Vermont 05401

Received May 1, 1969

The methylations of 2-carbomethoxy- and 2-cyano-4-*t*-butylcyclohexanone gave predominantly axial alkylation products. With 3-carbomethoxy- and 3-cyano-10-methyl-*trans*-2-decalones the opposite stereochemical result was obtained. While a boat or twist conformation is indicated for the substituted ring product in the former case by nmr and vpc, a chair conformation was found for the nitrile product.

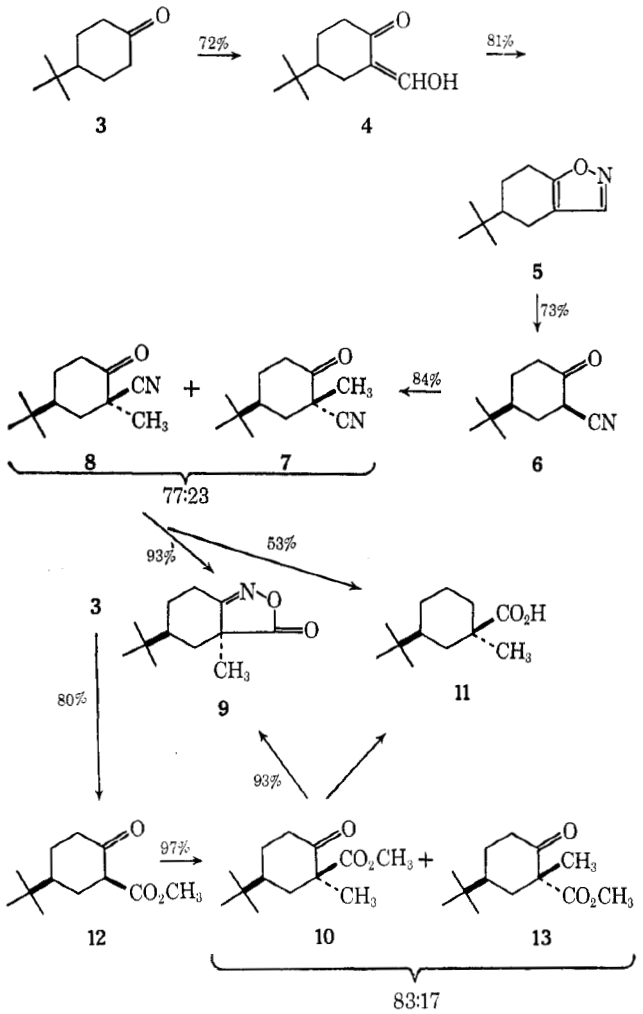
Observation of the remarkable stereoselective reversal in methylations of bicyclic and tricyclic β-keto nitriles and β-keto esters[1] **1** (A = CN or CO_2CH_3, B = H or OR) and **2** (A = CN or CO_2CH_3, B = OCH_3 or H) prompted a study of the methylations of additional β-keto nitriles and β-keto esters.





In the experiments described below, it was found that other pairs of β-keto esters and β-keto nitriles gave stereochemically parallel methylation products. Preponderant formation of axial alkylation products was found with unhindered enolates, while 1,3-axial shielding to alkylation led to the stereochemically alternative products.

The alkylations were first studied in monocyclic compounds with conformational preference imparted by a *t*-butyl substituent. Claisen condensation of 4-*t*-butylcyclohexanone (**3**) with methyl formate and reaction of the resultant formyl ketone **4** with hydroxylamine gave the isoxazole **5**, which was opened with sodium methoxide to 2-cyano-4-*t*-butylcyclohexanone (**6**). Methylation of the lithium enolate of this β-keto nitrile in a benzene–dimethylformamide mixture gave a 23:77 ratio of *cis*- (**7**) and *trans*- (**8**) 2-methyl-4-*t*-butyl-2-cyanocyclohexanone. The relative amounts of the crystalline products were established by nmr, vpc, and preparative separation. The major product with the more shielded tertiary methyl group (see Table I) and higher vpc and tlc retention times was assigned the *t*-butyl (*e*) to methyl (*a*) *trans* configuration. Reaction of this compound with hydroxylamine hydrochloride furnished an oxazolone **9**, which was identical with the oxazolone derived from the corresponding β-keto ester **10**. Alternatively, Clemmensen and catalytic reductions and subsequent hydrolysis gave a desoxy acid **11**, which could be matched with the product of corresponding reactions of the β-keto ester **10**.



Acylation of the sodium enolate of 4-*t*-butylcyclohexanone (**3**) with dimethyl carbonate gave 2-carbomethoxy-4-*t*-butylcyclohexanone (**12**). Methylation of this β-keto ester, under conditions used for the methylation of nitrile **6**, led to a 17:83 ratio of 2-carbomethoxy-*cis*- (**13**) and -*trans*- (**10**) 2-methyl-4-*t*-butylcyclohexanones, comparable with the 30:70 ratio found on methylation of the sodium enolate of 2-carbethoxy-4-*t*-butylcyclohexanone in ethanol.[2] Again an nmr spectrum of the major product showed a more shielded tertiary methyl group (Table I) and a higher vpc retention time.

