VOLUME 39 NOVEMBER 1, 1974 / NUMBER 22 JOCEAH

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Published biweekly by the American Chemical Society at 20th and Northampton Sts., Easton, Pa. 18042. Second-class postage paid at Washington, D. C., and at additional mailing offices.

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JOCEAH(22) 3187-3308(1974)
ISSN 0022-3263

# THE JOURNAL OF Organic Chemistry®

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## NOTES



## COMMUNICATIONS

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* In papers with more than one author, the asterisk indicates the name of the author to whom inquiries about the paper should be addressed.

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THE JOURNAL OF Organic Chemistry®

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# Diaziridines. III. Reactions of Some 1-Alkyl- and 1,1-Dialkyl-1*H*-diazirino[1,2-*b*]phthalazine-3,8-diones

Harold W. Heine,* Robert Henrie, II, Larry Heitz, and Sudarsana Rao Kovvali

*Department of Chemistry, Bucknell University, Lewisburg, Pennsylvania 17837*

*Received May 21, 1974*

1,1-Dialkyl-1*H*-diazirino[1,2-*b*]phthalazine-3,8-diones isomerize in boiling toluene into 2-(1-alken-1-yl)-4-hydroxy-1(2*H*)-phthalazinones and react with enamines and ynamines to yield derivatives of pyrazolo[1,2-*b*]- and indazolo[1,2-*b*]phthalazinediones.

The thermal conversions of 1-(2,4-dinitrophenyl)-3,3-dialkyl- and 1-(2,4-dinitrophenyl)-2,3,3-trialkyldiaziridines into 2,4-dinitrophenylhydrazones and 2-alkyl-6-nitrobenzotriazole 1-oxides, respectively, and the addition of 3,3-dialkyl- and 1,3,3-trialkyldiaziridines to electrophilic acetylenes have been the subjects of earlier reports in this series.[1,2] In the present paper the synthesis and reactions of 1-alkyl- and 1,1-dialkyl-1*H*-diazirino[1,2-*b*]phthalazine-3,8-diones (**1–7**) and the related systems **8** and **9** are described. These versatile compounds are thermally isomerized into 2-(1-alken-1-yl)-4-hydroxy-1-(2*H*)phthalazinones and react with ynamines and enamines to give pyrazolo[1,2-*b*]- and indazolo[1,2-*b*]phthalazinediones. Reactions with nitrones are presented in the following paper.

## Results

The 1,1-dialkyl-1*H*-diazirino[1,2-*b*]phthalazine-3,8-diones (**1–5**) were prepared by the addition of phthaloyl chloride to ethereal solutions of 3,3-dialkyldiaziridines containing triethylamine (Scheme I, Table I). The 1-alkyl-1*H*-diazirino[1,2-*b*]phthalazine-3,8-diones **6** and **7** were synthesized by generating the 3-alkyldiaziridines *in situ* from the corresponding chloral adducts, $RCHNHNCH(OH)CHCCl_3$, in the presence of o-phthaloyl chloride. Compounds **8** and **9** were made in much the same manner as **1–5** by employing the appropriate diacid chloride and 3,3-pentamethylenediaziridine.

**Scheme I**

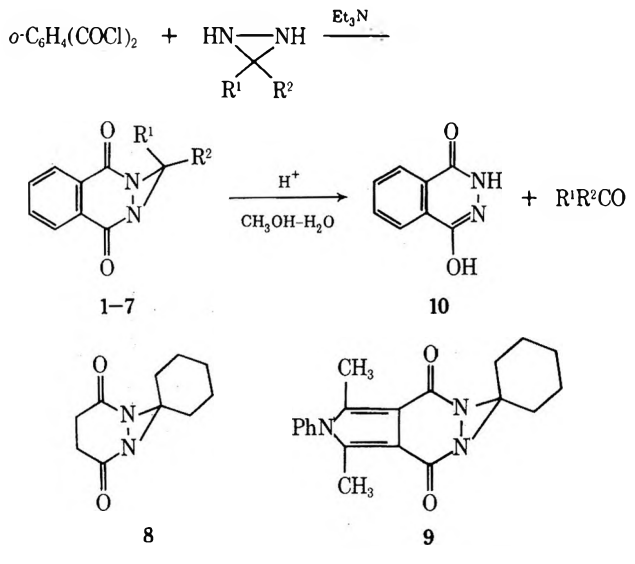
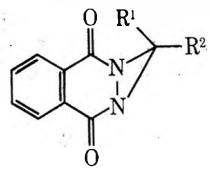



**Table I**
**1-Alkyl- and 1,1-Dialkyl-1*H*-diazirino[1,2-*b*]phthalazine-3,8-diones[a]**



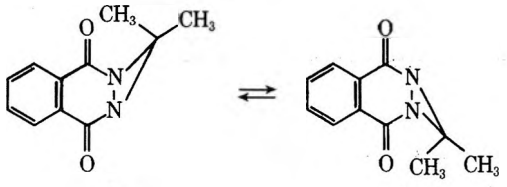
| Compd[b] | $R^1$ | $R^2$ | Yield,[c] % | Mp, °C |
|---|---|---|---|---|
| 1 | Me | Me | 58 | 98–99 |
| 2 | Et | Et | 35 | 70–71 |
| 3 | *n*-Pr | *n*-Pr | 47 | 108–109 |
| 4 | $-(CH_2)_5-$ | | 75 | 110–111 |
| 5 | Me | Et | 71 | 76–77 |
| 6 | H | *n*-Pr | 61 | 71–72.5 |
| 7 | H | *t*-Bu | 51 | 110–111 |

[a] Satisfactory analytical data for C, H, and N were obtained for all compounds listed in the table. Ed. [b] Compounds 1–7 were recrystallized from cyclohexane. [c] Yields are reported on the basis of recrystallized products.

The structures of **1–9** were assigned on the basis of elemental analyses, nmr spectroscopy, and by the hydrolysis of **2**, **4**, and **7** into 4-hydroxy-1(2*H*)-phthalazinone (**10**) and the corresponding carbonyl compounds 3-pentanone, cyclohexanone, and pivalaldehyde, respectively (Scheme I). The nmr spectrum of 1,1-dimethyl-1*H*-diazirino[1,2-*b*]phthalazine-3,8-dione (**1**) taken in $C_6D_6$ shows two peaks at $\delta$ 1.45 and 1.25 for the two methyl groups on the diaziridinyl carbon. On heating to about 60° the two peaks coalesce to a broad singlet which on further heating to 75° becomes a sharp singlet at $\delta$ 1.55. If the temperature is lowered to 40° the two signals for the methyl groups reappear. The temperature variance of the nmr spectrum of **1** indicates inversions of the nitrogen atoms (Scheme II) and is of some interest, since the *N*-aroyl moieties are perforce cis to

each other. Most equilibration studies of diaziridines have been concerned with those substrates having the N substituents trans to each other.[3,4]

**Scheme II**

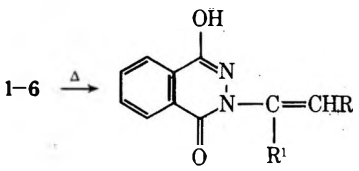


1 1

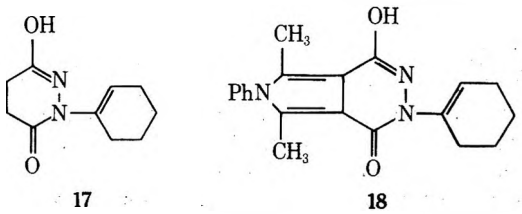
An examination of the nmr spectrum of 1-ethyl-1-methyl-1*H*-diazirino[1,2-*b*]phthalazine-3,8-dione (**5**) in $C_6D_6$ taken at several temperatures also indicated that inversions were taking place at the nitrogens. Thus at 0° two peaks were clearly observed for the methyl group but at 75° these signals became one sharp singlet and the ethyl group exhibited the sharp characteristic quartet–triplet splitting pattern.

Compounds **1–5** in refluxing toluene were converted into 2-(1-alken-1-yl)-4-hydroxyl-1(2*H*)-phthalazinones **11–16**, respectively (Scheme III). In the case of the thermolysis of **5** a 2:1 mixture of **15** and **16** was obtained. It was possible by fractional crystallization to obtain a sample of pure **15**. Thermolysis of **8** and **9** gave the cyclohexene derivatives **17** and **18**, respectively. Compound **9** isomerized with such ease that it was not possible to determine its melting point.

**Scheme III**



**11**, R = H; R¹ = $CH_3$
**12**, R = $CH_3$; R¹ = $C_2H_5$
**13**, R = $C_2H_5$; R¹ = $n$-$C_3H_7$
**14**, R, R¹ = $(CH_2)_4$
**15**, R = H; R¹ = $C_2H_5$
**16**, R = R¹ = $CH_3$
**19**, R = $C_2H_5$; R¹ = H



**17** **18**

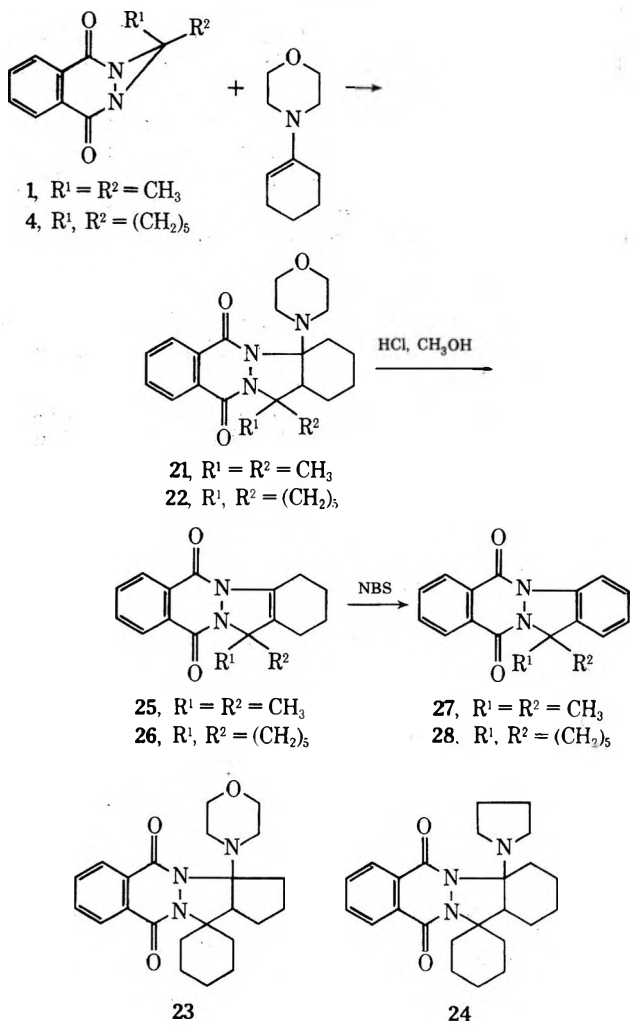
The structures of **11–16** followed from their nmr spectra and elemental analyses. Thus, in $CDCl_3$ the absorption peaks for the vinylic protons of **11–14** appeared at δ 5.32, 5.80, 5.80, and 6.04, respectively, and the absorption peaks for the OH proton appeared at δ 10.00, 10.20, 10.92, and 10.92. That the thermolysis of **5** gave a 2:1 mixture of **15** and **16** was clearly demonstrated by the nmr spectrum of the reaction products. The olefinic protons for **15** gave a broad singlet at δ 5.33 (2 H) and the ethyl group gave the characteristic quartet for the methylene group at δ 2.55 and a triplet for the methyl group at δ 1.14. The vinylic proton of **16** appeared as a quartet at δ 5.78, the methyl group adjacent to the methine hydrogen as a doublet at δ 1.88, and the remaining methyl group as a singlet at δ 2.08. The nmr spectra of **17** and **18** showed the same absorption pattern for the cyclohexenyl protons as **14**.

The assignment of the enamide structure to **12** is further supported by its hydrolysis into 3-pentanone and 4-hydroxy-1(2*H*)-phthalazinone (**10**) (Scheme III). Similarly, hydrolysis of **14** gave cyclohexanone and **10**.

Compounds **6** and **7** did not undergo thermolysis with ease. In the case of **6** reaction times of 7 hr in refluxing *o*-xylene gave ill-defined products from which a small quantity of the anticipated 2-(1-buten-1-yl)-4-hydroxy-1(2*H*)-phthalazinone (**19**) was isolated. However, high yields of **19** were obtained if **6** was refluxed in *o*-xylene containing some triethylamine hydrochloride (Scheme III). Compound **7** after many hours in refluxing o-xylene gave a material (**20**) which melted at 210–214°. This substance underwent acid hydrolysis to give **10** and pivalaldehyde. A mass spectrum showed a molecular ion at *m/e* 460 indicating a dimeric structure. The nmr spectrum of **20** did not show any signal in the olefinic region and the aliphatic protons appeared as a complex and broad multiplet extending from δ 0.3 to 1.4. No further work was attempted with this material nor do we feel confident, given the nmr spectrum, to assign a structure to the dimer at this time.

Refluxing the 1,1-dialkyl-1*H*-diazirino[1,2-*b*]phthalazine-3,8-diones **1** and **4** in benzene with equimolar quantities of the morpholine enamine of cyclohexanone yielded the adducts **21** and **22**, respectively (Scheme IV). Similar

**Scheme IV**



**1**, R¹ = R² = $CH_3$
**4**, R¹, R² = $(CH_2)_5$

**21**, R¹ = R² = $CH_3$
**22**, R¹, R² = $(CH_2)_5$

**25**, R¹ = R² = $CH_3$
**26**, R¹, R² = $(CH_2)_5$

**27**, R¹ = R² = $CH_3$
**28**, R¹, R² = $(CH_2)_5$

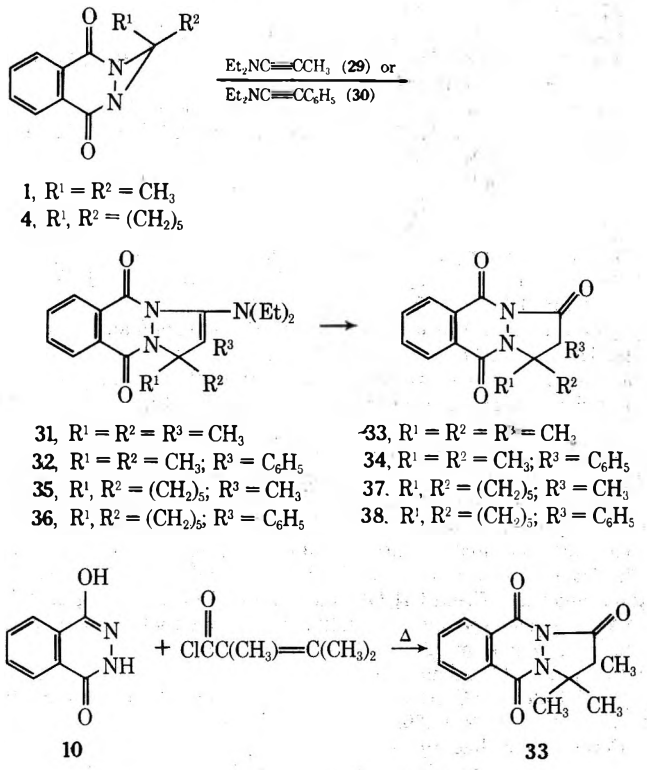
**23** **24**

adducts, namely, **23** and **24**, were formed when **4** was treated with 1-*N*-morpholino-1-cyclopentene and 1-*N*-pyrrolidino-1-cyclohexene (Scheme IV).

Upon heating in methanol containing a few drops of hydrochloric acid **21** and **22** eliminated morpholine and formed **25** and **26**. Aromatization of the cyclohexene ring of **25** and **26** was achieved by heating them with *N*-bromosuccinimide (Scheme IV).

When **1** and **4** were treated with 1-(*N,N*-diethylamino)propyne (**29**) or phenyl(*N,N*-diethylamino)acetylene (**30**) in refluxing toluene the enamines **31, 32, 35,** and **36** were obtained in good yields (Scheme V). The structures suggested for these products were in accord with their nmr spectra, mass spectra, and elemental analyses. Further evidence for structural assignments was gained by hydrolysis of **31, 32, 35,** and **36** to the 1*H*-pyrazolo[1,2-*b*]phthalazine-1,5,10-triones **33, 34, 37,** and **38,** respectively (Scheme V). Unambiguous proof of structure for **33** rested upon an alternate synthesis involving the reaction of 4-hydroxy-1(2*H*)-phthalazinone (**10**) with 2,3-dimethyl-2-butenoyl chloride in hot nitrobenzene (Scheme V). The preparation of 1*H*-pyrazolo[1,2-*b*]phthalazine-1,5,10-triones by treatment of **10** with $\alpha,\beta$-unsaturated acid chlorides has been described.[5]

**Scheme V**

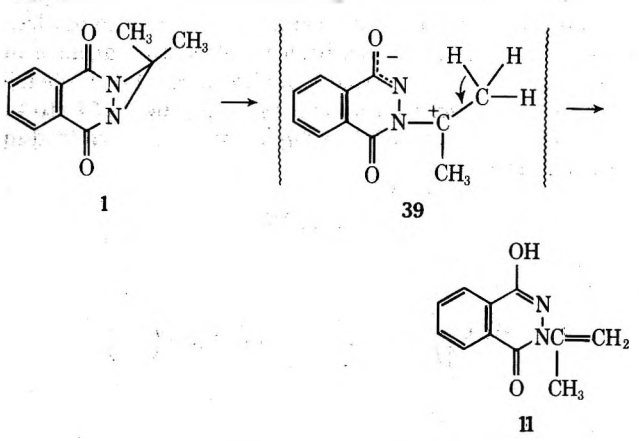



Significantly, compounds **1–5** did not react with electrophilic acetylenes such as diethylacetylene dicarboxylate and dibenzoylacetylene in boiling benzene. The products isolated in these instances were 2-(1-alken-1-yl)-4-hydroxy-1(2*H*)-phthalazinones and unreacted acetylene.