In order to study the influence of 1,3-axial shielding to alkylation of the β-keto ester and β-keto nitrile enolates, without the complication of *peri* interactions,

(1) M. E. Kuehne and J. A. Nelson, *J. Org. Chem.*, **35**, 161 (1970).

(2) F. Nerdel, D. Frank, and K. Rehse, *Chem. Ber.*, **100**, 2978 (1967).

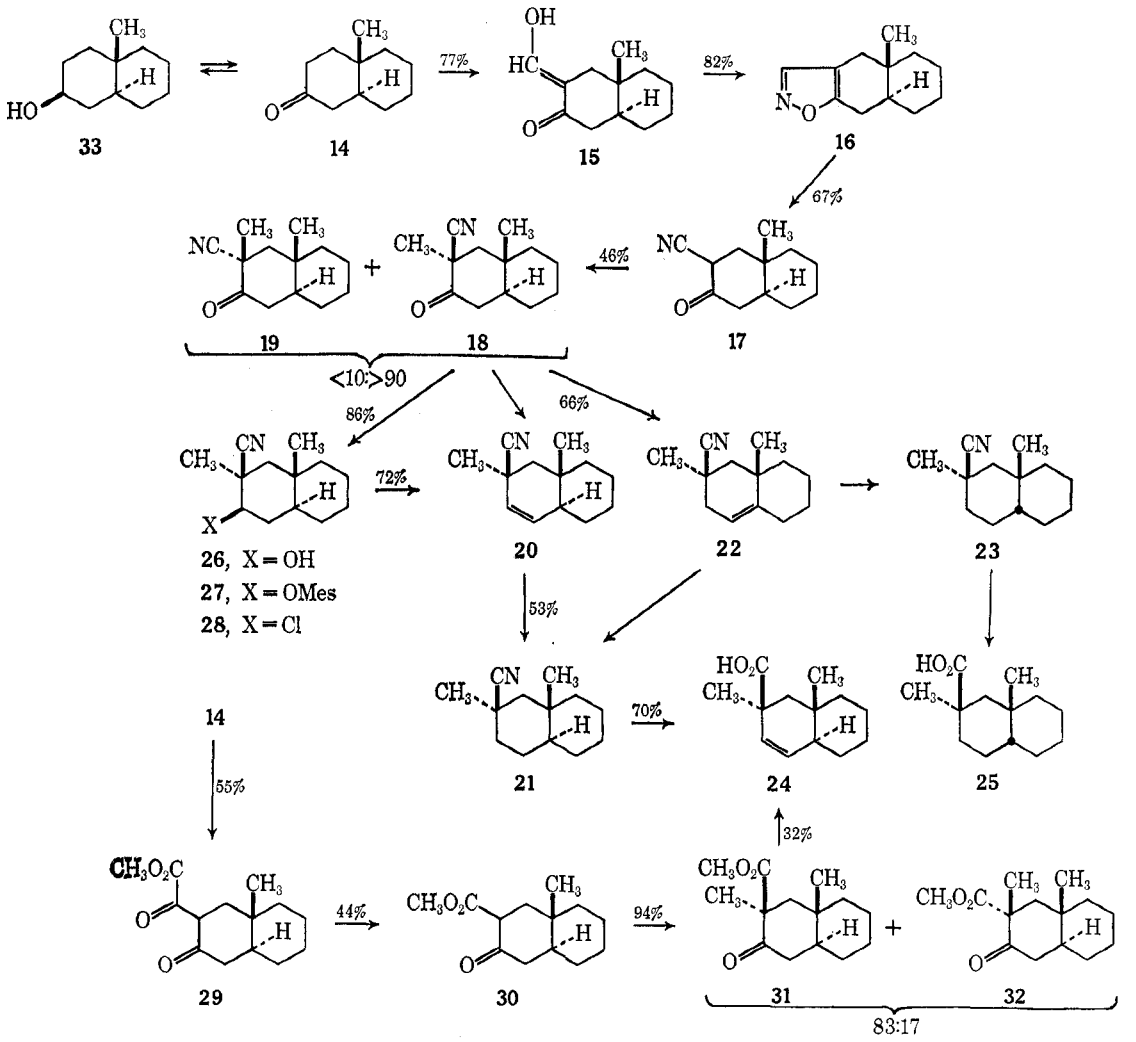


TABLE I
NMR CHEMICAL SHIFTS OF METHYL SUBSTITUENTS (δ, PPM)

Compd	α-Methyl	Angular methyl
7	1.28	...
8	1.66	...
10	1.48	...
13	1.28	...
14	...	1.06
17	...	1.13
18	1.45	1.38
20	1.45	1.08
21	1.34	1.15
22	1.62	1.03
23	1.30	0.96
24	1.19	0.78
25	1.57	1.01
26	1.46	1.17
27	1.49	1.18
28	1.52	1.18
30	...	0.83
31	1.28	0.95
32	1.37	0.82
33	...	0.83

which are possible in systems **1** and **2**, the corresponding 3-substituted 2-decalones were studied. Condensation of *trans*-10-methyl-2-decalone (**14**) with methyl formate gave the formyl ketone **15**, which was converted to the isoxazole **16** with hydroxylamine. Sodium methoxide induced rearrangement led to the β-keto nitrile **17**. On methylation of the lithium enolate of this compound, a minimum ratio of 90:10 of α (**18**) to β (**19**) alkylation products was produced, with the major epimer showing the expected lower vpc retention time. An nmr spectrum of this compound indicated deshielding of the angular 10-methyl group by the axial nitrile substituent. Clemmensen reduction of the β-keto nitrile **18** led to a mixture of three products. In addition to the expected olefin **20** and saturated nitrile **21**, the trisubstituted double bond isomer *22* was formed as the major product in the hot, acidic reaction medium. Its structure was assigned by comparison of its C-3 and C-10 nmr methyl singlets with those found in compounds **20** and **21**, obtained in pure form by an alternative route (see below). Catalytic reduction of the Clemmensen product mixture gave the saturated nitriles **21** and **23**, with the former predominating. On alkaline hydrolysis of the nitriles, a mixture of *trans*- (**24**) and *cis*- (**25**) decalin acids was formed.

Alternatively, the β-keto nitrile **18** was reduced with sodium borohydride to give an alcohol **26**, which was converted to its methanesulfonate **27** by a reaction with sulfene. When this derivative was heated with lithium carbonate and lithium chloride in dimethylformamide, the olefin **20** was formed, together with a small amount of the chloro compound **28**. Reduction of the olefin **20** to the saturated nitrile **21** and hydrolysis gave the acid **24**.

The parallel β-keto ester series was obtained by condensation of dimethyl oxalate with *trans*-10-methyl-

2-decalone, which led to the oxalyl ketone **29**. Decarbonylation to the β-keto ester **30** and methylation of its lithium salt gave an 83:17 ratio of α (**31**) to β (**32**) alkylation products. Stereochemical assignments to the epimers were based on a correlation with the nitrile series at the carboxylic acid **24**, obtained by Clemmensen reduction and hydrolysis. In contrast to the reduction of the β-keto nitriles **18** and **8**, Clemmensen reduction of the β-keto esters **31**, **32**, and **10** gave little, if any, olefinic products. Small amounts of lactones were seen in both series (ir 1770 cm^{-1}).

Deshielding of the 10-methyl group by an axial 3-β-carbomethoxy substituent[3] was not observed in the nmr spectrum of **31** relative to the epimer **32** (but an upfield shift relative to the decalone **14** was found). The relative vpc retention times expected for axial and equatorial β-keto esters were also reversed in the epimers **31** and **32**. A boat or twist conformation is thus indicated for the α-methylated keto ester ring in contrast to the chair conformation found in the α-methylated keto nitrile ring of these decalones.

The described methylation results suggest a transition state for β-keto ester and β-keto nitrile alkylations in which the geometry of products, rather than that of the enolate,[4] determines the course of the reaction (preferred chair–axial rather than boat or twist alkylation in unhindered enolates and the reverse in 1,3-axially shielded cases). While somewhat more "axial" methylation was found with the decalone 3-ester **30** than with the 3-nitrile **17**, its predominance in the corresponding 1-esters **1** and **2** may be ascribed to the greatly decreased acidity (increased enolate reactivity) of those systems, which is caused by *peri* interaction with an adjacent ring substituent.

Experimental Section

All melting points are corrected. All nmr spectra were taken on a Varian A-60 instrument as $CDCl_3$ solutions, with an internal tetramethylsilane reference.

2-Cyano-4-*t*-butylcyclohexanone (6).—A mixture of 15.5 g (0.10 mol) of 4-*t*-butylcyclohexanone, 30 ml (0.49 mol) of methyl formate, 15.0 g (0.23 mol) of sodium methoxide, and 100 ml of dry benzene was prepared with cooling in ice and stirred at 25° for 20 hr under nitrogen. The solidified reaction mixture was dissolved in ice–water and extracted with 100 ml of ether. The organic phase was extracted with five 30-ml portions of ice–3% sodium hydroxide, and the combined aqueous portions were acidified with concentrated hydrochloric acid and extracted with five 50-ml portions of ether. Concentration under vacuum gave 13 g of crude, crystalline formyl ketone **4**, which was recrystallized from petroleum ether (bp 30–60°) to give 11.1 g, mp 53–55°; uv λ_{max}^{MeOH} 285 mμ. A solution of 10.5 g (0.58 mol) of the formyl ketone in 60 ml of dry acetic acid and 4.8 g (0.69 mol) of hydroxylamine hydrochloride were refluxed for 4 hr under nitrogen. The cooled reaction mixture was poured into water, made basic with sodium hydroxide, and extracted with five 50-ml portions of dichloromethane. The combined extracts were washed with dilute sodium hydroxide solution, concentrated under vacuum, and distilled at 100–115° (0.05 mm) to give 8.4 g of the oily isoxazole **5**, uv λ_{max}^{MeOH} 240 mμ. A mixture of 1.3 g (0.57 g-atom) of sodium in 55 ml of methanol and 8.4 g (0.47 mol) of the isoxazole in 80 ml of benzene was stirred under nitrogen for 90 min, poured into ice–water, and extracted with eight 50-ml portions of ice–3% sodium hydroxide solution. The combined extracts were acidified with concentrated hydrochloric acid and extracted with dichloromethane. Concentration under vacuum and crystallization from benzene and petroleum ether gave 6.1 g of product, mp 73–75°; with mp 85–86° after recrystallization from petroleum ether and sublimation at 85° (0.001 mm).