## Discussion

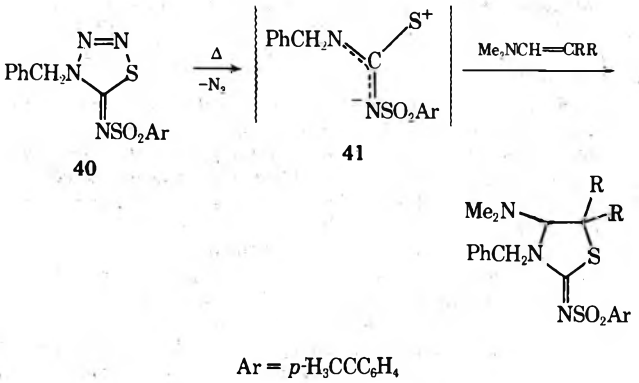
The formation of 2-(1-alken-1-yl)-4-hydroxy-1(2*H*)-phthalazinones when 1,1-dialkyl-1*H*-diazirino[1,2-*b*]-phthalazine-3,8-diones are heated (*e.g.*, **1** → **11**) and the formation of cycloadducts when **1** and **4** are heated with enamines and ynamines suggest that these reactions occur through the intermediacy of azomethine imines **39** (Scheme VI). The generation of a dipolar species such as **39** whose anionic charge is delocalized relative to its cationic charge may also explain why 1,1-dialkyl-1*H*-diazirino[1,2-*b*]phthalazine-3,8-diones react with electron-rich dipolarophiles and fail to react with the electron-poor dipolarophile

**Scheme VI**




diethylacetylene dicarboxylate. In this regard the reactions of the 1,1-dialkyl-1*H*-diazirino[1,2-*b*]phthalazine-3,8-diones appear similar to the thermolysis and reactions of 4-alkyl-5-sulfonylimino-$\Delta^2$-1,2,3,4-thiatriazoline (**40**). Compound **40** upon heating in benzene loses nitrogen to give the dipolar species **41** (also characterized by considerable delocalization of the negative charge relative to the cationic charge). The intermediate **41,** like **39,** undergoes reactions with enamines and ynamines (Scheme VII) and

**Scheme VII**

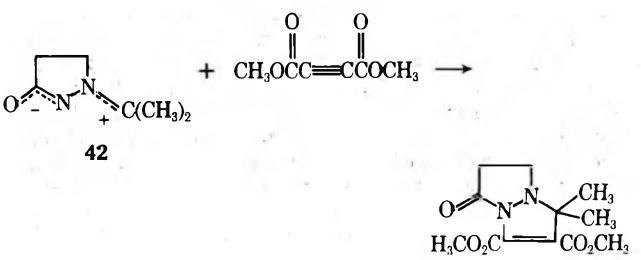



like **39** does not undergo cycloadditions with diethylacetylene dicarboxylate.[6] It is important to point out that the isolable azomethine imine **42** does form an adduct with dimethylacetylene dicarboxylate[7] (Scheme VIII). However, in this case the cationic charge is delocalized as extensively as the anionic charge.

The reaction of **1** and **4** with enamines and ynamines also may be accounted for by a nucleophilic attack on the diaziridinyl carbon by the electron-rich double bond or triple bond with ring opening followed by ring closure to a pyrazolo[1,2-*b*]- or indazolo[1,2-*b*]phthalazinedione.

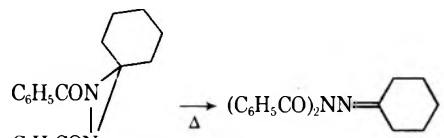
The facile acid-catalyzed isomerization of **6** to **19** is probably due to the protonation of the amido moiety of **6** followed by ring opening to a carbonium ion. Loss of a proton from the carbonium ion would give the product **19.**

**Scheme VIII**



1,2-Diaroyldiaziridines such as 1,2-dibenzoyl-3,3-pentamethylenediaziridine (**43**), compounds related to but less constrained than **1–7**, have been reported to rearrange in warm ethanol into β,β-diaroylhydrazones (**44**) (Scheme IX).[8] We have observed the same rearrangement of **43** to **44** in boiling benzene. Possibly a dipolar species is involved in this isomerization too.

**Scheme IX**




**43** **44**

## Experimental Section

**Materials.** 3,3-Dimethyl-, 3,3-diethyl-, 3,3-di-*n*-propyl-, and 3,3-pentamethylenediaziridine were prepared according to known procedures.[9,10] 3-Ethyl-3-methyldiaziridine was purchased from Aldrich.

**Syntheses of 1–5.** To a mixture of 10 mmol of a 3,3-dialkyldiaziridine in 75 ml of anhydrous ether was added dropwise and with stirring a solution of 10 mmol of *o*-phthaloyl chloride in 75 ml of anhydrous ether. After 0.5 hr the mixture was filtered and the filtrate was evaporated. The residual oily solid was slurried with a small amount of ethanol, filtered, and recrystallized (Table I). The recrystallized **1–5** should be stored in a desiccator and at refrigerator temperatures.

**Synthesis of 8.** **8** was prepared in the same manner as **1–5** but in 10% yield. It was recrystallized from cyclohexane, mp 119–121°.

*Anal.* Calcd for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.27; N, 14.42. Found: C, 61.50; H, 7.09; N, 14.21.

**Synthesis of 6.** A mixture of 1.12 g (4.85 mmol) of 1-(α-hydroxy-β,β,β-trichloroethyl)-3-*n*-propyldiaziridine[11] and 50 ml of 2 *N* NaOH was stirred for 0.5 hr. Several pellets of NaOH were added and the liberated 3-*n*-propyldiaziridine was extracted with five 20-ml portions of $Et_2O$. The ethereal extracts were dried over $MgSO_4$, filtered, and cooled. Triethylamine (967 mg, 9.4 mmol) was added to the cold ether solution of the diaziridine followed by the dropwise addition of a solution of 785 mg (3.87 mmol) of *o*-phthaloyl chloride in 100 ml of $Et_2O$. The reaction mixture was filtered and the solvent was evaporated. The residual oil solidified and was immediately recrystallized from cyclohexane to give 509 mg (61%) of **6**. Three recrystallizations from cyclohexane gave **6**, mp 71–72.5°, molecular ion *m/e* 216.

**Synthesis of 7.** A solution of 20 g of 2,4,6-tri-*tert*-butyl-1,3,5-triazabicyclo[3.1.0]hexane[12] in 50 ml of $CH_3OH$ was added dropwise over a period of 20 min to a mixture of 25 g of chloral hydrate and 250 ml of 2 *N* $H_2SO_4$ held at 50°. After the addition was complete the pivalaldehyde which had formed by some hydrolysis taking place was removed by means of a flash evaporator. The clear acidic residue was quickly cooled and neutralized with 250 ml of 2 *N* NaOH. The 1-(α-hydroxy-β,β,β-trichloroethyl)-3-*tert*-butyldiaziridine that had precipitated was quickly filtered, washed thoroughly with cold water, and dried under vacuum. The yield of crude product was 19.2 g, mp 149–150°, and it was pure enough for the next step.

To the above chloral derivative (5.7 g) suspended in 50 ml of 2 *N* NaOH was added 4.6 g of *o*-phthaloyl chloride. Heat is liberated in the reaction. After the reaction mixture returned to room temperature the chloroform that was liberated was removed with a flash evaporator. The crude **7** was filtered, washed with water, and vacuum dried. It weighed 2.7 g (51%). Recrystallization from cyclohexane gave **7**, mp 110–111°.

**Synthesis of 9.** Thionyl chloride (32 g) was added to 2.5 g (10 mmol) of 1-phenyl-2,5-dimethylpyrrole-3,4-dicarboxylic acid.[13] After the initial reaction had subsided the mixture was heated on a steam bath for 2 hr. The excess $SOCl_2$ was removed and the residue was dissolved in dry $C_6H_6$. This solution was added dropwise and with stirring to a mixture of 1.12 g (10 mmol) of 3,3-pentamethylenediaziridine and 2.02 g of triethylamine in 100 ml of $C_6H_6$. After 1 hr the reaction mixture was filtered and the benzene filtrate was washed with water and quickly dried over $Na_2SO_4$. The dried filtrate was filtered and the $C_6H_6$ was evaporated. The crude **9** (2.5 g, 75%) was recrystallized from a mixture of $C_6H_6$ and petroleum ether (bp 63–75°). All attempts to determine the melting point of **9** failed, since it isomerized to **18** during heating.

*Anal.* Calcd for $C_{20}H_{21}N_3O_2$: C, 71.60; H, 6.27; N, 12.54. Found: C, 71.25; H, 6.33; N, 12.36.

**Hydrolysis of 4.** A solution of 242 mg (1 mmol) of **4** in 10 ml of $CH_3OH$ containing 2 drops of concentrated hydrochloric acid was refluxed for 1.5 hr. The solution was cooled and the 4-hydroxy-1(2*H*)-phthalazinone (**10**) was filtered. A solution of 2,4-dinitrophenylhydrazine was added to the filtrate and the cyclohexanone-2,4-dinitrophenylhydrazone was filtered. It weighed 250 mg (89%), mp 157–160°.

**Hydrolyses of 2 and 7.** The hydrolyses of **2** and **7** were carried out in a similar manner as **4**. In each case **10** was obtained. The 3-pentanone from **2** and the pivalaldehyde from **7** were isolated as 2,4-dinitrophenylhydrazones.

**Thermolyses of 1–4, 8, and 9.** A solution of 2 mmol of **1–4, 8,** or **9** in 10 ml of anhydrous toluene was refluxed for 3 hr. The solvent was evaporated and the residue was slurried with a small quantity of cold toluene or cold $CH_3CN$ and filtered. The 2-(1-alken-1-yl)-4-hydroxyphthalazinones **11–14** were recrystallized from $CH_3CN$; **17** was recrystallized from toluene and **18** was recrystallized from ethanol.

Thermolysis of **1** gave **11**, mp 149–152°, in 76% yield.

*Anal.* Calcd for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.85. Found: C, 64.96; H, 4.97; N, 13.70.

Thermolysis of **2** gave **12**, mp 129–130°, in 60% yield.

*Anal.* Calcd for $C_{13}H_{14}N_2O_2$: C, 67.77; H, 6.13; N, 12.17. Found: C, 67.73; H, 6.29; N, 12.40.

Thermolysis of **3** gave **13**, mp 128–131°, in 59% yield.

*Anal.* Calcd for $C_{15}H_{18}N_2O_2$: C, 69.76; H, 7.02; N, 10.84. Found: C, 69.93; H, 7.12; N, 10.69.

Thermolysis of **4** gave **14**, mp 148–150°, in 70% yield.

*Anal.* Calcd for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.82; N, 11.56. Found: C, 69.15; H, 5.85; N, 11.96.

Thermolysis of **8** gave **17**, mp 167–170°, in 78% yield.

*Anal.* Calcd for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.27; N, 14.42. Found: C, 61.53; H, 7.25; N, 14.17.

Thermolysis of **9** gave **18**, mp 286–289°, in 78% yield.

*Anal.* Calcd for $C_{20}H_{21}N_3O_2$: C, 71.65; H, 6.27; N, 12.54. Found: C, 71.41; H, 6.32; N, 12.29.

**Conversion of 6 into 19.** A mixture of 113 mg of **6** and 17 mg of $Et_3NHCl$ in 6 ml of o-xylene was refluxed for 1 hr. The mixture was filtered and then was cooled. The crude **19** (94 mg, 83%) was filtered and recrystallized from $CH_3CN$ to give **19**, mp 170–173°, molecular ion *m/e* 216.

**Reactions of 4 with Enamines.** A mixture of 4 mmol of **4** with equimolar quantities of 1-*N*-morpholino-1-cyclohexene, 1-*N*-morpholino-1-cyclopentene, or 1-*N*-pyrrolidino-1-cyclohexene in 20 ml of dry $C_6H_6$ was refluxed for 5 hr. The reaction mixture was cooled and the small quantity of **10** that precipitated was filtered. The filtrate was evaporated and the residual oil was slurried with a small quantity of cold $CH_3OH$ and filtered. Purification of **22, 23,** or **24** was achieved by recrystallization from absolute methanol. The crude yields varied from 40 to 70%.

Compound **22** had mp 188–193°.

*Anal.* Calcd for $C_{24}H_{31}N_3O_3$: C, 70.39; H, 7.63; N, 10.26. Found: C, 70.65; H, 7.76; N, 10.39.

Compound **23** had mp 162–164°.

*Anal.* Calcd for $C_{23}H_{29}N_3O_3$: C, 69.85; H, 7.39; N, 10.36. Found: C, 69.55; H, 7.52; N, 10.33.

Compound **24** had mp 164–169°.

*Anal.* Calcd for $C_{24}H_{31}N_3O_2$: C, 73.25; H, 7.94; N, 10.68. Found: C, 73.64; H, 8.00; N, 10.58.

**Reaction of 1with 1-*N*-Morpholino-1-cyclohexene.** When **1** was treated with 1-*N*-morpholino-1-cyclohexene, compound **21**, mp 191–194°, was obtained in 55% yield.

*Anal.* Calcd for $C_{21}H_{27}N_3O_3$: C, 68.27; H, 7.36; N, 11.37. Found: C, 68.32; H, 7.42; N, 11.85.

**Synthesis of 25.** A mixture of 370 mg (1 mmol) of **21**, 10 ml of $CH_3OH$, and 3 drops of concentrated hydrochloric acid was refluxed for 1 hr. The solvent was evaporated and the residual oily solid was slurried with a small quantity of methanol. The crude **25** (100%) was filtered and then recrystallized from methanol. The purified **25** melted at 198–200°, molecular ion *m/e* 282.

**Synthesis of 27.** A mixture of 282 mg (1 mmol) of **25** and 356 mg (2 mmol) of *N*-bromosuccinimide in 10 ml of $CCl_4$ was refluxed for 2 hr. The mixture was cooled and the precipitated succinimide was filtered. The filtrate was evaporated and the crude **27** was slurried with a small quantity of methanol and filtered. The crude yield was quantitative.

Compound **27** was recrystallized from $CH_3OH$, mp 197–200°.

*Anal.* Calcd for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.07. Found: C, 73.25; H, 5.11; N, 9.83.

**Synthesis of 26.** Using the same procedure as described for the synthesis of **25**, compound **22** was converted to **26** in quantitative yield. It melted at 173–175° after recrystallization from $CH_3OH$, molecular ion *m/e* 322.

*Anal.* Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.34; H, 6.90; N, 8.75.

**Synthesis of 28.** Treatment of **26** with *N*-bromosuccinimide gave **28** in quantitative yield. **28** melted at 140–142° after recrystallization from methanol.

*Anal.* Calcd for $C_{20}H_{18}N_2O_2$: C, 75.44; H, 5.70; N, 8.80. Found: C, 75.15; H, 5.89; N, 8.98.

**Synthesis of 31.** A mixture of 277 mg (1.38 mmol) of **1** and 158 mg (1.42 mmol) of $Et_2NC{\equiv}CCH_3$ (**29**) in 5 ml of dry toluene was refluxed for 1 hr. On cooling a small quantity of material precipitated and was filtered. This product melted at 177–179° but it was not **31** as shown by the nmr spectrum. The filtrate was evaporated and the crude **31** was recrystallized from 95% ethanol. A 35% yield of **31**, mp 125–128°, was obtained.

*Anal.* Calcd for $C_{18}H_{23}N_3O_2$: C, 68.98; H, 7.40; N, 13.41. Found: C, 68.78; H, 7.30; N, 13.54.

**Preparation of 32.** A mixture of 328 mg (1.62 mmol) of **1** and 291 mg (1.68 mmol) of $Et_2NC{\equiv}CC_6H_5$ in 10 ml of dry toluene was refluxed for 2 hr. The solvent was evaporated and the crystalline residue was recrystallized from 2 ml of absolute ethanol, yielding 307 mg (50.3%) of **32**. Two more recrystallizations gave an analytical sample of **32**, mp 173–175°.

*Anal.* Calcd for $C_{23}H_{25}N_3O_2$: C, 73.18; H, 7.21; N, 11.13. Found: C, 73.47; H, 6.89; N, 11.07.

**Preparation of 33. Method A.** To a solution of 235 mg (0.751 mmol) of **31** in 5 ml of 95% ethanol was added 1 ml of $H_2O$ and 20 drops of concentrated hydrochloric acid. The mixture was refluxed for 5 min. Within 2 min the yellow color had disappeared. The solvent was evaporated and the residue was recrystallized from 95% ethanol to give 151 mg (77%) of **33**, mp 201–204°.

*Anal.* Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 65.33; H, 5.28; N, 10.77.

**Preparation of 33. Method B.** A mixture of 832 mg (5.13 mmol) of compound **10** and 773 mg (5.82 mmol) of 2,3-dimethyl-2-butenoyl chloride[14] in 2 ml of nitrobenzene was refluxed for 1.5 hr. To the cooled dark solution was added 20 ml of petroleum ether (bp 63–75°). Filtration of this mixture gave 1.24 g (93%) of **33** as a brown powder. Recrystallization from 95% ethanol and activated charcoal gave **33**, mp 200–203°. The nmr and ir spectra of this material were identical with those obtained employing method A. A mixture melting point of samples from methods A and B showed no depression. Method B is a modification of a published procedure for preparing triones such as **33**.[5]

**Conversion of 32 into 34.** To a solution of 212 mg (0.56 mmol) of **32** in 5.0 ml of 95% ethanol was added 1 ml of water and 20 drops of concentrated hydrochloric acid. The mixture was refluxed for 5 min. The solvent was evaporated and the crystalline residue was recrystallized from methanol to give 110 mg (61%) of **34**, mp 171–173°.