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.78; H, 9.58; N, 8.04.

2-Cyano-*cis*-2-methyl-4-*t*-butylcyclohexanone (7) and 2-Cyano-*trans*-2-methyl-4-*t*-butylcyclohexanone (8).—A mixture of 3.0 g (16.7 mmol) of the α-cyano ketone **6** and 1.5 g (65.3 mmol) of lithium amide was refluxed for 6 hr in 100 ml of dry benzene, under nitrogen and cooled, and a solution of 18 ml (55 mmol) of methyl iodide in 20 ml of benzene and 6 ml of dimethylformamide was added to the enolate suspension. The reaction mixture was stirred at room temperature for 14 hr, poured into iced, dilute sodium hydroxide solution, and extracted with seven 50-ml portions of ether. The combined extracts were washed once with saturated brine, dried over magnesium sulfate, concentrated under vacuum, and flash-distilled at 120° (0.001 mm). (Acidification of the aqueous solution and analogous extraction and distillation gave 1.3 g of acidic material.) The 1.4 g of neutral methylation products showed a 77:23 ratio of axial **8** to equatorial **7** methyl epimer by vpc, using an F & M Model 700 flame ionization instrument with a 10% ethylene glycol on Diatoport S column at 230° and a flow rate of 25.8 ml/min. The ratio of retention times was 1:3 for **7**:**8**. Equivalent results were obtained with an Aerograph Model A-90-P thermal conductivity instrument with a 20% silicone Dow 11 on firebrick column at 220° and a flow rate of 1 ml/sec. The assignment of vpc peaks was based on enrichment with pure samples of the two epimers. The same ratio of epimers was seen in nmr spectra of the total methylation product, which showed δ 1.66 (s, axial methyl for **8**), 1.28 (s, equatorial methyl for **7**), 0.93 (s, *t*-butyl), and 1.43 (small s). Crystallization of the neutral methylation products from petroleum ether gave 0.52 g of the less soluble epimer **8**, mp 78–79°, recrystallized to mp 80–81°.

Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.61; H, 10.00; N, 7.39.

From the mother liquor, 0.75 g of a mixture of **7** and **8**, with mp 40–55°, was isolated. Separation by tlc on silica gel, with benzene, gave the faster moving epimer **7**, mp 53–54°, which distilled at 90° (0.001 mm).

Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.42; H, 9.78; N, 7.11.

A methylation of 0.10 g (0.56 mmol) of the keto nitrile **6** with 0.055 g (2.4 mmol) of lithium amide in 15 ml of benzene and 3 ml (9.3 mmol) of methyl iodide in 1 ml of dimethylformamide and 5 ml of benzene gave 0.090 g of neutral, distilled alkylation product, from which 0.070 g of crude axial methyl epimer **8**, mp 74–75°, could be crystallized.

Methylation of 2-Carbomethoxy-4-*t*-butylcyclohexanone (12).—Condensation of 4-*t*-butylcyclohexanone with dimethyl carbonate and sodium hydride in benzene[5] gave an 80% yield of the β-keto ester **12**, bp 75° (0.001 mm).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.97; H, 9.48.

A mixture of 0.60 g (2.8 mmol) of the β-keto ester **12**, 0.30 g (13.0 mmol) of lithium amide, and 40 ml of dry benzene was stirred for 6 hr at 23°; 14 ml (43 mmol) of methyl iodide and 1 ml of dimethylformamide in 10 ml of dry benzene were added, and stirring was continued for 18 hr. The reaction mixture was poured into dilute sodium hydroxide solution and extracted with seven 20-ml portions of ether. The extracts were washed with saturated brine, concentrated under vacuum, and distilled at 100° (0.001 mm) to give 0.62 g of neutral methylation products. Vpc analysis, under conditions described for the β-keto nitrile methylation (except for a column temperature of 200°), showed an 83:17 ratio of axial (**10**) to equatorial (**13**) methyl epimer with a 1.6:1 ratio of retention times. The same abundance ratio was found by nmr spectra of the alkylation mixture, which showed δ 1.48 (s, axial methyl), 1.28 (s, equatorial methyl), and 0.93 (s, *t*-butyl). Crystallization of the major epimer **10** from petroleum ether gave 420 mg, mp 61–63°, recrystallized to mp 67–68°.

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.24; H, 9.95.

***trans*-1-Methyl-3-*t*-butylcyclohexanecarboxylic Acid (11). A.**—A mixture of 160 mg of the β-keto ester **10**, 12 g of amalgamated zinc (prepared from 12 g of mossy zinc, 0.8 ml of hydrochloric

(3) E. Wenkert, A. Afonso, P. Beak, R. W. J. Carney, P. W. Jeffs, and J. D. McChesney, *J. Org. Chem.*, **30**, 713 (1965).

(4) H. O. House, B. A. Tefertiller, and H. D. Olmstead *ibid.*, **33**, 935 (1968).

(5) A. P. Krapcho, J. Diamanti, C. Cayen, and R. Bingham, *Org. Syn.*, **47**, 20 (1967).

acid in 12 ml of water, and 1.2 g of mercuric chloride, shaken for 15 min and thoroughly washed with water), and 24 ml of 15% hydrochloric acid was refluxed for 3 days, with addition of 1 ml of concentrated hydrochloric acid every 6–10 hr. The cooled reaction mixture was extracted with five 30-ml portions of dichloromethane and the extracts were concentrated and distilled to a maximum of 130° (0.003 mm). The mixture of crystals and oil, 98 mg with ir ν_{max} 1730 (ester C=O) and 1700 cm^{-1} (acid C=O), was combined with 0.05 g of 10% palladium on charcoal and 20 ml of ether and stirred under a hydrogen atmosphere for 1 hr. After filtration and concentration under vacuum, 10 ml of methanol and 2 g of potassium hydroxide were added and the mixture was heated in a steel bomb at 165° for 24 hr. The hydrolysis mixture was poured into water, extracted once with ether, acidified, and extracted with dichloromethane. Concentration of the acidic extract under vacuum, recrystallization of the residue from aqueous methanol, then from petroleum ether, and sublimation at 95° (0.003 mm) gave the product **11**, mp 110–111°.

Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.40; H, 11.01.

B.—Clemmensen reduction of 50 mg of the β-ketonitrile **8**, according to the procedure above, gave 38 mg of an olefinic nitrile product, showing two components by vpc. Hydrogenation and hydrolysis gave 27 mg of crude carboxylic acid, which was crystallized and sublimed to a sample with mp 110–111°, and showed no depression of a mixture melting point with the product obtained above.

Correlation of β-Keto Ester 10 and β-Ketonitrile 8 through Isoxazole 9.—To 10-ml methanolic solutions of 144 mg (0.75 mmol) of the β-keto nitrile **8** and 169 mg (0.75 mmol) of the β-keto ester **10**, 105 mg (1.5 mmol) of hydroxylamine hydrochloride was added. The reaction mixtures were warmed for 5 min and stored at 24° for 48 hr, and 3 ml of water was added. After 18 hr at 24°, 145 mg of isoxazolone **9** was filtered from each reaction mixture and recrystallized from petroleum ether to mp and mmp 77–78°. The ir spectra with ν_{max} 1780 and 1610 cm^{-1} were identical.

Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.86; H, 9.15; N, 6.69. Found: C, 69.07; H, 9.10; N, 6.73.

3-Cyano-4aβ-methyl-1,2,3,4,4a,5,6,7,8a-α-decahydro-2-naphthalene (17).—A mixture of 1.67 g (10.0 mmol) of *trans*-10-methyldecal-2-one,[6,7] 6.0 g (0.10 mol) of methyl formate, 1.70 g (31 mmol) of sodium methoxide, and 25 ml of dry benzene was stirred under nitrogen for 48 hr at 25°. The reaction mixture was poured into ice–3% potassium hydroxide and extracted with 50 ml of ether. Extraction of the ether with several portions of cold 3% potassium hydroxide, acidification of the combined aqueous portions, extraction with dichloromethane, concentration under vacuum, and recrystallization from petroleum ether gave 1.5 g (7.7 mmol) of the 3-formyl ketone **15**, mp 73–75°. This product was refluxed for 4 hr with 0.90 g (12.7 mmol) of hydroxylamine hydrochloride in 20 ml of dry acetic acid. The cooled solution was poured into ice–water, made strongly basic with sodium hydroxide, and extracted with dichloromethane. Concentration under vacuum, distillation at 110–120° (0.001 mm), and crystallization from aqueous methanol gave 1.2 g of isoxazole **16**, mp 60–61°.

Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.62; H, 8.96; N, 7.43.