*Anal.* Calcd for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.74. Found: C, 71.14; H, 5.13; N, 8.81.

**Synthesis of 35.** A mixture of 1.537 g (6.36 mmol) of **4** and 767 mg (6.90 mmol) of $Et_2NC{\equiv}CCH_3$ in 40 ml of dry toluene was refluxed for 2 hr. The toluene was evaporated and the residual yellow gum was recrystallized from 95% ethanol to give 1.78 g (78%) of **35**, mp 118–122°. Two recrystallizations from methanol gave yellow crystals of **35**, mp 120–123°.

*Anal.* Calcd for $C_{21}H_{27}N_3O_2$: C, 71.36; H, 7.70; N, 11.89. Found: C, 71.31; H, 7.88; N, 11.70.

**Synthesis of 36.** A mixture of 242 mg (1.0 mmol) of **4** and 185 mg (1.07 mmol) of $Et_2NC{\equiv}CC_6H_5$ in 10 ml of dry toluene was refluxed for 2 hr. The toluene was evaporated and the crystalline residue was recrystallized from 7 ml of $CH_3CN$ to give 254 mg (63%) of **36**, mp 189–193°. Three more recrystallizations from absolute ethanol gave **36** melting at 191–193°.

*Anal.* Calcd for $C_{26}H_{29}N_3O_2$: C, 75.15; H, 7.03; N, 10.11. Found: C, 74.97; H, 6.94; N, 9.90.

**Conversion of 35 into 37.** To a solution of 160 mg (0.454 mmol) of **35** in 9 ml of 95% ethanol was added 2 ml of water and 20 drops of concentrated hydrochloric acid. The mixture was refluxed for 5 min and the solvent was evaporated. The residue was recrystallized from 1 ml of 95% ethanol to give 110 mg (82%) of **37**, mp 162–165°. Two more crystallizations from 95% ethanol gave **37**, mp 165–167°.

*Anal.* Calcd for $C_{17}H_{18}N_2O_3$: C, 68.45; H, 6.09; N, 9.39. Found: C, 68.36; H, 6.15; N, 9.43.

**Conversion of 36 into 38.** A mixture of 103 mg (0.257 mmol) of **36**, 6.5 ml of 95% ethanol, 1 ml of $H_2O$, and 20 drops of concentrated hydrochloric acid was refluxed for 10 min. Evaporation of volatiles and recrystallization of the residue from 95% ethanol gave 83 mg (93%) of **38**, mp 249–252°. Three recrystallizations from $CH_3CN$ gave **38**, mp 250–254°.

*Anal.* Calcd for $C_{22}H_{20}N_2O_3$: C, 73.32; H, 5.59; N, 7.77. Found: C, 73.46; H, 5.67; N, 7.84.

**Acknowledgment.** We thank Professor Charles C. Sweeley for the mass spectra of many of the compounds reported in this paper. We thank the Henry and Camille Dreyfus Foundation and the National Institutes of Health for financial support. Acknowledgment is also made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work.

**Registry No.**—**1**, 52165-36-3; **2**, 52175-66-3; **3**, 52165-37-4; **4**, 52165-38-5; **5**, 52175-67-4; **6**, 52175-68-5; **7**, 52175-69-6; **8**, 52175-70-9; **9**, 52175-71-0; **10**, 1445-69-8; **11**, 52175-72-1; **12**, 52175-73-2; **13**, 52175-74-3; **14**, 52216-83-8; **17**, 52175-75-4; **18**, 52175-76-5; **19**, 52175-77-6; **21**, 52175-78-7; **22**, 52175-79-8; **23**, 52175-80-1; **24**, 52175-81-2; **25**, 52175-82-3; **26**, 52175-83-4; **27**, 52175-84-5; **28**, 52175-85-6; **29**, 4231-35-0; **30**, 4231-26-9; **31**, 52175-86-7; **32**, 52175-87-8; **33**, 52175-88-9; **34**, 52175-89-0; **35**, 52175-90-3; **36**, 52175-91-4; **37**, 52175-92-5; **38**, 52175-93-6; 3,3-dimethyldiaziridine, 4901-76-2; 3,3-diethyldiaziridine, 52175-94-7; 3,3-di-*n*-propyldiaziridine, 5701-90-6; 3,3-pentamethylenediaziridine, 685-79-5; 3-ethyl-3-methyldiaziridine, 4901-75-1; 1-(α-hydroxy-β,β,β-trichloroethyl)-3-*n*-propyldiaziridine, 52175-95-8; 1-(α-hydroxy-β,β,β-trichloroethyl)-3-*tert*-butyldiaziridine, 14373-42-3; *o*-phthaloyl chloride, 88-95-9; 1-phenyl-2,5-dimethylpyrrole-3,4-dicarboxylic acid, 52175-96-9; 1-*N*-morpholino-1-cyclohexene, 670-80-4; 1-*N*-morpholino-1-cyclopentene, 936-52-7; 1-*N*-pyrrolidino-1-cyclohexene, 1125-99-1.

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# Diaziridines. IV. Reaction of Some 1,1-Dialkyl-1*H*-diazirino[1,2-*b*]phthalazine-3,8-diones with Nitrones

Harold W. Heine* and Larry Heitz

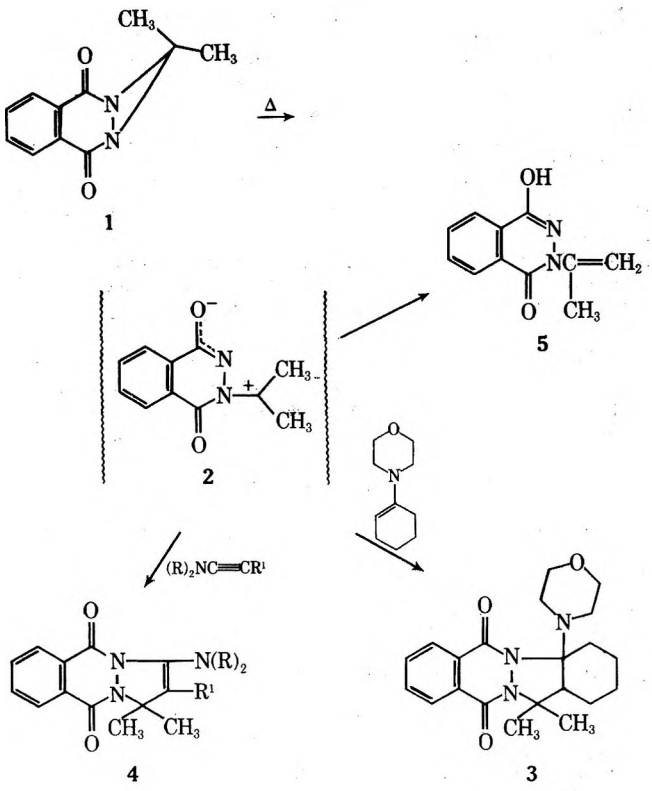
*Department of Chemistry, Bucknell University, Lewisburg, Pennsylvania 17837*

*Received May 21, 1974*

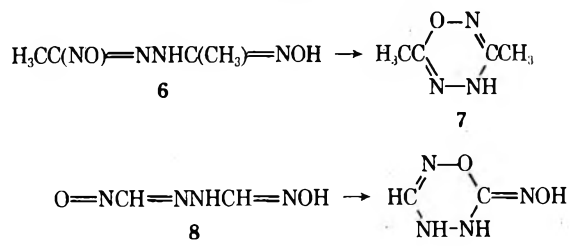
Reaction of 1,1-dialkyl-1*H*-diazirino[1,2-*b*]phthalazine-3,8-diones with nitrones in refluxing benzene gave 1*H*-[1,2,4,5]oxatriazino[4,5-*b*]phthalazine-6,11-diones. The latter compounds are hydrolyzed in aqueous methanol to 4-hydroxy-1(2*H*)-phthalazinone, ketones, and nitrones. It was also shown that 2-isopropenyl-4-hydroxy-1(2*H*)-phthalazinone reacted with nitrones in benzene to also form 1*H*-[1,2,4,5]oxatriazino[4,5-*b*]phthalazine-6,11-diones in low yields.

Recently reported reactions of 1,1-dialkyl-1*H*-diazirino[1,2-*b*]phthalazine-3,8-diones suggest that these substances are prone to form azomethine imines as reaction intermediates.[1] It appears, for example, that 1,1-dimethyl-1*H*-diazirino[1,2-*b*]phthalazine-3,8-dione (**1**) in boiling toluene or benzene is converted to **2**, which then adds to enamines or ynamines to give **3** and **4**, respectively, or in the absence of these reagents rearranges to **5** (Scheme I).[1]

**Scheme I**

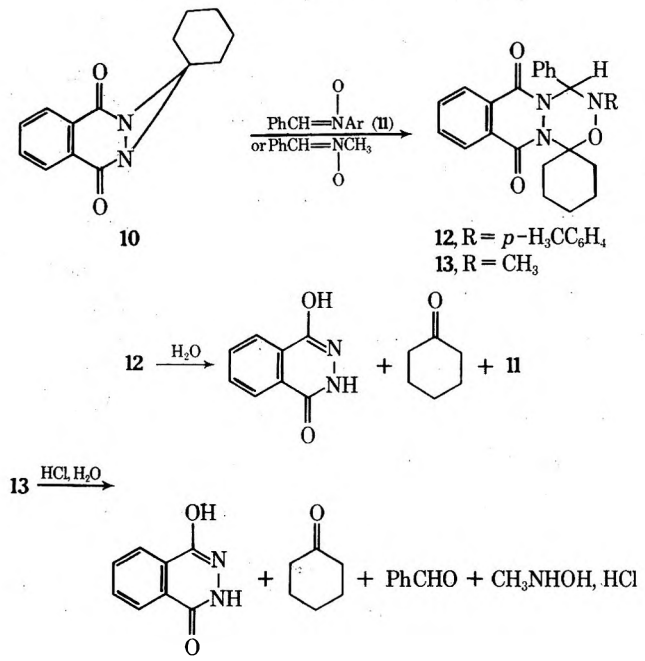


**Scheme II**



phenyl-*N*-methylnitrone gave **12** and **13**, respectively (Scheme III).

**Scheme III**



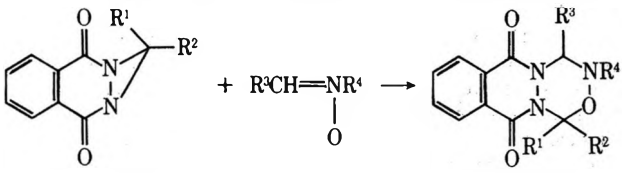
The present paper deals with the reaction of 1,1-dialkyl-1*H*-diazirino[1,2*b*]phthalazine-3,8-diones with nitrones. The products are derivatives of the virtually unknown 1,2,4,5-oxatriazine system. Wieland was the first and perhaps the only one to synthesize 1,2,4,5-oxatriazines. He claimed that **6** was transformed into **7** in boiling water[2] and that **8** isomerized to **9** in acid[3] (Scheme II).

## Results and Discussion

Heating of 1,1-dialkyl-1*H*-diazirino[1,2-*b*]phthalazine-3,8-diones with nitrones in benzene gives 1*H*-[1,2,4,5]oxatriazino[4,5-*b*]phthalazine-6,11-diones (Table I). Thus reaction of **10** with α-phenyl-*N*-*p*-tolylnitrone (**11**) and α-

The structure of **12** was established by mass spectroscopy, by nmr spectroscopy, and by the hydrolysis of **12** in aqueous methanol to 4-hydroxy-1(2*H*)-phthalazinone, cyclohexanone, and α-phenyl-*N*-*p*-tolylnitrone (**11**) (Scheme III). The acid hydrolysis of **13** gave analogous products, namely, 4-hydroxy-1(2*H*)-phthalazinone, cyclohexanone, benzaldehyde, and *N*-methylhydroxylamine hydrochloride. Most probably during the hydrolysis of **13**, α-phenyl-*N*-methylnitrone was produced and subsequently hydrolyzed to benzaldehyde and *N*-methylhydroxylamine hydrochloride. *N*-Alkylnitrones have been reported to be far more susceptible to hydrolysis than *N*-arylnitrones.[4]

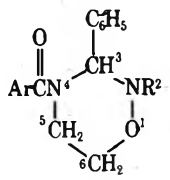
**Table I**
**1*H*-[1,2,4,5]Oxatriazino[4,5-*b*]phthalazine-6,11-diones from the Reaction of Nitrones with 1,1-Dialkyl-1*H*-diazirino[1,2-*b*]phthalazine-3,8-diones[a]**



| Compd | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Crude yield, % | Mp, °C[b] |
|---|---|---|---|---|---|---|
| 12 | $-(CH_2)_5-$ | | Ph | *p*-$H_3CC_6H_4$ | 85 | 171–172 |
| 13 | $-(CH_2)_5-$ | | Ph | Me | 84 | 160–162 |
| 14 | $-(CH_2)_5-$ | | Me | $C_6H_{11}$ | 71 | 139–141 |
| 15 | Me | Me | Ph | *p*-$H_3CC_6H_4$ | 80 | 157–159 |
| 16 | Me | Me | Ph | Me | 66 | 137–140 |
| 17 | *n*-Pr | *n*-Pr | Ph | *p*-$H_3CC_6H_4$ | 50 | 163–165 |

[a] Satisfactory analytical data for C, H, and N were obtained for all compounds listed in this table. Ed. [b] Compounds **12–17** were recrystallized from acetonitrile.

The nmr spectra of **12–17** were consistent with the proposed structures. The *N*-methyl groups of **13** and **16** appeared at $\delta$ 2.50 and 2.60, respectively, and the *gem*-dimethyl groups of **16** at $\delta$ 2.30 and 1.67. The *p*-tolylmethyl group of **15** appeared at $\delta$ 2.37 and the *gem*-dimethyl groups gave signals at $\delta$ 2.28 and 1.80. Those 1,2,4,5-oxatriazino derivatives bearing *N*-alkyl groups, *i.e.*, **13, 14,** and **16,** showed the methine hydrogens at $\delta$ 6.00, 6.10, and 6.01, respectively. The signals for the methine hydrogens of those 1,2,4,5-oxatriazines bearing *N*-aryl groups (**12, 15,** and **17**) were obscured by the absorption of the aromatic protons. The chemical shifts of the methine protons of **12–17** are analogous to those observed for the similar system, 4-aroyltetrahydro-2*H*-1,2,4-oxadiazines (**18**).[5] The



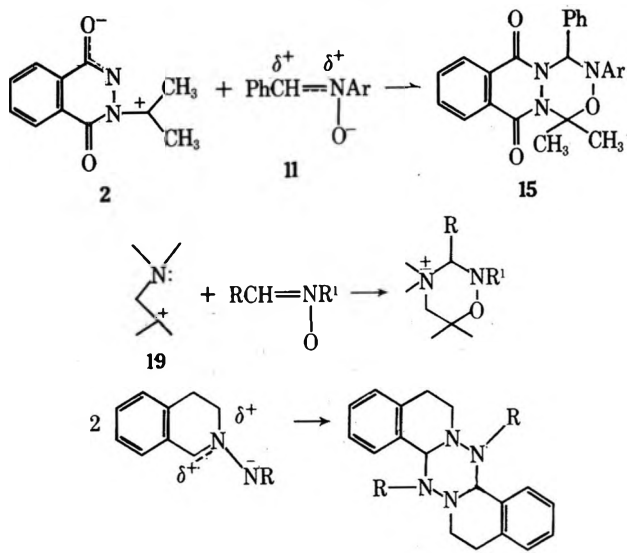
**18**

methine hydrogen at C-3 absorbed in the aromatic region for those 1,2,4-oxadiazines substituted with aryl groups in the 2 position of the ring while those examples of **18** with methyl groups in the 2 position absorbed at $\delta$ 5.8.

The 1,2,4,5-oxatriazines may be regarded as arising from the cycloaddition of two different 1,3-dipolar species, namely, the azomethine imine generated from the 1,1-dialkyl-1*H*-diazirino[1,2-*b*]phthalazine-3,8-diones (*e.g.*, **2**) and the nitrone (Scheme IV). Few examples of cycloaddition reactions between dissimilar 1,3-dipoles are known, although an interesting case of a cycloaddition of a nitrone with the 1,3-polar moiety **19** formed from an aziridinium ring has recently been reported by Leonard[6] and his colleagues (Scheme IV). Cycloadditions of similar 1,3-dipoles, such as the cyclodimerizations of azomethine imines, have been observed[7-10] (Scheme IV).

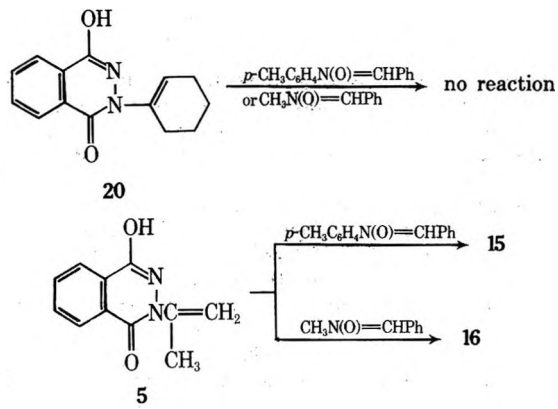
Since nitrones are known to react with alkenes to yield isoxazolidines[11-13] and since 1,1-dialkyl-1*H*-diazirino[1,2-*b*]phthalazine-3,8-diones isomerize into 2-(1-alken-1-yl)-4-hydroxy-1(2*H*)-phthalazinones (*e.g.*, **1** → **5**, Scheme I), experiments were conducted to see if the latter compounds would react with nitrones. There was no reaction when

**Scheme IV**



mixtures of **20** and $\alpha$-phenyl-*N*-*p*-tolylnitrone or $\alpha$-phenyl-*N*-methylnitrone were heated in benzene for 7.5 hr. Treatment of **5** with the above nitrones for 7.5 hr did not form isoxazolidines but surprisingly did give small yields ($\simeq$15%) of **15** and **16** (Scheme V). This is to be contrasted with the high yields of **15** and **16** (80 and 66%, Table I) that were obtained when mixtures of **1** and $\alpha$-phenyl-*N*-*p*-tolylnitrone and **1** and $\alpha$-phenyl-*N*-methylnitrone were heated in benzene for 6 hr.