A solution of 0.30 g (13 mg-atoms) of sodium in 20 ml of methanol and 1.2 g (6.3 mmol) of the isoxazole **16** in 15 ml of dry benzene was stirred for 65 min under nitrogen at 23°. The reaction mixture was poured into cold water and extracted with 50 ml of ether, and the ether was extracted with eight 25-ml portions of 3% sodium hydroxide. Acidification, extraction with dichloromethane, concentration under vacuum, and crystallization from benzene–petroleum ether gave 0.80 g of the β-keto nitrile **17**, mp 96–97°; nmr δ 1.13 for 4a-methyl singlet.

Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.12; H, 8.75; N, 7.60.

3-Cyano-3α-4aβ-dimethyl-1,2,3,4,4a,5,6,7,8a-α-decahydro-2-naphthalene (18).—A mixture of 0.20 g (1.05 mmol) of the β-keto nitrile **17**, 0.116 g (5.05 mmol) of lithium amide, and 30 ml of dry benzene was refluxed under nitrogen for 6 hr and cooled, and a solution of 6 ml (18 mmol) of methyl iodide in 10 ml of benzene and 2 ml of dimethylformamide was added. The reaction mixture was stirred at 23° for 16 hr, poured into cold, dilute sodium hydroxide, and extracted with ether, and the extracts were washed with saturated brine, concentrated under vacuum, and distilled to a maximum of 135° (0.001 mm). The 0.121 g of distillate showed a vpc 90:10 ratio of α- (**18**) to β- (**19**) methylation products with a retention ratio of 1.0:1.1, under conditions described for the β-keto nitrile **8**. An nmr spectrum showed the 4aβ- and 3α-methyl singlets at δ 1.38 and 1.45, and a smaller singlet at δ 1.26. Crystallization from aqueous methanol, then from petroleum ether at −20°, and sublimation at 65° (0.001 mm) gave 60 mg of the β-keto nitrile **18**, mp 73–75°, lacking the nmr δ 1.26 singlet.

Anal. Calcd for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82. Found: C, 76.24; H, 9.15; N. 7.10.

The initial alkylation product was contaminated by about 20 mg of a polar compound, which sublimed at 100° (0.001 mm), showed ir ν_{max} 3400, 3300, 3200, 2180, 1630, and 1600 cm^{-1}, and is assumed to be the vinylogous cyanamide derived from reaction of ammonia with the starting β-keto nitrile **17**. An alkylation with lithium hydride gave a larger amount of neutral alkylation product, but purification by recrystallization was more difficult and thus the same yield of β-keto nitrile **18** was produced.

3-Carbomethoxy-4aβ-methyl-1,2,3,4,4a,5,6,7,8aα-decahydro-2-naphthalone (30).—A mixture of 1.67 g (10.0 mmol) of *trans*-10-methyldecal-2-one,[6,7] 7.2 g (61 mmol) of dimethyl oxalate, 1.70 g (31 mmol) of sodium methoxide, and 50 ml of dry benzene was stirred under nitrogen in an ice bath for 1 hr and then at 24° for 28 hr. The reaction mixture was poured into ice–3% sodium hydroxide and extracted with ether, and the organic phase was extracted with seven 25-ml portions of 3% sodium hydroxide. Acidification of the combined aqueous solution, extraction with dichloromethane, and concentration under vacuum gave 1.4 g of oily oxalyl derivative **29**, which was heated for 15 min with 4 g of powdered soft glass at 220–250°. Flash distillation at 190° (0.05 mm) gave 0.55 g of crude β-keto ester **30**, which was purified by tlc on silica gel with 1:1 benzene–petroleum ether and redistilled at 80° (0.001 mm): nmr δ 0.83 (s, 4aβ-methyl); uv $\lambda_{max}^{0.1\ N\ KOH\ in\ methanol}$ 285 mμ (ε 11,400).

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.90; H, 9.10.

Methylation of 3-Carbomethoxy-4aβ-methyl-1,2,3,4,4a,5,6,7,-8aα-decahydro-2-naphthalone (30).—A solution of 225 mg (1.0 mmol) of the β-keto ester **30** in 15 ml of dry benzene was stirred under nitrogen with 0.10 g (4.3 mmol) of lithium amide at 23°. With cooling in ice, 6 ml (18 mmol) of methyl iodide in 10 ml of dry benzene and 0.7 ml of dimethylformamide were added and the mixture was stirred at 23° for 20 hr. Addition of cold, dilute sodium hydroxide solution, extraction with dichloromethane, concentration under vacuum, and distillation at 100° (0.001 mm) gave 0.225 g of methylation products. Vpc, under conditions described for the β-keto nitrile **8**, showed an 83:17 ratio of α (**31**) to β (**32**) methylation products with a ratio of retention times of 1.2:1. Nmr spectra showed the major alkylation product with δ 1.28 (s, 3α-methyl) and 0.95 (s, 4aβ-methyl) and the minor epimer with δ 1.37 (s, 3β-methyl), 0.82 (s, 4aβ-methyl), and 3.76 (s, methyl ester). The ratio of signals remained constant in a temperature range of 40 to −60°, but a downfield shift of 1 cps at δ 0.82 and 0.95, 2.5 cps at δ 1.28 and 1.37, and 6 cps at δ 3.76 was found at −40°, with 1-cps splitting of the methyl ester singlet.