**Scheme V**



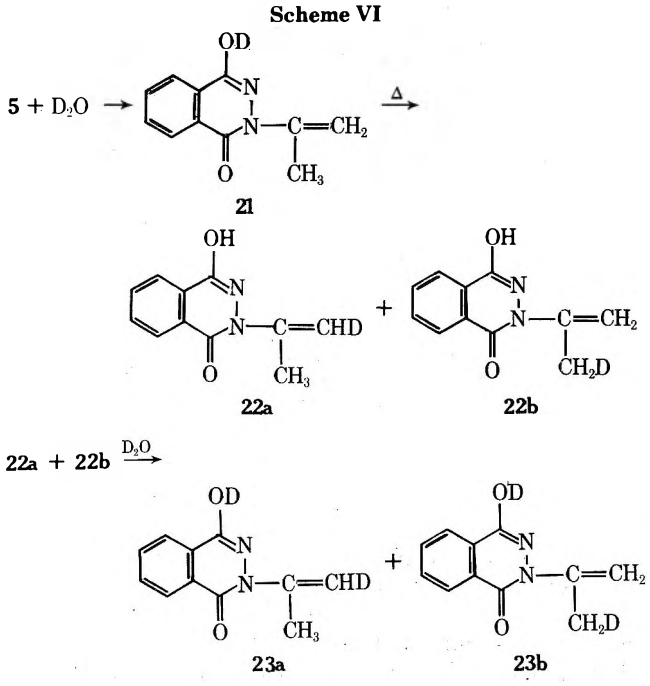
That **5** interacts with $\alpha$-phenyl-*N*-*p*-tolylnitrone and $\alpha$-phenyl-*N*-methylnitrone to give small amounts of **15** and **16** is explicable if **5** is in equilibrium with the azomethine imine **2** which undergoes a cycloaddition reaction with the nitrones.

$$5 \rightleftharpoons 2$$

The following experiments suggest that such an equilibrium exists. When a chloroform solution of **5** was treated with deuterium oxide, the nmr absorption for the OH proton at $\delta$ 10.00 disappeared immediately. This peak reappeared after heating **21** at reflux in toluene overnight owing to exchange of the OD with the protons of the isopropenyl group. The latter material was probably a mixture of **22a** and **22b** and some **21** (Scheme VI). The mixture of **22a** and **22b** was then treated again with $D_2O$ to give a mixture of **23a** and **23b** (Scheme VI). The latter mixture was analyzed by mass spectroscopy and its mass spectrum was compared to that of some untreated **5.** Significant quantities of the mixture **23a** and **23b** showed a molecular ion *m/e* 204 (*i.e.*,

18.6% relative to the standard **5** which gave only 1.1% of *m/e* 204).

**Scheme VI**



That the reaction of **5** with α-phenyl-*N*-*p*-tolylnitrone and α-phenyl-*N*-methylnitrone results in only about 15% of **15** or **16** is probably due to the greater basicity of **15** and **16** relative to the alkene moiety of **5**. As **15** and **16** accumulate in the reaction mixture they capture the acidic proton of **5**, thus preventing further formation of the azomethine imine **2**.

## Experimental Section

**Materials.** The nitrones were prepared by reaction of N-substituted hydroxylamines with aldehydes according to literature procedures[14,15] and were known compounds.

**Syntheses of 1*H*-[1,2,4,5]Oxatriazino[4,5-*b*]phthalazine-6,11-diones 12–17 (Table I).** A mixture of 2 mmol of the nitrone and 2 mmol of the 1,1-dialkyl-1*H*-diazirino[1,2-*b*]phthalazine-3,8-dione in 15 ml of anhydrous benzene was refluxed for 6 hr. The cooled reaction mixture was filtered and the solvent was evaporated. The residue was slurried with a small quantity of cold methanol and the crude crystalline **12–17** were filtered and recrystallized from acetonitrile.

**Hydrolysis of 12.** A solution of 453 mg (1 mmol) of **13** in 10 ml of $CH_3OH$ containing 6 drops of water was refluxed for 2 hr. The cooled reaction mixture was filtered to give 120 mg (77%) of the 4-hydroxy-1(2*H*)-phthalazinone. Evaporation of the filtrate gave 150 mg (71%) of α-phenyl-*N*-tolylnitrone.

**Hydrolysis of 13.** A solution of 377 mg (1 mmol) of **13** in 10 ml of $CH_3OH$ containing 1 drop of hydrochloric acid was refluxed for 1 hr. The solution was cooled and the 4-hydroxy-1(2*H*)-phthalazinone (130 mg, 81%) was filtered. A solution of 2,4-dinitrophenylhydrazine was added to the filtrate and the precipitate (450 mg) of a mixture of 2,4-dinitrophenylhydrazones of benzaldehyde and cyclohexanone was filtered. Separation of the 2,4-dinitrophenylhydrazones was easily achieved by recrystallizing from ethanol. The benzaldehyde 2,4-dinitrophenylhydrazone precipitated selectively from the hot solvent and was filtered. The cooled filtrate yielded the cyclohexanone 2,4-dinitrophenylhydrazone.

The *N*-methylhydroxylamine hydrochloride was isolated by repeating the hydrolysis of **13**, filtering the 4-hydroxy-1(2*H*)-phthalazinone, and evaporating the filtrate to dryness. The residue weighed 50 mg (60%) and its infrared spectrum was identical with that of a commercial sample of *N*-methylhydroxylamine hydrochloride.

**Acknowledgment.** We thank Professor Charles C. Sweeley for the mass spectra of some of the compounds reported in this paper. Financial support from the Henry and Camille Dreyfus Foundation and the National Institutes of Health is gratefully acknowledged.

**Registry No.**—**1**, 52165-36-3; 1 *n*-Pr analog, 52165-37-4; **10**, 52165-38-5; **12**, 52165-39-6; **13**, 52165-40-9; **14**, 52165-41-0; **15**, 52165-42-1; **16**, 52165-43-2; **17**, 52165-44-3; α-phenyl-*N*-*p*-tolylnitrone, 19064-77-8; α-phenyl-*N*-methylnitrone, 3376-23-6; α-methyl-*N*-cyclohexylnitrone, 3376-30-5.

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# Evidence for the Formation of Diimide in the Thermal Fragmentation of 1-Amino-2,2-diphenylaziridine

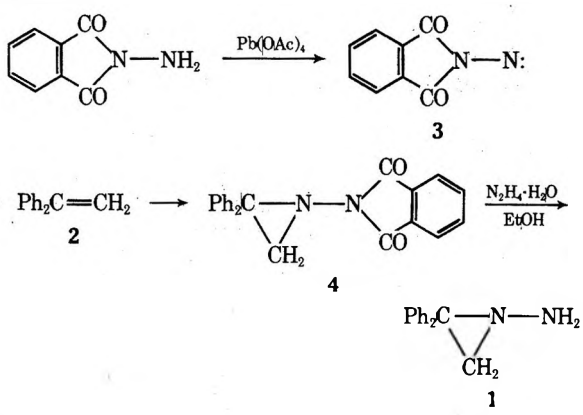
Rita Annunziata, Roberto Fornasier, and Fernando Montanari*

*Centro C. N. R. e Istituto di Chimica Industriale dell'Universita', Via C. Golgi 19, 20133 Milano, Italy*

*Received December 3, 1973*

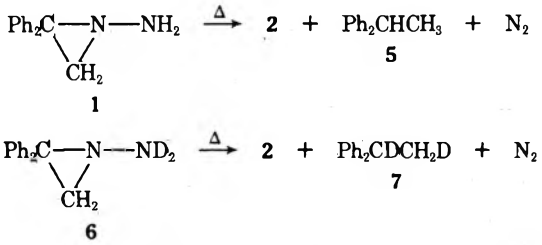
Thermal decomposition of 1-amino-2,2-diphenylaziridine gives a mixture of 1,1-diphenylethylene and 1,1-diphenylethane. When the decomposition is carried out in the presence of highly reactive, strained olefins, these are selectively hydrogenated. Starting from *N,N*-dideuterio-2,2-diphenyl-1-aminoaziridine, deuterium is added to ethylenic double bonds. Comparison with the stereochemical results obtained in reductions with different sources of diimide supports the conclusion that the latter is the reducing species.

In connection with the synthesis of compounds whose molecular asymmetry is due solely to a tricovalent nitrogen atom,[1,2] 1-amino-2,2-diphenylaziridine (**1**) has been prepared *via* addition of phthalimidonitrene (**3**) to 1,1-diphenylethylene (**2**) according to Rees,[3] and hydrazinolysis of the adduct **4**.

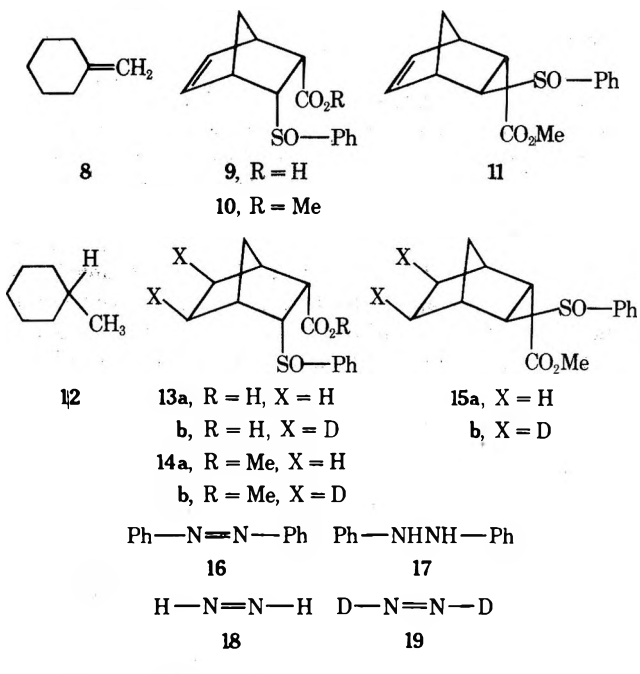


In the nmr spectra of aziridines **1** and **4** phenyls bound to the heterocyclic ring appear as a doublet and the methylene protons as an AB quartet, thus indicating the existence of a high barrier to pyramidal inversion at nitrogen, in agreement with the structural characteristics of the molecule.[4] The spectrum of **4** remains unaltered up to 150°.

Aziridine **1** is thermally unstable and at room temperature decomposes in a few hours, with evolution of gas and formation of a mixture of 1,1-diphenylethylene (**2**) and 1,1-diphenylethane (**5**).[5] The fragmentation can be easily followed by nmr spectroscopy. If aminoaziridine **1** is converted into the *N,N*-dideuterio derivative **6** by isotopic exchange with $D_2O$, fragmentation affords a mixture of 1,2-dideuterio-1,1-diphenylethane (**7**) and 1,1-diphenylethylene (**2**).



To ascertain if the formation of diphenylethane (**5**) and of the dideuterio derivative **7** occurs through an internal rearrangement or the formation of a species capable of hydrogenating (or deuterating) the double bond of diphenylethylene in an intermolecular process, decomposition of aziridine **1** was repeated in the presence of highly reactive, strained olefins. Starting from methylenecyclohexane (**8**) and from norbornenes **9–11**, methylcyclohexane (**12**) and norbornanes **13a–15a** were obtained, respectively. Azobenzene (**16**) afforded hydrazobenzene (**17**). When the reaction was carried out with dideuterioaziridine **6**, a molecule of deuterium was added to the C–C double bond. In the cases examined, the 5,6-dideuterionorbornanes **13b–15b** were identical with the products of addition (very likely from the cis-exo direction) of dideuteriodiimide (**19**), produced *via* azodicarboxylic acid,[7] to norbornenes **9–11**.



The facile fragmentation of *N*-aminoaziridines analogous to **1** is known.[8-10] The main products are the corresponding ethylene derivatives, which often are formed in a very stereospecific way.[8] In the thermal decomposition of *trans*-2,3-diphenyl-1-aminoaziridine (**20**), 1,2-diphenylethane has been isolated together with *trans*-stilbene, whereas *N,N*-dimethylaminocarbonyl-1-aminoaziridine (**21**) gives *N,N*-dimethylpropionamide.[8] The formation of

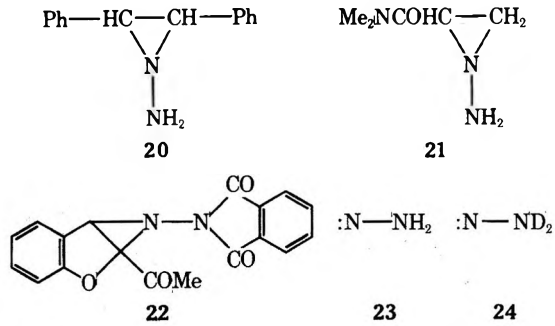


**Table I**
**Reduction of Camphene (25)**

| Reagent | Yield, % | Endo, % 27 | Exo, % 28 |
|---|---|---|---|
| **1** | 39 | 92.5 | 7.5 |
| $N_2H_4$, $NaIO_4$ | 33 | 88.2 | 11.8 |
| $HO_2CN{=}NCO_2H$ | 18 | 91.5 | 8.5 |
| $N_2H_4$, $O_2$ | | 92[a] | 8[a] |
| $H_2$, C/Pd | 100 | 72.3 | 27.7 |
| $H_2$, C/Pt | | 75[a] | 25[a] |

[a] Reference 15.

**Table II**
**Reduction of 4-*tert*-Butylmethylenecyclohexane (26)**

| Reagent | Yield, % | Cis, % 29 | Trans, % 30 |
|---|---|---|---|
| **1** | 77 | 48.1 | 51.9 |
| $N_2H_4$, $NaIO_4$ | 50 | 51.0 | 49.0 |
| $HO_2CN{=}NCO_2H$ | 44 | 49.6 | 50.4 |
| $N_2H_4$, $O_2$ | | 49[a] | 51[a] |
| $H_2$, C/Pd | 100 | 81.1 | 18.9 |
| $H_2$, C/Pt | | 83[a] | 17[a] |

[a] Reference 15.

the latter has been interpreted[8] by the intervention of an intramolecular process. Phthalimidonitrene (**3**) is produced by heating bicyclic aziridine **22**,[10] and finally aminonitrene (**23**) has been considered[9] as a possible transient product of the thermal fragmentation of *cis*- and *trans*-2,3-diphenyl-1-aminoaziridine (**24**). On this basis it seemed likely that fragmentation of aminoaziridines **1** and **6** could yield aminonitrenes **23** and **24**, which as such or through conversion to the tautomeric diimides **18** and **19** are the reducing species. Cis hydrogenation by a nonsymmetric isomer **23** of diimide cannot be ruled out *a priori*, even if, for diimide obtained by conventional methods, spectroscopic results and chemical behavior seem to exclude the existence of nonsymmetric species.[11,12]

In order to obtain information on this point, we hydrogenated camphene (**25**) and 4-*tert*-butylmethylenecyclohexane (**26**) with aminoaziridine **1**, with diimide produced by oxidation of hydrazine with sodium metaperiodate[13] and by decarboxylation of azodicarboxylic acid,[7,14] and with hydrogen on Pd/C catalyst.

It was known[15] that in these substrates catalytic and diimide reductions occur with different diastereomeric selectivities.

As shown in Tables I and II, the results of the reactions with aziridine **1** are consistent with those obtained with known sources of diimide and differ from those obtained in catalytic conditions.

It seems therefore that diimides **18** and **19** are the reducing species produced by fragmentation of **1** and **6**. At this moment it is only an hypothesis that diimides in their turn come from an internal rearrangement of aminonitrenes **23** and **24**.

## Experimental Section

Nuclear magnetic resonance and infrared spectra were determined with a Varian A-60 instrument and a Perkin-Elmer 237 spectrometer, respectively. Glc analyses were performed on a Fractovap GP chromatograph equipped with flame detectors. The columns were a 0.8 in. × 3.2 ft 3% SE-30, 10% Carbowax 20M on 60–80 mesh Chromosorb W, and a 0.1 in. × 163.8 ft glass capillary column on OV-101.

**2,2-Diphenyl-1-phthalimidoaziridine (4).** A solution of lead tetraacetate (4.9 g, 11 mmol) in anhydrous dichloromethane (15 ml) was added to a stirred suspension of *N*-aminophthalimide[3,16] (1.62 g, 10 mmol) in 1,1-diphenylethylene (9.0 g, 50 mmol) and anhydrous dichloromethane (25 ml) at room temperature under a dry nitrogen atmosphere during 10 min. After a further 30 min the mixture was filtered, the precipitate was washed with anhydrous dichloromethane, and the combined solutions were evaporated to dryness under vacuum at 15–20°. The oily, yellow residue was purified by dry column chromatography on basic alumina (about 30 g, eluent diethyl ether). Extraction with chloroform gave **4** (1.1 g, 32%) as a yellowish solid, mp 167–168°, from methanol: nmr ($CDCl_3$) $\tau$ 2.45 (4 H, s), 2.7 (10 H, m), 5.3, 7.14 (2 H, q, $J$ = 3 Hz).

*Anal.* Calcd for $C_{22}H_{16}O_2N_2$: C, 77.64; H, 4.71; N, 8.22. Found: C, 77.40; H, 4.56; N, 8.14.

**1-Amino-2,2-diphenylaziridine (1).** A suspension of phthalimidoaziridine **4** (500 mg, 1.47 mmol) in hydrated hydrazine (147 mg, 2.94 mmol) and 95% ethanol (12 ml) was stirred at room temperature until complete solution (5 min). After 10 min the precipitated *N,N*-phthaloylhydrazine, mp >300°, was filtered and washed with ethanol, and the combined solutions were evaporated under vacuum at 15–20°. Ice water was added and the organic phase was extracted five times with cold dichloromethane. The combined solutions of dichloromethane were washed with 2 *N* aqueous potassium hydroxide, water, and saturated aqueous sodium chloride, dried over magnesium sulfate, and evaporated to dryness under vacuum. Work-up was carried out below 5°, and as fast as possible. The oily residue was 1-amino-2,2-diphenylaziridine (**1**), together with minor amounts (about 5–10%) of 1,1-diphenylethylene (**2**), as shown by aromatic and ethylenic absorptions in the nmr spectrum ($CDCl_3$) at $\tau$ 2.71 and 4.6, respectively: nmr ($CDCl_3$) $\tau$ 2.7 (10 H, d), 6.97 (2 H, broad s, disappears in $D_2O$), 7.65 (2 H, q, $J$ = 0.7 Hz). The thermal instability of **1** prevented further purification and elemental analysis.

**Fragmentation of 1-Amino-2,2-diphenylaziridine. 1,1-Diphenylethane (5).** Aziridine **1** in $CDCl_3$ solution at 40° decomposed in 3 hr to give nitrogen and a mixture of 1,1-diphenylethylene (**2**) and 1,1-diphenylethane (**5**), in a ratio of 3:7 (by nmr).

The presence of **5** in the reaction mixture was confirmed by comparison with an authentic sample:[17] nmr ($CDCl_3$) $\tau$ 2.85 (10 H, s), 5.95 (1 H, q), 8.40 (3 H, d).

**Fragmentation of *N,N*-Dideuterio-1-amino-2,2-diphenylaziridine. 1,2-Dideuterio-1,1-diphenylethane (7).** A solution of aziridine **1** (80 mg) in $CDCl_3$ (2 ml) was shaken with $D_2O$ (1 ml) at about 5°, the organic phase was separated, and the operation was repeated twice, until disappearance of the nmr absorption at $\tau$ 6.57. The $CDCl_3$ solution was dried over anhydrous magnesium sulfate. Nmr spectra indicated disappearance of aziridine **1**, and progressive appearance during about 4.30 hr of 1,2-dideuterio-1,1-diphenylethane (**7**) (broad singlet at $\tau$ 8.40, $CH_2D$, centered with respect to the $CH_3$ doublet of **5**), together with minor amounts of diphenylethylene (**2**) and isotopically normal diphenylethane (**5**).

A sample of **7** was prepared by slow addition at 0° of $CH_3COOD$ (1.2 g, 20 mmol) in $CH_3OD$ (0.5 ml) to a solution of 1,1-diphenylethylene (**2**, 360 mg, 2 mmol) and potassium azodicarboxylate (98 mg, 5 mmol) in $CH_3OD$ (7 ml). After 1 hr pentane was added, and the solution was washed with water, concentrated sulfuric acid, and again with water. Evaporation of the solvent and distillation of the oily residue afforded 1,2-dideuterio-1,1-diphenylethane (**7**): bp 148° (22 mm); $n_D$ 1.5759; nmr ($CDCl_3$) $\tau$ 2.81 (10 H, s), 8.40 (2 H, broad s).

**Methylcyclohexane (12).** A solution of aziridine **1** (84 mg, 0.4 mmol) and methylenecyclohexane (**8**, 19 mg, 0.2 mmol) in $CDCl_3$ (1 ml) was kept at 40° for 12 hr to give methylcyclohexane (**12**), diphenylethylene (**2**), and diphenylethane (**5**) in a ratio of 50:35:15 (glc analysis).

**3-*endo*-*syn*-Phenylsulfinylbicyclo[2.2.1]heptane-2-*endo*-carboxylic Acid (13a).** A solution of aziridine **1** (84 mg, 0.4 mmol) and norbornene derivative **9**[18] (52 mg, 0.2 mmol) in $CD_3OD$ (1.5 mol) was left at room temperature for 2 hr until no more gas was evolved. The nmr spectrum ($CD_3OD$) indicated disappearance of vinylic absorption at $\tau$ 3.6. The solvent was evaporated, 5% aqueous sodium hydroxide was added, and the alkaline solution was washed with diethyl ether and acidified to give **13a** (50 mg, 96%), mp 180–182° (lit.[19] mp 184–185°). The nmr spectrum (NaOD, $D_2O$) of **13a** was identical with that of an authentic sample.[19]

The methyl ester **14a** was similarly obtained from **10** and **1** in $CHCl_3$ solution: mp 117–118° from light petroleum (lit.[18] mp 119–120°); nmr ($CDCl_3$) $\tau$ 2.40 (5 H, m), 6.50 (3 H, s), 6.70–8.75 (10 H, m); no vinylic absorption at $\tau$ 3.55.

**5,6-Dideuterio-3-*endo*-*syn*-phenylsulfinylbicyclo[2.2.1]heptane-2-*endo*-carboxylic Acid (13b).** A solution of aziridine **1** (84 mg, 0.4 mmol) in anhydrous DMSO (3 ml) and $D_2O$ (0.5 ml) was added to a solution of acid **9**[20] (52 mg, 0.2 mmol) in anhydrous DMSO (4 ml) at room temperature. Immediate evolution of gas was observed. After 30 min aqueous sodium hydrogen carbonate was added, and the mixture was washed with diethyl ether and acidified with aqueous hydrochloric acid. The precipitated norbornane was filtered, washed with water, and dried: 45 mg (90%); mp 183–184° also in mixture with the hydrogenated analogous **13a**; nmr (DMSO-$d_6$) $\tau$ 2.68 (5 H, s), 5.63 (1 H, m), 5.83 (1 H, m), 6.32 (1 H, m), 6.52 (1 H, m), 7.40 (2 H, m), 8.51 (2 H, broad s). From the ethereal phase a mixture of diphenylethylene and diphenylethane was recovered.

Acid **13b** was also prepared as follows. $CH_3COOD$ (1.2 g) was slowly dropped into a solution of acid **9** (200 mg, 1 mmol) and potassium azodicarboxylate (400 mg, 2.5 mmol) in DMSO (7 ml). After 4 hr, 160 mg (75%) of **13b**, mp 183–184°, was isolated. Nmr spectra of this sample and of that obtained from dideuterioaziridine were identical.

The **methyl ester 14b** was obtained by shaking a solution of **1** (84 mg, 0.5 mmol) in $CDCl_3$ (1 ml) with $D_2O$ (1 ml), and adding to the organic phase a solution of **10**[21] (56 mg, 0.2 mmol) in $CDCl_3$ (0.5 ml). The mixture was left 2 hr at room temperature. Work-up afforded **14b**, which was purified by column chromatography (silica, light petroleum–diethyl ether): 35 mg (60%); mp 115–117°, not depressed in mixture with a nondeuterated sample of **14a**; nmr ($CDCl_3$) $\tau$ 2.40 (5 H, m), 6.50 (3 H, s), 7.0 (2 H, m), 7.30 (2 H, m), 8.45 (2 H, broad s), 8.75 (2 H, s).

**Methyl 3-*exo*-*anti*-phenylsulfinylbicyclo[2.2.1]heptane-2-*endo*-carboxylate (15a)** was obtained similarly to ester **14a** from ester **11**[21] and aziridine **1** in 83% yield: mp 115–116° from cyclohexane; nmr ($CDCl_3$) $\tau$ 2.48 (5 H, m), 6.56 (3 H, s), 6.82 (1 H, m), 7.25 (3 H, m), 8–9 (6 H, m).

*Anal.* Calcd for $C_{15}H_{18}O_3S$: C, 64.7; H, 6.5. Found: C, 64.42; H, 6.60.

**Methyl 5,6-dideuterio-3-*exo*-*anti*-phenylsulfinylbicyclo-[2.2.1]heptane-2-*endo*-carboxylate (15b)** was obtained similarly to ester **14b** from ester **11** and aziridine **1** in $CDCl_3$–$D_2O$ in 80% yield, and purified by column chromatography (silica, light petroleum–diethyl ether): mp 108–109°, not depressed in mixture with the nondeuterated analogous **15a**; nmr ($CDCl_3$) $\tau$ 2.48 (5 H, m), 6.55 (3 H, s), 6.82 (1 H, m), 7.25 (3 H, m), 8–9 (4 H, m).

The same compound, with identical melting point and nmr spectrum, was obtained from ester **11** and potassium azodicarboxylate in DMSO–$CH_3CO_2D$, as described above for acid **13b**.

**Hydrazobenzene (17).** Azobenzene (19 mg, 0.1 mmol) and aziridine **1** (84 mg, 0.4 mmol) in $CH_2Cl_2$ solution (1 ml) were left for 3 hr at room temperature until no more gas was evolved. Column chromatography (silica, light petroleum) afforded 16 mg (84%) of hydrazobenzene, mp 124–125°.

**Reductions of Camphene (25) and of 4-*tert*-Butylmethylenecyclohexane (26). A. With Aziridine 1.** A solution of **1** (420 mg, 2 mmol) and **25** or **26**[22] (0.5 mmol) in $CH_2Cl_2$ (2 ml) was left at room temperature for 24 and 4 hr, respectively, until no more gas was evolved.

**B. With Hydrazine and Sodium Metaperiodate.**[14] To a solution of **25** or **26** (1 mmol) and hydrated hydrazine (40 mmol) in ethanol (5 ml) were added 2 drops of glacial acetic acid, 2 drops of saturated aqueous copper sulfate, and (dropwise, 1 hr) a solution of sodium metaperiodate (1.06 g, 5 mmol) in $H_2O$ (10 ml) at room temperature. The reaction mixture was filtered, diluted with brine, and extracted with pentane.

**C. With Potassium Azodicarboxylate.**[7,15] Glacial acetic acid (1.2 g, 20 mmol) in methanol (1 ml) was added dropwise at room temperature to a solution of **25** or **26** (1 mmol) and potassium azodicarboxylate (776 mg, 4 mmol) in methanol (5 ml). After 1 hr the mixture was diluted with brine and extracted with pentane.

**D. Catalytic Reduction.** It was carried out in ethanol with 10% Pd/C catalyst and the products were extracted with pentane.

The solvent (methylene chloride or pentane) was evaporated under vacuum at about 10° and the reaction mixture was analyzed by glc on capillary columns at 80° (see Tables I and II).

**Acknowledgments.** We thank Dr. M. Ghirga, SIR Research Laboratories, Paderno Dugnano, for glc analyses on capillary columns, and Dr. G. Borgogno for assistance in the experimental work.

**Registry No.**—**1**, 52165-45-4; **2**, 530-48-3; **4**, 52165-46-5; **5**, 612-00-0; **6**, 52165-47-6; **7**, 52165-48-7; **8**, 1192-37-6; **9**, 52194-78-2; **10**, 52224-95-0; **11**, 52194-79-3; **12**, 108-87-2; **13a**, 52165-49-8; **13b**, 52194-80-6; **14a**, 52224-96-1; **14b**, 52165-35-2; **15a**, 52194-76-0; **15b**, 52194-77-1; **17**, 122-66-7; *N*-aminophthalimide, 1875-48-5; potassium azodicarboxylate, 4910-62-7; azobenzene, 103-33-3.

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# Reaction of Diaziridines with Diphenylketene and Isocyanates

Mitsuo Komatsu,* Nobuo Nishikaze, Makoto Sakamoto, Yoshiki Ohshiro, and Toshio Agawa

*Department of Petroleum Chemistry, Faculty of Engineering, Osaka University, Yamadakami, Suita, Osaka 565, Japan*

*Received May 6, 1974*

The reactions of 1,2,3-trialkyldiaziridines **1** with diphenylketene, phenyl isocyanate, and benzoyl isocyanate were studied. The products of **1** with diphenylketene were acyclic 1:2 adducts, *N*-alkyl-*N*-(1-alkylamino-2-alkyl-3-oxo-4,4-diphenylbut-1-en-1-yl)diphenylacetamides **3**. The products of **1** with benzoyl isocyanate were triazolidinones **15**. With phenyl isocyanate, reactions of **1** were complicated. Mechanisms for these reactions were suggested.

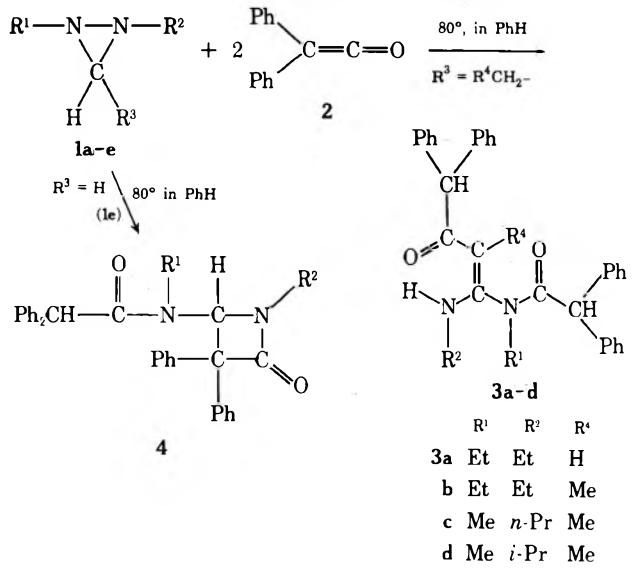
In contrast to the widely investigated chemistry of three-membered heterocycles such as oxiranes and aziridines, chemical properties of three-membered rings containing two heteroatoms such as diaziridines and oxaziridines have been less known. Their preparation and behaviors in some typical reactions (hydrolysis, reduction, acylation, rearrangement, etc.) have been reported by Schmitz and his coworkers, but there are few reports on their synthetic applications.[1]

We previously reported that the reactions of oxaziridines with heterocumulenes result in five- or six-membered heterocyclic compounds. In the reactions, oxaziridines undergo 1,3-cycloaddition in some cases and, in other cases, form unstable three-membered intermediates, which in turn decompose or react with additional cumulenes, followed by elimination of carbonyl compounds. Thus a new aspect of the chemistry of oxaziridines has been established.[2,3]

We have now compared the behavior of diaziridines with that of oxaziridines[2] or aziridines[4] toward heterocumulenes. As we have stated in a preliminary report,[5] diaziridines react with diphenylketene in a completely different manner from those of other three-membered heterocycles. In this paper, reactions with heterocumulenes as well as mechanistic discussion are described.

## Results

**Reaction with Diphenylketene.** 1,2,3-Trialkyldiaziridines **1a–d** reacted with diphenylketene (**2**) in refluxing benzene to give the acyclic 1:2 adducts, *N*-alkyl-*N*-(1-alkylamino-2-alkyl-3-oxo-4,4-diphenylbut-1-en-1-yl)diphenylacetamides **3a–d**, while the 1,2-dialkyldiaziridine **1e** gave the azetidinone derivative **4**. These products would not be anticipated from the known reactions of oxiranes,[6,7] thiiranes,[8] or oxaziridines[2,3] with diphenylketene.




| | R¹ | R² | R⁴ |
|---|---|---|---|
| 3a | Et | Et | H |
| b | Et | Et | Me |
| c | Me | *n*-Pr | Me |
| d | Me | *i*-Pr | Me |

**Table I**
**Reaction of Diaziridines with Diphenylketene**

| Diaziridine (1) R¹ | R² | R³ | Mole ratio 1:2[a] | Reaction[b] Temp, °C | Time, min | Product[c] | Yield, % |
|---|---|---|---|---|---|---|---|
| 1a | Et | Et | Me | 0.5 | 80 | 5 | 3a | 6 |
| 1b | Et | Et | Et | 0.5 | 80 | 5 | 3b | 53 |
| 1b | Et | Et | Et | 0.5 | 70 | 5 | 3b | 32 |
| 1b | Et | Et | Et | 1.0 | 80 | 5 | 3b | 17 |
| 1c | Me | *n*-Pr | Et | 0.5 | 80 | 5 | 3c | 15 |
| 1c | Me | *n*-Pr | Et | 0.5 | 45 | 5 | | |
| 1d | Me | *i*-Pr | Et | 0.5 | 80 | 5 | 3d | 31 |
| 1e | Et | Et | H | 0.5 | 80 | 5 | 4 | 26 |

[a] **2**: diphenylketene. [b] Benzene was employed as a solvent. [c] Considerable amounts of *N*-ethyldiphenylacetamide (**5**) and polymeric substances were also obtained and the latter remarkably increased in low-yield runs.

The results listed in Table I show that the reaction temperature should not be lower than 70°, since polymerization of the ketene is rather faster at such temperatures in the presence of the diaziridines. This was probably due to the action of the diaziridines as a basic catalyst. Even when equimolar quantities of diphenylketene and diaziridines were employed, only the 1:2 adduct **3** was isolated.

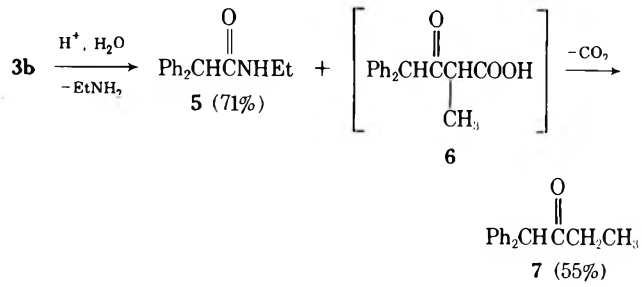
Mass spectra and analytical data show that the amide **3** is a 1:2 adduct of the diaziridine and the ketene, and the structure was confirmed satisfactorily by the spectral data (see Experimental Section and the preliminary report[5]). In the nmr spectra of the amides **3**, the signals due to the alkyl substituent $R^3$ in the starting materials **1a–d** could not be found but a singlet at $\delta$ 4.93 assignable to an olefinic proton (**3a**) or a singlet around $\delta$ 1.6 assignable to methyl protons adjacent to a vinyl group (**3b–d**) were found, indicating the migration of the two $\alpha$-methylene protons of the 3-alkyl substituent. An exchangeable NH peak at $\delta$ 10–11 is consistent with that observed in other enamino ketones.[9] The amino function was inert to such acylating agents as acetyl chloride, acetic anhydride, diphenylketene, or phenyl isocyanate.