3β-Carboxy-3α,4aβ-dimethyl-1,2,3,4,4a,5,6,7,8aα-decahydronaphthalene (24). A.—A mixture of 0.27 g of the methylated β-keto ester **30** (83% **31** and 17% **32**) and 24 g of amalgamated zinc (24 g of mossy zinc, 1.6 ml of hydrochloric acid, 24 ml of water, and 2.4 g of mercuric chloride, shaken 15 min and washed with water) in 50 ml of 15% hydrochloric acid was refluxed for 3 days with addition of 2 ml of concentrated hydrochloric acid every 6–10 hr. The reaction mixture was extracted with dichloromethane, and the extracts were concentrated under vacuum and heated with 2 g of potassium hydroxide and 10 ml of methanol at 155° for 24 hr in a steel bomb. Addition of water, extraction with ether, reextraction of the ether with dilute sodium hydroxide solution, acidification of the combined aqueous solutions, extraction with dichloromethane, and concentration gave 0.1 g of crude acidic product. This was dissolved in 5 ml of ethanol, 20 mg of 10% palladium on charcoal was added, and the mixture was stirred under hydrogen for 2 hr. Filtration, addition of water, extraction with dichloromethane, concentration, and distillation at 105° (0.001 mm) gave 76 mg of gummy crys-

(6) N. C. Ross and R. Levine, *J. Org. Chem.*, **29**, 2341 (1964).
(7) B. Gaspert, T. G. Halsall, and D. Willis, *J. Chem. Soc.*, 624 (1958).

talline material with nmr δ 1.19 (s, 3α-methyl) and 0.78 (s, 4aβ-methyl). The minor epimeric product could not be detected.

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.04; H, 10.30.

B.—A solution of 0.10 g (0.49 mmol) of the β-keto nitrile **18** and 0.10 g (2.6 mmol) of sodium borohydride in 10 ml of ethanol was stored at 22° for 20 hr, poured into water, made basic with sodium hydroxide and then acidic with hydrochloric acid, and extracted with dichloromethane. Concentration and distillation at 90–110° (0.3 mm) gave 87 mg of material, lacking ir carbonyl absorption and consisting of a small amount of oil and predominantly of a crystalline product **26**, mp 133–134°; nmr δ 1.46 (s, 3α-methyl) and 1.17 (s, 4aβ-methyl). The reduction product was dissolved in 10 ml of dry benzene and 15 drops of dry triethylamine. A solution of 10 drops of methanesulfonyl chloride in 10 ml of dry benzene was added, under nitrogen, during 30 min. After 9 hr the mixture was poured into water and extracted with dichloromethane, and the extracts were washed with dilute hydrochloric acid and sodium bicarbonate solution. Concentration under vacuum gave a mesylate with nmr δ 3.12 (s, mesylate methyl), 1.49 (s, 3α-methyl), and 1.18 (s, 4aβ-methyl). A solution of the mesylate in 5 ml of dry dimethylformamide, 50 mg of lithium carbonate, and 50 mg of lithium chloride was heated at 210–220° for 4 hr in a sealed tube. The reaction mixture was poured into water and extracted with ether, and the extracts were concentrated and distilled to a maximum of 120° (0.3 mm). The nmr showed δ 5.56 (olefinic protons), 1.45 and 1.08 (s, 3α- and 4aβ-methyl in **20**), and 1.52 and 1.18 [s, 3α- and 4aβ-methyl in **28** (minor component)]. The distillate, taken up in 5 ml of petroleum ether, gave 15 mg of the chloronitrile **28**, mp 164–165°, which sublimed at 120° (0.3 mm).

Anal. Calcd for $C_{18}H_{20}NCl$: C, 69.14; H, 8.93; N. 6.21. Found: C, 69.36; H, 9.06; N, 6.17.

The petroleum ether soluble portion, redistilled at 90° (0.3 mm), gave 57 mg of olefinic nitrile **20**, which was hydrogenated in 5 ml of ethanol with 50 mg of 10% palladium on charcoal during 4 hr. Filtration, addition of water, extraction with dichloromethane, concentration, and distillation at 90° (0.3 mm) gave 44 mg of the saturated nitrile **21**, mp *ca.* 30°, nmr δ 1.34 (s, 3α-methyl) and 1.15 (s, 4aβ-methyl). The nitrile **21** was hydrolyzed to the acid **24** by heating in a steel bomb with 2 g of potassium hydroxide and 10 ml of methanol for 20 hr at 170° and 24 hr at 210°. The reaction mixture was poured into water and extracted with ether, the ether was extracted with dilute sodium hydroxide, and the combined aqueous portions were acidified and extracted with dichloromethane. Concentration and distillation at 105° (0.001 mm) gave 34 mg of acid **24**, mp 81–83°. The nmr and ir spectra of this product were identical with those of the sample obtained from the ester **31**. Vpc on an SE 30 column at 240 and 200° showed identical retention times of the samples.