It should be also noted that highly complex multiplets were observed for the signals of *N*-methylene protons of the substituents $R^1$ and $R^2$ of **3a** and **3b**. The complexity derives from nonequivalence of the geminal protons of the methylene moiety adjacent to the nitrogens and is ascribable mainly to the sterically restricted free rotation of the carbon–nitrogen bonds. Similar nonequivalence is also found for the methylene group of **3c** or the two methyl groups of the isopropyl function of **3d**. These multiplets were successfully assigned with the aid of spin decoupling by double resonance.

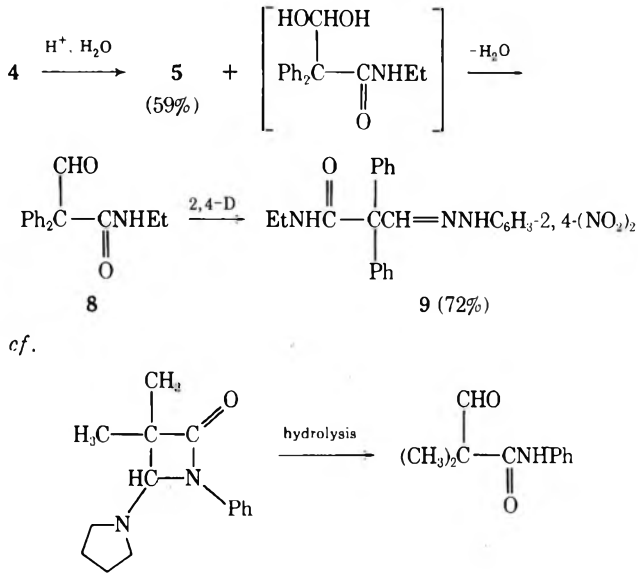
The two alkyl substituents $R^1$ and $R^2$ are easily distinguishable by observing the coupling with the amino pro-

tons. The substituent $R^1$ proved to be the less bulky one. It was also found that difference between the chemical shifts of the geminal methylene protons of $R^1$ is greater than that of $R^2$. The nmr spectrum of **3a** observed at higher temperature indicates reduction of rotational restriction; the two complex multiplets at $\delta$ 2.5–3.2 (three protons) and at $\delta$ 3.3–4.2 (one proton) observed at 23° in benzonitrile altered into a clear quartet at $\delta$ 2.96 (two protons) and a complex multiplet at $\delta$ 3.4–3.8 (two protons) at 120°.

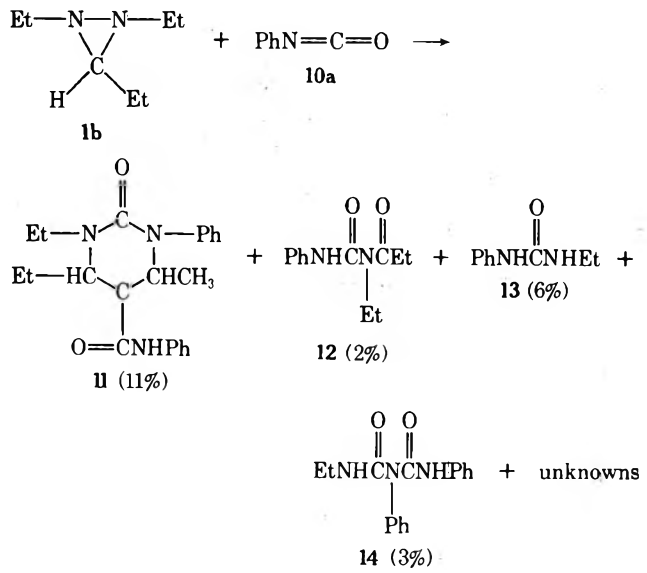
Chemical evidence for the structure of **3** was obtained by the acidic hydrolysis of **3b**, which gave *N*-ethyldiphenylacetamide (**5**) and 1,1-diphenylbutan-2-one (**7**). The latter product is considered to be formed by decarboxylation of the initially produced $\beta$-ketocarboxylic acid **6**.



The $\beta$-lactam **4**, the main product of the reaction of 1,2-diethyldiaziridine (**1e**) which has no 3-alkyl substituent to participate in the reaction, is also a 1:2 adduct. The adduct shows strong ir absorptions at 1755 (lactam CO) and 1633 $cm^{-1}$ (amide CO). The mass and nmr spectra are wholly compatible with the structure. Hydrolysis of the lactam **4** in refluxing aqueous ethanol in the presence of sulfuric acid gave the amide **5** and 2-ethylcarbamoyl-2,2-diphenylethanal (**8**), which was isolated as its 2,4-dinitrophenylhydrazone **9**. The hydrolysis probably occurs on the aminal-like linkage and is comparable to the hydrolysis of a $\beta$-amino-$\beta$-lactam which forms an $\alpha$-carbamoylaldehyde.[10]

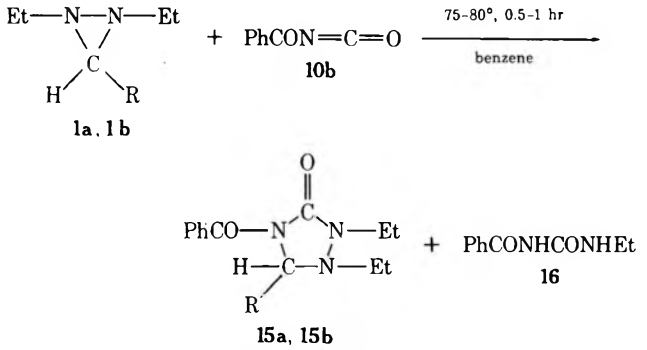


**Reaction with Isocyanates.** The reaction of 1,2,3-triethyldiaziridine (**1b**) with phenyl isocyanate (**10a**) in refluxing benzene or acetonitrile gave 2-methyl-5,6-diethyl-3-phenyl-1-phenylcarbamoylhexahydro-1,3,5-triazin-4-one (**11**), *N*-ethyl-*N*-propionyl-*N'*-phenylurea (**12**), *N*-ethyl-*N'*-phenylurea (**13**), and 1-ethyl-3,5-diphenylbiuret (**14**). The first compound **11** was proved to consist of 1 mol of the diaziridine **1b** and 2 mol of the isocyanate **10a** by elemental analysis and its molecular weight determined by mass spectroscopy. In the infrared spectrum, two strong absorption bands at 1685 and 1622 $cm^{-1}$ (C=O) and an absorption at



3200 $cm^{-1}$ (NH) were observed. In the nmr spectrum, the signals due to the EtCH moiety were found at $\delta$ 1.02 (triplet, 3, $J$ = 7.5 Hz), 2.03 (pentuplet, 2, $J$ = 7.5 Hz), and 5.44 (triplet, 1, $J$ = 7.5 Hz). Nevertheless, only one of the *N*-ethyl functions was found as signals at $\delta$ 1.16 (triplet, 3, $J$ = 7.1 Hz), 3.20 and 3.64 (double quartet, 1, $J_{vic}$ = 7.1, $J_{gem}$ = 14.2 Hz, NCHH– and NCHH–, respectively). A doublet at $\delta$ 1.35 (3, $J$ = 6.0 Hz) and a quartet at $\delta$ 5.78 (1, $J$ = 6.0 Hz) indicated that the other *N*-ethyl group in the starting diaziridine had been converted to a $-NCHCH_3$ moiety. The proton of the original *N*-ethyl group appeared as an NH proton whose signal was included in those of aromatic protons at $\delta$ 6.9–7.5. These spectral and mass spectral data (see Experimental Section) support the structure of **11**, and the other products were identified with authentic samples or confirmed by spectral and analytical data.

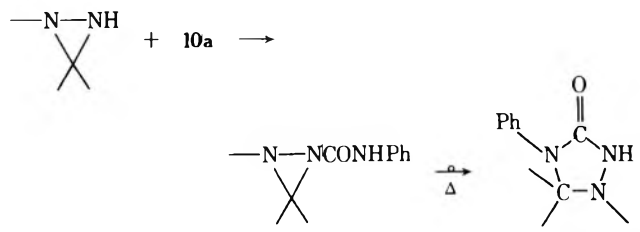
Because of the complexity of this reaction which might have been caused by the low reactivity of the isocyanate **10a** (reaction time 8–16 hr compared to 5 min for the ketene **2**), it was decided to employ benzoyl isocyanate (**10b**) in place of **10a**. The isocyanate **10b**, however, reacted with 1,2,3-trialkyldiaziridines **1a** and **1b** to give the 1:1 cycloadducts **15** and *N*-ethyl-*N'*-benzoylurea (**16**). This seems to be the first example of a cycloaddition reaction of a diaziridine.



| | Yield, % | |
|---|---|---|
| | **15** | **16** |
| **a**, R = Me | 30 | 18 |
| **b**, R = Et | 44 | 39 |

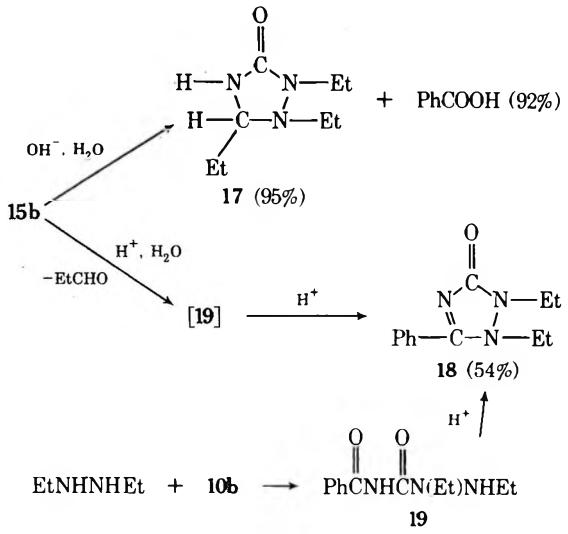
Though 1:1 cycloaddition of *N*-alkyloxaziridines to phenyl isocyanate[2] and addition reactions of N-substituted aziridines to the isocyanate under catalysis of lithium halide have been known, N,N'-dialkylated diaziridines do not undergo 1:1 cycloaddition with phenyl isocyanate or with diphenylketene. Nabeya and her coworkers recently reported

the anilinoformylation of 1,3-dialkyl-3-aryl- or 1-alkyl-3-aryldiaziridines with phenyl isocyanate and the rearrangement of the resulting 1-anilinoformyl-2-alkyl-3-aryldiaziridines to the isomeric triazolidinones.[12] Schmitz has also reported the formation of an anilinoformyl derivative of 1,3-dialkyldiaziridine and a triazolidinone from 1,3,3-trialkyldiaziridine,[13] showing subtle effects of the substituents. In view of Nabeya's results, the latter product is considered to be given not by a 1:1 cycloaddition but by a rearrangement of a labile anilinoformyldiaziridine.




The triazolidinones **15** show two strong carbonyl stretching vibrations at 1720 and 1650 $cm^{-1}$ in their ir spectra. Fragmentations in the mass spectra and the nmr signals are also in good agreement with the structure of **15.** In the nmr spectra, the methylene protons of the ethyl group of the 2 position are nonequivalent ($J_{gem}$ = 7.0 Hz), as is observed for the *N*-alkyl groups of the amides **3.**

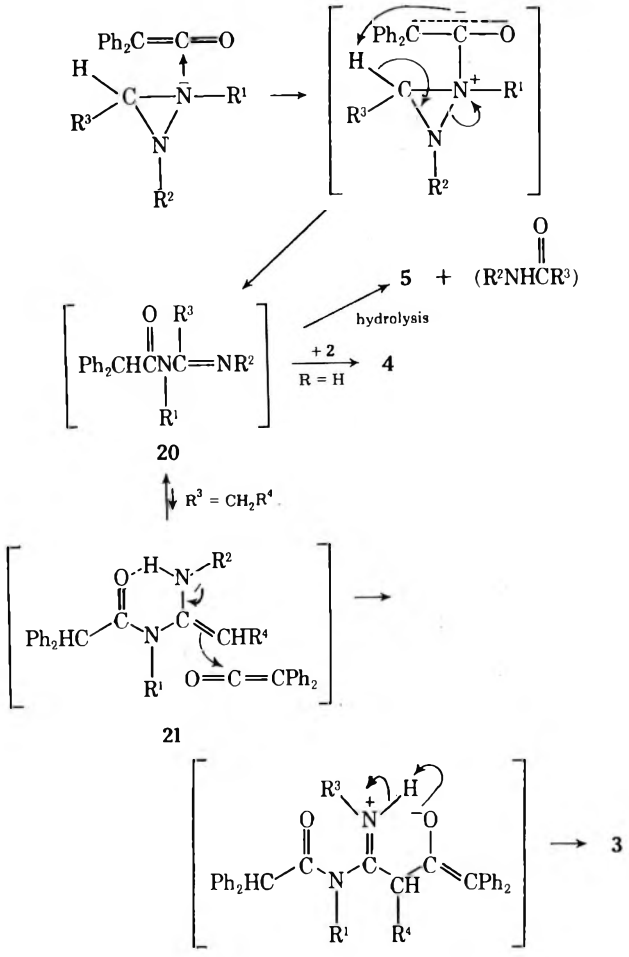
Hydrolysis of the 1:1 adduct **15b** gave further chemical evidence for the structure; alkaline hydrolysis gave 1,2,5-triethyl-1,2,4-triazolidin-3-one (**17**) and benzoic acid quantitatively, while acidic hydrolysis afforded 1,2-diethyl-5-phenyl-1,2,4-triazolin-3-one (**18**). The latter compound **18** is formed *via* the 4-acylsemicarbazide intermediate **19,** which was verified by the acidic treatment of the acylsemicarbazide **19** prepared from *N,N'*-diethylhydrazine and the isocyanate **10b.**[14]




## Discussion

A possible mechanism for the reaction of 1,2-dialkyldiaziridines with diphenylketene involves a nucleophilic attack of the nitrogen atom of a diaziridine to a central carbon atom of a cumulative bond of the ketene **2** followed by ring opening and transfer of the hydrogen on the ring carbon, leading to an amidine-type intermediate **20**[30] (Scheme I). The intermediate **20** probably tautomerizes into a ketene aminal-type intermediate **21** if the substituent $R^3$ is a primary alkyl group and the latter intermediate **21** in turn attacks the ketene, affording the amide **3.** When the substituent $R^3$ is a hydrogen (*i.e.*, **1e**), the intermediate **20** cannot convert into the aminal-type intermediate **21.** In this case, **20** reacts with diphenylketene to give the β-lactam **4.** Similar cycloadditions of ketenes to azomethines, including benzamidine derivatives,[15] are known to give β-lactams, 1,3-oxazin-6-ones, or piperidine-2,4-diones.[16]

**Scheme I**




In the reactions of **1a–e** with **2,** a considerable amount of *N*-ethyldiphenylacetamide (**5**) was produced. The formation of **5** is ascribed to the hydrolysis of the intermediate **20.** The other reason for the low yields of the amides **3** is polymerization of the ketene catalyzed by the basic species in the system, *e.g.*, starting diaziridines.

Steric factors apparently are important in the addition of the diaziridine to the ketene, since it is the nitrogen bearing the least bulky substituent that adds to the carbonyl carbon of the ketene.

Our attempts to isolate the intermediate **20** from a reaction mixture containing equimolar quantities of the diaziridine and the ketene were in vain. As an alternative path to the intermediate **20,** the reaction of amidines **22,** isomers of the diaziridines **1,** with the ketene **2** was studied, since it is reasonable to expect the formation of **20** in this system.

The reactions of amidines instead of diaziridines under the same conditions resulted in the same products in better yields and the results (listed in Table II) apparently indi-

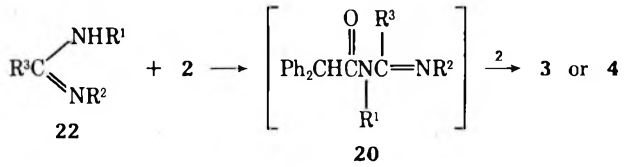
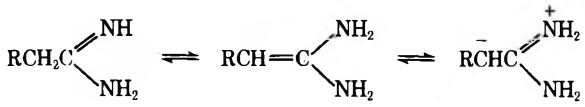


**Table II**
**Reaction of Amidines with Diphenylketene**

| | Amidine (22) | | | Reaction conditions[a] | | | |
|---|---|---|---|---|---|---|---|
| | $R^1$ | $R^2$ | $R^3$ | Temp, °C | Time, min | Product | Yield, % |
| **22a** | Et | Et | Me | 80 | 10 | **3a** | 12 |
| **22b** | Et | Et | Et | 80 | 10 | **3b** | 51 |
| **22e** | Et | Et | H | 70 | 10 | **4** | 63 |

[a] Benzene was employed as a solvent. Mole ratio of the amidine **22** to diphenylketene (**2**) was 0.5.

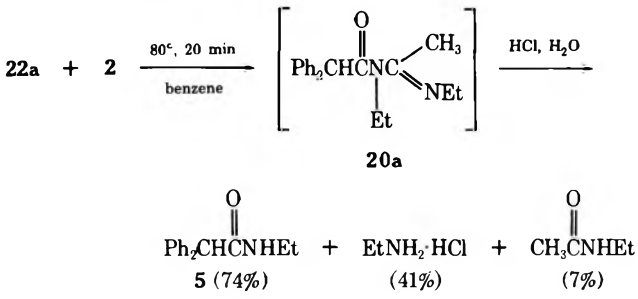
cate the intermediacy of **20**. The nucleophilicity of $\alpha$ carbons of amidines having $\alpha$-methylene groups as is present in **20** has been reported by Schaefer and his coworkers in the reactions of amidines with *s*-triazines; the ketene aminal form of the amidine is postulated to be the reactive



species as our assumption in Scheme I.[17] In addition, ketene aminals have been reported to form linear 1:1 or 1:2 adducts when treated with ketenes[18] or isocyanates[19] in accord with the assumed mechanism. Similar equilibria between azomethines and enamines have been proved[20] and enamines having a hydrogen on their $\beta$ carbons also give linear 1:1 adducts with heterocumulenes.[21]

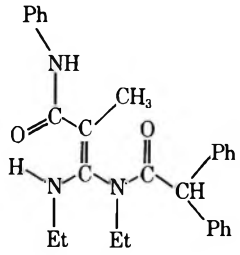
Since attempts to isolate the amidine-type intermediate **20** by chromatography or vacuum distillation from the reaction mixtures were unsuccessful, the nature of these reaction mixtures was studied.

The infrared spectrum of the mixture obtained by treating the ketene **2** with an excess of *N,N'*-diethylacetamidine (**22a**) followed by removal of the excess **22a** showed an intense absorption at 1640 $cm^{-1}$ and no absorption due to the 1:2 adduct. This mixture was hydrolyzed in the presence of hydrochloric acid and the resultant products imply that the main component of the mixture was the amidine **20a**.



An equimolar mixture of *N,N'*-diethylpropioamidine (**22b**), the isomer of the diaziridine **1b**, and the ketene **2** in benzene was warmed to 80° for 1 min. The ir spectrum of the mixture showed a deep and broad absorption band at 1640 $cm^{-1}$ and none of the bands due to the amide **3b**. The nmr spectrum of the mixture exhibited a sharp singlet at $\delta$ 5.6 assignable to the amino proton of the unreacted amidine **22b** and a singlet at $\delta$ 4.89 assignable to the methine proton of the diphenylacetyl moiety of the 1:1 adduct **20**. The reaction did not proceed so far in the state of this mixture. The spectrum was then taken soon after an additional 1 mol of the ketene had been added to this mixture. At this stage, the signal of the amino proton of the unreacted amidine diminished and the signals which coincided well with those of the 1:2 adduct **3b** increased in intensity. Though a considerable amount of the 1:1 adduct **20** was detected, none of the signals due to the aminal structure **21** (*e.g.*, a doublet of methyl protons of $C{=}CHCH_3$) was observed in the spectra. Thus the equilibrium between the intermediattattates is completely in favor of the amidine form **20**.

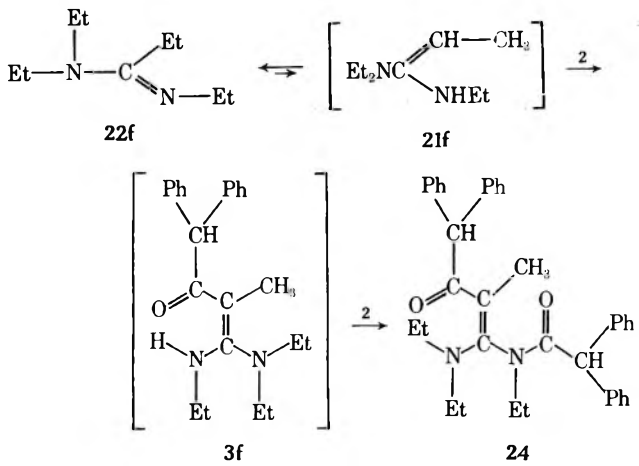
When the equimolar mixture of **22b** and **2** was treated with phenyl isocyanate instead of the ketene, the reaction was very slow and gave but a trace amount of the adduct **23**, corresponding to the amide **3**. This is consistent with



**23**

the result that the reaction of phenyl isocyanate (**10a**) with a diaziridine gave no 1:2 adduct corresponding to the amide **3** (or **23**).

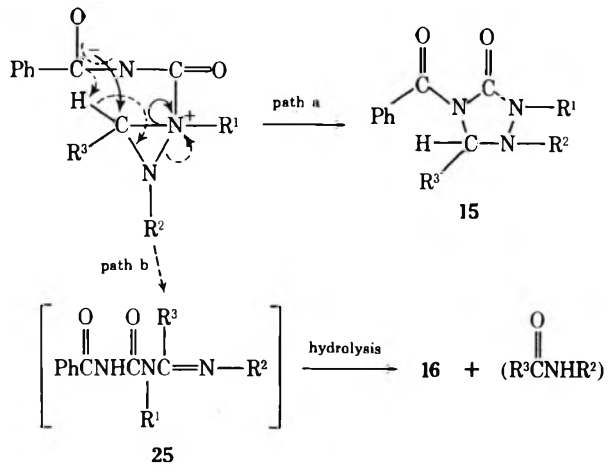
The entire spectral and chemical evidence on the mixtures is a satisfactory rationale for the postulated mechanism. Furthermore, *N,N,N'*-triethylpropioamidine (**22f**), a model compound for the intermediate **20**, was allowed to react with the ketene **2** to give the amide **24** (12% yield), which is considered to be formed *via* the amide **3f** corresponding to the amide **3**. The low reactivity of the model compound **22f** compared with the intermediate **20** may be attributed to the lack of contribution of the hydrogen bonding in the form of the aminal-type intermediate **21f** in contrast to **21**. Though the amide **3f** further reacts with the ketene to give the amide **24**, the amino function of



the amide **3** was not susceptible to the ketene or other acylating agents. This is because of replacement of an ethyl group by diphenylacetyl moiety that reduces the nucleophilicity of the amino nitrogen with its electron-withdrawing and steric hindrance.

In contrast to the reaction of diaziridines with diphenylketene, whereby the nitrogen–nitrogen bond of the ring is cleaved, diaziridines react with benzoyl isocyanate by rupture of the carbon–nitrogen bond of the ring (path a in Scheme II). The formation of the urea **16**, however, suggests hydrolysis of an amidine-type 1:1 adduct **25**,[30] which corresponds to the intermediate **20**. Hence, both fissions of the carbon–nitrogen and the nitrogen–nitrogen bonds were observed in this reaction. The difference from the reaction with the ketene **2** would be attributable to the higher basicity of the anion developed on the ketene upon nucleophilic attack of a diaziridine compared with the de-

**Scheme II**



localized one on the isocyanate **10b.** The more basic anion on the ketene will cause the exclusive hydrogen abstraction from the diaziridine which leads to the intermediate **20.**

In the case of phenyl isocyanate (**10a**), the situation is expected to be intermediate between the above two cumulenes. The products identified in the reaction with **10a** can be interpreted as depicted in Scheme III. Path b is similar to that for the other cumulenes and further reaction of the intermediate **25'** [30] to the hexahydrotriazinedione **27** is deducible from the reported reaction of formamidine and isocyanates.[22] The formation of the urea **12,** the urea **13,** and the biuret **14** is ascribable to hydrolysis of **25'** and **27,** respectively. Path c does not lead to a 1:1 cycloadduct but instead to the hexahydrotriazinone **28** as a result of a hydride shift. Such hydride shifts giving a hexahydrotriazine structure have been observed in the reaction of oxaziridines with diphenylcarbodiimide.[2] These hexahydrotriazine derivatives, including the intermediates, are generally unstable and their decomposition and further reactions with **10a** are also possible. For example, the intermediate **26** may be in equilibrium with ethyl isocyanate and *N*-ethyl-*N*-anilinoformyl-*N'*-propioamidine through a diazetidinone.[22] Hence, these complicated systems will make the reaction complex. The behavior of diaziridines, however, is similar to that in the reaction with the ketene showing the nitrogen–nitrogen bond cleavage.

## Experimental Section

All melting points were determined on a Yanagimito micro melting point apparatus and are uncorrected. Infrared, nuclear magnetic resonance, and mass spectra were taken on a Jasco IR-E spectrophotometer, JEOL LNM-PS-100 and JEOL LNM-3H-60 spectrometers, and a Hitachi RMU-6E spectrometer, respectively.

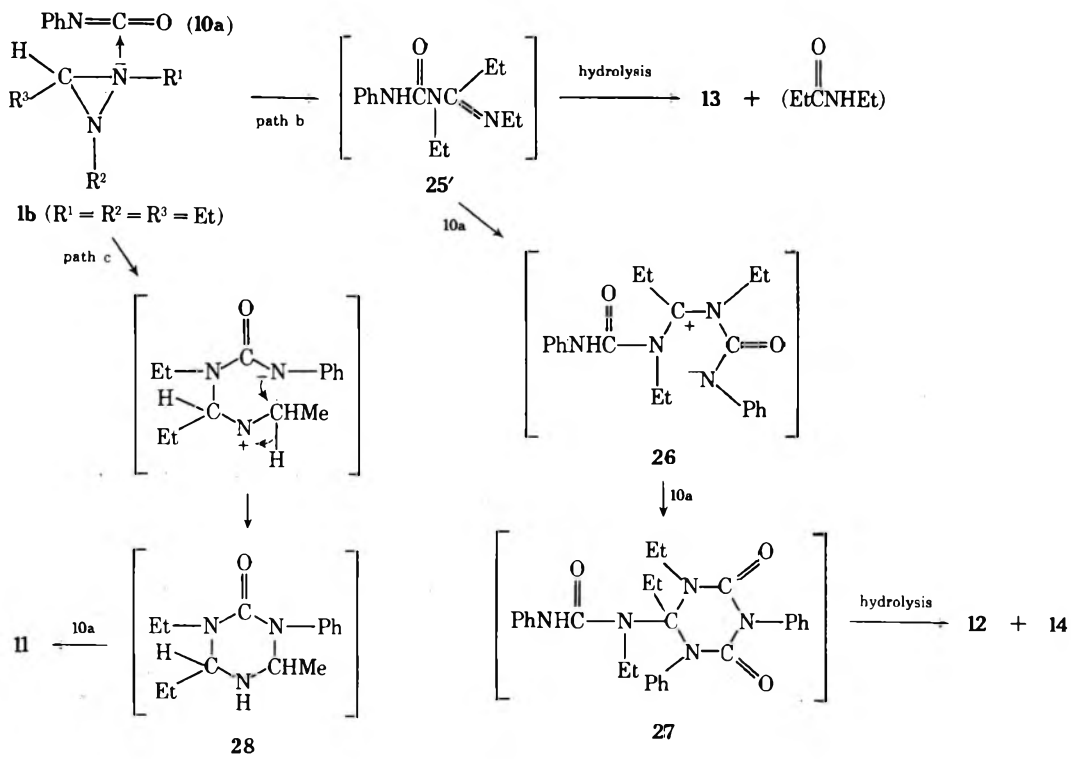
All reactions were carried out under a nitrogen stream in a 50-ml four-necked flask equipped with a stirrer, a reflux condenser, a dropping funnel, and a thermometer. Products were isolated by column chromatography (basic aluminum oxide–benzene).

**Materials.** Diphenylketene (**2**) and benzoyl isocyanate (**10b**) were prepared by known methods.[23,24] Commercially available phenyl isocyanate (**10a**) was used after distillation. Diaziridines **1a–e** were prepared according to Schmitz's procedures.[25] Boiling points, purities determined by iodometry[25] and glpc, and yields are as follows: 1,2-diethyl-3-methyldiaziridine (**1a**), 53–55° (70 mm), 90%, 14%; 1,2,3-triethyldiaziridine (**1b**), 56° (40 mm), 93%, 35%; 1-methyl-2-*n*-propyl-3-ethyldiaziridine (**1c**), 63° (60 mm), 93%, 16%; 1-methyl-2-isopropyl-3-ethyldiaziridine (**1d**), 74–77° (62 mm), 84%, 4%; 1,2-diethyldiaziridine (**1e**), 95°, 91%, 5%.

Preparations of the amidines **22a** and **22b** were done by a modified procedure of Brown[26] and the amidines **22e** and **22f** were prepared by known methods.[27,28] Boiling points, purities checked by glpc and nmr spectra, and yields are as follows: *N,N'*-diethylacetamidine (**22a**), 80° (30 mm), 98%, 61%; *N,N'*-diethylpropioamidine (**22b**), 88° (28 mm), 92%, 31%; *N,N'*-diethylformamidine (**22e**), 69° (20 mm), 92%, 24%; *N,N,N'*-triethylacetamidine (**22f**), 87° (27 mm), 96%, 33%.

**Reaction with Diphenylketene (2). Reaction of the Diaziridine 1a.** A solution of the ketene **2** (5.8 g, 30 mmol) in benzene (10 ml) was heated to 75° under a nitrogen atmosphere. Then 1,2-diethyl-3-methyldiaziridine (**1a,** 1.7 g, 15 mmol) was added dropwise with stirring at such a rate that the reaction temperature did not rise above 80°. The ir spectrum of the mixture showed disappearance of **2** in 5 min. The reaction mixture was concentrated and chromatographed to give 421 mg (6%) of *N*-ethyl-*N*-(1-ethylamino-3-oxo-4,4-diphenylbut-1-en-1-yl)diphenylacetamide (**3a**), a small amount of *N*-ethyldiphenylacetamide (**5**), and a large amount of viscous oil. The amide **3a** was recrystallized from benzene–ethanol to give colorless granules: mp 175–176°; ir (Nujol) 3350 (broad and weak, NH), 1655 (amide C=O), 1615 (C=O),

**Scheme III**



1582 (sh) and 1568 $cm^{-1}$ (C=C or C=N); nmr ($CDCl_3$) $\delta$ 0.93 (t, $J$ = 7.2 Hz, 3, $CH_3$), 1.10 (t, $J$ = 7.0 Hz, 3, $CH_3$), 2.65 (ddq, $J$ (*gem*) = 13.1, $J$ ($CH_3$) = 7.2, $J$ (NH) = 5.8 Hz, 1, HNCHH–), 2.97 (ddq, $J$ (*gem*) = 13.1, $J$ ($CH_3$) = 7.2, $J$ (NH) = 5.8 Hz, 1, HNCHH–), 3.02 (dq, $J$ (*gem*) = 14.0, $J$ ($CH_3$) = 7.0 Hz, 1, NCHH–), 3.92 (dq, $J$ (*gem*) = 14.0, $J$ ($CH_3$) = 7.0 Hz, 1, NCHH–), 4.89 (s, 1, $Ph_2CH$), 4.96 (s, 1, C=CCH), 5.13 (s, 1, $Ph_2CH$), 6.9–7.5 (m, 20, 4 Ph), 10.3 (t, $J$ = 5.8 Hz, 1, NH); mass spectrum (70 eV) *m/e* 502 ($M^+$, calcd 502), 335 ($M^+ - Ph_2CH$), 307 ($M^+ - Ph_2CHCO$), 264 ($M^+ -$ PhCHCONEt), 222 ($Ph_2CCNEt^+$), 194 ($Ph_2CCO^+$).

*Anal.* Calcd for $C_{34}H_{34}N_2O_2$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.00; H, 6.86; N, 5.81.

**Reactions of the Diaziridine 1b.** The diaziridine **1b** (0.93 g, 7.3 mmol) was treated with the ketene **2** (2.9 g, 15 mmol) in refluxing benzene for 5 min by the same procedure as above. The reaction mixture was concentrated to precipitate 1.99 g (53%) of crystalline *N*-ethyl-*N*-(1-ethylamino-2-methyl-3-oxo-4,4-diphenylbut-1-en-1-yl)diphenylacetamide (**3b**) and the residue was viscous oily materials. Recrystallization of the amide **3b** from benzene–hexane afforded colorless granules: mp 153–154°; ir (Nujol) 3400 (broad and weak, NH), 1668 (amide C=O), 1610 (C=O), 1580 (sh) and 1560 $cm^{-1}$ (C=C or C=N); nmr ($CDCl_3$) $\delta$ 0.85 (t, $J$ = 6.9 Hz, 3, $CH_3$), 1.11 (t, $J$ = 7.1 Hz, 3, $CH_3$), 1.51 (s, 3, C=C$CH_3$), 2.60 (ddq, $J$ (*gem*) = 13.2, $J$ ($CH_3$) = 6.9, $J$ (NH) = 5.5 Hz, 1, NHCHH–), 2.96 (ddq, $J$ (*gem*) = 13.2, $J$ ($CH_3$) = 6.9 Hz, 1, NHCHH–), 3.41 (dq, $J$ (*gem*) = 14.3, $J$ ($CH_3$) = 7.1 Hz, 1, NCHH–), 3.68 (dq, $J$ (*gem*) = 14.3, $J$ ($CH_3$) = 7.1 Hz, 1, NCHH–), 4.86 (s, 1, $Ph_2CH$), 5.38 (s, 1, $Ph_2CH$), 6.9–7.6 (m, 20, 4 Ph), 11.3 (t, $J$ = 5.5 Hz, 1, NH); mass spectrum (70 eV) *m/e* 516 ($M^+$, calcd 516), 349 ($M^+ - Ph_2CH$), 321 ($M^+ - Ph_2CHCO$), 278 ($M^+ - Ph_2 -$ CHCONEt), 221 ($Ph_2CCNEt^+$), 194 ($Ph_2CCO^+$).

*Anal.* Calcd for $C_{35}H_{36}N_2O_2$: C, 81.36; H, 7.02; N, 5.42. Found: C, 81.59; H, 7.11; N, 5.49.

When the reaction temperature was a little lower (70°), the yield of the amide **3b** decreased; from 2.1 g (16 mmol) of **1b** and 6.1 g (31 mmol) of **2**, 2.56 g (32%) of the amide **3b** was obtained. An equimolar reaction also gave the amide in a low yield: 1.25 g (17%) of **3b** was obtained from the reaction mixture of 5.7 g (29 mmol) of **2** and 3.9 g (30 mmol) of **1b** treated at 80° for 5 min. The amide **3b** was isolated by column chromatography in the latter two reactions and 50–100 mg of the amide **5** and large amount of polymeric substances were obtained.