C.—Clemmensen reduction of 66 mg of the β-keto nitrile **18**, according to the procedure described for the β-keto ester **31**, gave 40 mg of an olefinic nitrile with the expected methyl singlets at δ 1.45 and 1.08 for **20** as well as major singlets at δ 1.62 and 1.03 ascribed to the isomeric olefin **22** and minor singlets for the dihydro compound **21** at δ 1.34 and 1.15. Catalytic reduction, as described above, gave primarily the nitrile **21** with δ 1.34 and 1.15 singlets and the *cis*-decalin **23** with δ 1.30 and 0.96 as minor singlets. Hydrolysis gave a mixture of decalin acids with nmr δ 1.19 and 0.78 methyl singlets for **24** and δ 1.57 and 1.01 for **25**.

Registry No.—**4**, 22252-96-6; **5**, 22252-97-7; **6**, 22249-29-2; **7**, 22249-30-5; **8**, 22249-31-6; **9**, 22249-32-7; **10**, 22249-33-8; **11**, 22249-34-9; **12**, 22256-09-3; **15**, 22256-10-6; **16**, 22256-11-7; **17**, 22256-12-8; **18**, 22256-13-9; **24**, 22256-14-0; **26**, 22256-15-1; **28**, 22256-16-2; **30**, 22256-17-3.

Acknowledgment.—This work was supported by funds from the National Institutes of Health, Research Grant GM 09381-06. We thank Professor Ernest Wenkert for informing us of parallel results in the methylation of a tricyclic β-keto ester.

Photochemical Routes to Aporphines. New Syntheses of Nuciferine and Glaucine[1]

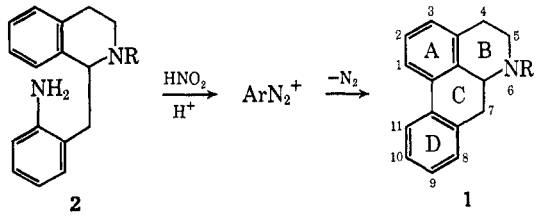
M. P. CAVA,[2] M. J. MITCHELL, S. C. HAVLICEK, A. LINDERT, AND R. J. SPANGLER

Department of Chemistry, Wayne State University, Detroit, Michigan 48202

Received May 23, 1969

The stilbene–phenanthrene photocyclization reaction has been employed as the key step in new synthetic routes to the aporphine alkaloids nuciferine (**4**) and glaucine (**3**). Thus, oxidative irradiation of 1-benzylidene-2-carbethoxy-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**6**) or 1-veratrylidene-2-carbethoxy-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**8**) yields, respectively, N-carbethoxy-6a,7-dehydronornuciferine (**13**) or N-carbethoxy-6a,7-dehydronorglaucine (**14**). An efficient two-step reduction procedure is described for the conversion of the photolysis products **13** and **14** into nuciferine and glaucine. A cleaner variation of this aporphine synthesis consists in the *nonoxidative* formation of urethans **13** and **14** by the irradiation of the 2′-chloro derivative (**7**) of **6** and the 6′-bromo derivative (**9**) of **8**, respectively. The latter transformations represent the first examples of photochemical syntheses of phenanthrenes by the loss of hydrogen chloride or hydrogen bromide from a simple stilbene system.

The aporphines comprise a group of about 90 alkaloids, all of which contain the tetracyclic ring system shown in structure **1**.[3] Despite continuing interest in both the chemistry and pharmacology of these compounds, all aporphines synthesized up to 1966 were obtained only from the corresponding 1-(2′-aminobenzyl)-1,2,3,4-tetrahydroisoquinolines (*e.g.*, **2**) by way



2 **1**

of a Pschorr-type cyclization, sometimes in quite low yield.[4] Gadamer's synthesis of glaucine (**3**) in 1911 was the first successful application of the reaction.[5]

(1) A portion of this work (the synthesis of **4** from **6**) was reported as a preliminary communication: M. P. Cava, S. C. Havlicek, A. Lindert, and R. J. Spangler, *Tetrahedron Lett.*, 2937 (1966).

(2) To whom all inquiries should be addressed: Department of Chemistry, University of Pennsylvania, Philadelphia, Pa. 19104.

(3) For recent reviews of the aporphine alkaloids, see (a) M. Shamma in "The Alkaloids," Vol. 7, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1967, p 1; (b) M. P. Cava and A. Venkateswarlu, *Ann. Rep. Med. Chem.*, 331 (1968).

(4) For a brief review of the synthesis of aporphines up to 1960, see A. R. Pinder in "Chemistry of Carbon Compounds," Vol. IV, E. H. Rodd, Ed., Elsevier Publishing Co., New York, N. Y., 1960, Chapter 25.

(5) J. Gadamer, *Arch. Pharm.* (Weinheim), **249**, 680 (1911).