**Reactions of the Diaziridine 1c.** The same treatment (80°, 5 min) of the diaziridine **1c** (1.9 g, 15 mmol) and the ketene **2** (5.2 g, 27 mmol) as in the above reactions gave 1.02 g (15%) of *N*-methyl-*N*-(1-*n*-propylamino-2-methyl-3-oxo-4,4-diphenylbut-1-en-1-yl)-diphenylacetamide (**3c**) and polymeric materials with a small amount of the amide **5**.

When the reaction was carried out at 45°, the infrared spectrum of the reaction mixture showed the rapid consumption of **2** and the formation of a large amount of poymers of **2**.

The amide **3c** was recrystallized from benzene–hexane to give colorless granules: mp 110–111°; ir (Nujol) 3350 (broad and weak, NH), 1665 (amide C=O), 1612 (C=O), 1580 (sh) and 1562 $cm^{-1}$ (C=C or C=N); nmr ($CDCl_3$) $\delta$ 0.71 (t, $J$ = 7.4 Hz, $CH_3$), 1.52 (s, 3, C=C$CH_3$), 1.57 (dq, $J$ ($CH_2$) = 6.6, $J$ ($CH_3$) = 7.4 Hz, 2, $CH_2CH_3$), 2.58 (ddt, $J$ (*gem*) = 13.3, $J$ ($CH_2$) = 6.6, $J$ (NH) = 5.8 Hz, 1, NHCHH–), 2.87 (ddt, $J$ (*gem*) = 13.3, $J$ ($CH_2$) = 6.6, $J$ (NH) = 5.8 Hz, 1, NHCHH–), 3.01 (s, 3, $NCH_3$), 4.86 (s, 1, $Ph_2CH$), 5.36 (s, 1, $Ph_2CH$), 7.0–7.6 (m, 20, 4 Ph), 11.2 (t, $J$ = 5.8 Hz, 1, NH); mass spectrum (70 eV) *m/e* 516 ($M^+$, calcd 516), 349 ($M^+ - Ph_2CH$), 321 ($M^+ - Ph_2CHCO$), 292 ($M^+ - Ph_2CHCONMe$), 207 ($Ph_2CCNMe^+$), 194 ($Ph_2CCO^+$).

*Anal.* Calcd for $C_{35}H_{36}N_2O_2$: C, 81.36; H, 7.02; N, 5.42. Found: C, 81.21; H, 7.03; N, 5.70.

**Reaction of the Diaziridine 1d.** From the reaction of 0.80 g (6.2 mmol) of the diaziridine **1d** and 2.46 g (13 mmol) of the ketene **2**, 0.98 g (31%) of *N*-methyl-*N*-(1-isopropylamino-2-methyl-3-oxo-4,4-diphenylbut-1-en-1-yl)diphenylacetamide (**3d**) and 0.1 g of the amide **5** were obtained after the same treatment as above. Recrystallization of **3d** from benzene–ether gave colorless granules: mp 149–151°; ir (Nujol) 3350 (broad and weak, NH), 1657 (amide C=O), 1615 (C=O), 1580 (sh) and 1562 $cm^{-1}$ (C=C or C=N); nmr ($CDCl_3$) $\delta$ 0.68 and 1.08 (d, $J$ (CH) = 6.6 Hz, 3, $CH_3$, respectively), 1.45 (s, 3, C=C$CH_3$), 3.04 (s, 3, $NCH_3$), 3.40 (d–septet, $J$ ($CH_3$) = 6.6, $J$ (NH) = 9.6 Hz, 1, NHCH–), 4.90 (s, 1, $Ph_2CH$), 5.36 (s, 1, $Ph_2CH$), 6.9–7.7 (m, 20, 4 Ph), 11.3 (d, $J$ = 9.6 Hz, 1, NH); mass spectrum (70 eV) *m/e* 516 ($M^+$, calcd 516), 349 ($M^+ - Ph_2CH$), 322 ($M^+ - Ph_2CCO$), 207 ($Ph_2CCNMe^+$), 194 ($Ph_2CCO^+$).

*Anal.* Calcd for $C_{35}H_{36}N_2O_2$: C, 81.36; H, 7.03; N, 5.42. Found: C, 81.50; H, 6.96; N, 5.58.

**Reaction of the Diaziridine 1e.** The treatment of the diaziridine **1e** (1.53 g, 15 mmol) with the ketene **2** (5.82 g, 30 mmol) at 80° for 5 min resulted in 1.90 g (26%) of 1-ethyl-3,3-diphenyl-4-(*N*-ethyldiphenylacetamido)azetidin-2-one (**4**) and the amide **5** (380 mg).

The azetidinone **4** for analysis was obtained by recrystallization from benzene–ethanol as colorless granules: mp 154°; ir (KBr disk) 1755 and 1633 $cm^{-1}$ (C=O); nmr ($CDCl_3$) $\delta$ 0.99 (t, $J$ = 7.2 Hz, 3, $CH_3$), 1.15 (t, $J$ = 7.2 Hz, 3, $CH_3$), 2.63 (dq, $J$ (*gem*) = 14.4, $J$ ($CH_3$) = 7.2 Hz, 1, –CHH– on the ring nitrogen), 2.70 (dq, $J$ (*gem*) = 14.4, $J$ ($CH_3$) = 7.2 Hz, 1, –CHH– on the ring nitrogen), 2.89 (dq, $J$ (*gem*) = 14.2, $J$ ($CH_3$) = 7.2 Hz, 1, NCHH–), 3.59 (dq, $J$ (*gem*) = 14.2, $J$ ($CH_3$) = 7.2 Hz, 1, NCHH–), 5.12 (s, 1, $Ph_2CH$), 6.80 (s, 1, NCHN), 6.9–7.9 (m, 20, 4 Ph); mass spectrum (70 eV) *m/e* 488 ($M^+$, calcd 488), 294 ($M^+ - Ph_2CCO$), 222 ($M^+ - Ph_2CHCO - EtNCO$), 71 ($EtNCO^+$).

*Anal.* Calcd for $C_{33}H_{32}N_2O_2$: C, 81.12; H, 6.60; N, 5.73. Found: C, 81.39; H, 6.71; N, 5.62.

**Hydrolysis of the Amide 3b.** To a solution of the amide **3b** (3.0 g, 5.8 mmol) in tetrahydrofuran (30 ml), 5 ml of 47% hydrobromic acid was added and the mixture was refluxed for 36 hr. Then the solvent was removed and extracted (ether). The aqueous layer was made alkaline and extracted (ether). The combined ethereal extract was dried ($Na_2SO_4$), concentrated, and chromatographed to give 992 mg (71%) of *N*-ethydiphenylacetamide (**5**) and 710 mg (55%) of 1,1-diphenylbutan-2-one (**7**). The amide **5** was identical with an authentic sample and the latter compound **7** was purified by pot distillation (110°, 20 mm): ir (neat) 1720 $cm^{-1}$ (C=O); nmr ($CCl_4$) $\delta$ 1.02 (t, 3, $J$ = 7.2 Hz, $CH_3$), 2.49 (q, 2, $J$ = 7.2 Hz, $CH_2$), 5.01 (s, 1, CH), 7.0–7.3 (10, 2 Ph); mass spectrum (70 eV) *m/e* 224 ($M^+$, calcd 224), 167 ($Ph_2CH^+$).

**Hydrolysis of the Azetidinone 4.** A solution of the azetidinone **4** (845 mg) in ethanol (50 ml) containing 2.5 ml of 50% sulfuric acid was refluxed for 20 hr. Then 300 mg of 2,4-dinitrophenylhydrazine and 2 ml of dilute sulfuric acid were added and the solution was refluxed for an additional 1 hr. The solution was concentrated, extracted (benzene), and dried ($Na_2SO_4$). From the organic layer, 165 mg (72%) of *N*-ethyl-2,2-diphenyl-3-(2,4-dinitrophenylhydrazono)propanamide (**9**), 72 mg (59%) of the amide **5**, and 595 mg of the unreacted **4** were obtained. The yields are calculated on the hydrolyzed **4**.

The hydrazone **9** was recrystallized from benzene–ethanol to give a yellow powder: mp 238–240°; ir (Nujol) 3400 and 3220 (NH), 1650 (C=O), 1610 (C=N), 1580 (NH), and 1500 $cm^{-1}$ ($NO_2$); nmr ($CDCl_3$) $\delta$ 1.17 (t, 3, $CH_3$), 3.45 (q, 2, $CH_2$), 5.60 (s, 1, CONH), 7.1–7.5 (m, 10, 2 Ph), 7.58 (d, 1), 8.27 (dd, 1), 8.47 (s, 1, N=CH), 9.14 (d, 1), 11.23 (s, 1, NHN) (the unassigned three signals are due to the protons of the 6, 5, and 3 position of the dinitrophenyl group, respectively; the singlet in the lowest field disappeared upon addition of deuterium oxide); mass spectrum (70 eV) *m/e* 447 ($M^+$, calcd 447), 375 ($M^+ - EtNHCO$), 341 ($M^+ - Ph - Et$), 239 ($EtNHCOCHPh_2^+$).

*Anal.* Calcd for $C_{23}H_{21}N_5O_5$: C, 61.74; H, 4.73; N, 15.65. Found: C, 61.74; H, 4.53; N, 15.61.

**Reactions of the Amidines 22a, 22b, and 22e.** Reactions of these amidines with the ketene **2** were carried out under such conditions as those in the reactions of the corresponding diaziridines **1a**, **1b**, and **1e**. The results are listed in Table II.

**Acidic Hydrolysis of the Reaction Mixture of the Amidine 22a and the Ketene 2.** To a solution of 5.70 g (50 mmol) of the amidine **22a** in 10 ml of benzene, 5.20 g (27 mmol) of the ketene **2** was added dropwise with stirring at 80° over 5 min and the mixture was stirred and refluxed for another 20 min. The ir spectrum of the reaction mixture showed a strong absorption band at 1640 $cm^{-1}$ and none of those corresponding to the 1:2 adduct **3a**. Then the mixture was distilled to remove the solvent and the excess amidine, which amounted to 1.95 g (74% yield calculated on the basis of the equimolar reaction). The residue indicated no essential changes in the infrared spectrum and 4.05 g of the residue was hydrolyzed in refluxing ethanol containing 1 ml of concentrated hydrochloric acid for 12 hr. Concentration and cooling of the mixture gave 1.27 g of the amide **5** and 0.42 g (41%) of ethylamine hydrochloride. The filtrate was alkalified and extracted ($CHCl_3$), dried ($Na_2SO_4$), concentrated, and distilled under reduced pressure up to 70° (1 mm). The distillate was proved to contain 77 mg (7%) of *N*-ethylacetamide. The residue was chromatographed to give 1.04 g of the amide **5** whose total yield was 74%.

**Treatment of an Equimolar Reaction Mixture of the Ami-**

**dine 22b and the Ketene 2 with Phenyl Isocyanate (10a).** Only a trace amount of 1:1:1 adduct, *N*-ethyl-*N*-(1-ethylamino-2-phenylcarbamoyl-1-propen-1-yl)diphenylacetamide (**23**), was obtained. The ir and mass spectra showed replacement of one of the diphenylacetyl groups of **3b** with a phenylcarbamoyl group: ir (Nujol) 3300 (NH), 1650 (C=O), 1600, and 1545 $cm^{-1}$; mass spectrum (70 eV) *m/e* 441 ($M^+$).

**Reaction of the Amidine 22f.** Treatment of the amidine **22f** (1.1 g, 7.0 mmol) and the ketene **2** (1.75 g, 9.0 mmol) in refluxing benzene for 1 hr yielded 0.29 g (12% of *N*-ethyl-*N*-(1-diethylamino-2-methyl-3-oxo-4,4-diphenylbut-1-en-1-yl)diphenylacetamide (**24**). The amide **24** was recrystallized from benzene to afford colorless granules: mp 136–138°; ir (Nujol) 1660 (amide C=O), 1625 (C=O), and 1580 $cm^{-1}$ (C=C); nmr ($CDCl_3$) $\delta$ 0.88 (t, 6, 2 $CH_3$), 1.17 (t, 3, $CH_3$), 1.72 (s, 3, C=$CCH_3$), 2.5–3.4 (m, 5, 2 $CH_2$ and a proton of $CH_2$), 3.5–4.2 (m, 1, a proton of $CH_2$), 5.24 (s, 1, $Ph_2CH$), 5.46 (s, 1, $Ph_2CH$), 6.9–7.5 (m, 20, 4 Ph); nonequivalent *N*-methylene protons were similar to those of the amides **3**; mass spectrum (70 eV) *m/e* 377 ($M^+ - Ph_2CH$), 349 ($M^+ - Ph_2CCO$), 221 ($Ph_2CCNEt^+$).

*Anal.* Calcd for $C_{37}H_{40}N_2O_2$: C, 81.58; H, 7.40; N, 5.88. Found: C, 81.59; H, 7.51; N, 5.52.

**Reaction with Isocyanates. Reaction of the Diaziridine 1b with the Isocyanate 10a.** A mixture of 3.9 g (30 mmol) of the diaziridine **1b**, 4.8 g (40 mmol) of the isocyanate **10a** and 15 ml of acetonitrile was refluxed for 10 hr. The mixture was then concentrated and chromatographed to give 770 mg (11%) of 4-methyl-1,6-diethyl-3-phenyl-5-phenylcarbamoylhexahydro-1,3,5-triazin-2-one (**11**), 190 mg (2%) of *N*-ethyl-*N*-propionyl-*N'*-phenylurea (**12**), 405 mg (6%) of *N*-ethyl-*N'*-phenylurea (**13**), 155 mg (3%) of 1-ethyl-3,5-diphenylbiuret (**14**), small amounts of unidentified materials, and a large amount of viscous oil. The yields are calculated on the basis of **10a**.

Changes in the reaction temperature, the mole ratio of **1b** to **10a**, or solvents caused no essential changes in the products but slightly influenced on their yields.

The triazinone **11** was recrystallized from benzene–ethanol to afford colorless granules: mp 175–176°; ir (Nujol) 3200 (NH), 1685 (C=O), and 1622 $cm^{-1}$ (C=O); nmr ($CDCl_3$) $\delta$ 1.02 (t, 3, $J$ = 7.5 Hz, $CHCH_2CH_3$), 1.16 (t, 3, $J$ = 7.1 Hz, $NCH_2CH_3$), 1.35 (d, 3, $J$ = 6.0 Hz, $CHCH_3$), 2.03 (p, 2, $J$ = 7.5 Hz, $CHCH_2$–), 3.20 and 3.64 (dq, 1, $J$ (*vic*) = 7.1, $J$ (*gem*) = 14.2 Hz, NCHH– and NCHH–, respectively), 5.44 (t, 1, $J$ = 7.5 Hz, $CHCH_2$–), 5.78 (q, 1, $J$ = 6.0 Hz, $CHCH_3$), 6.9–7.5 (m, 11, NH and aromatic protons); mass spectrum (70 eV) *m/e* 366 ($M^+$, calcd 366), 337 ($M^+ - Et$), 295 ($M^+ - EtNCO$), 274 ($M^+ - PhNH$), 247 ($M^+ - PhNCO$), 218 (337 – PhNCO), 204 ($M^+ - EtNCONPh$), 162 (247 – EtCHNEt), 134 ($PhNCONH^+$), 120 ($PhNHCO^+$), 119 ($PhNCOSUPN^+$), 85 ($EtCH{=}NEt^+$).

*Anal.* Calcd for $C_{21}H_{26}N_4O_2$: C, 68.83; H, 7.15; N, 15.29. Found: C, 69.13; H, 7.19; N, 14.97.

The urea **12** for analysis was obtained by recrystallization from benzene–hexane as colorless needles: mp 91–92°; ir (Nujol) 3380 (NH), 1700, 1648, 1592, and 1545 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ 1.21 (t, 3, $J$ = 7.1 Hz, $CH_3$), 1.29 (t, 3, $J$ = 7.0 Hz, $CH_3$), 2.64 (q, 2, $J$ = 7.1 Hz, $CH_2$), 3.87 (q, 2, $J$ = 7.0 Hz, $NCH_2$), 6.9–7.6 (m, 5, Ph), 11.6 (broad, 1, NH); mass spectrum (70 eV) *m/e* 220 ($M^+$, calcd 220), 163 ($M^+ - EtCO$), 119 ($PhNCO^+$), 101 ($M^+ - PhNCO$).

Recrystallization of the biuret **14** from benzene–hexane gave colorless needles: mp 148–150°; ir (Nujol) 3280 and 3150 (NH), 1702, 1615, 1590, 1550 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ 1.35 (t, 3, $J$ = 7.0 Hz, $CH_3$), 3.93 (q, 2, $J$ = 7.0 Hz, $CH_2$), 6.9–7.6 (m, 10, 2 Ph), 9.18 (s, 2, 2 NH); mass spectrum (70 eV) *m/e* 283 ($M^+$, calcd 283), 212 ($M^+ - EtNCO$), 164 ($M^+ - PhNCO$), 163 ($M^+ - PhNHCO$), 119 ($PhNCO^+$).

**Reaction of the Diaziridine 1a with the Isocyanate 10b.** A solution of 3.4 g (30 mmol) of the diaziridine **1a** in 10 ml of benzene was warmed to 80° and 3.8 g (26 mmol) of the isocyanate **10b** in 5 ml of benzene was added dropwise to the solution with stirring over 15 min. The mixture was stirred and refluxed for 20 min until ir absorption of the isocyanate disappeared. The mixture was concentrated and chromatographed to give 2.0 g (30%) of 5-methyl-1,2-diethyl-4-benzoyl-1,2,4-triazolidin-3-one (**15a**) and 0.87 g (18%) of *N*-ethyl-*N'*-benzoylurea (**16**). The former product was recrystallized from benzene–hexane to give colorless granules: mp 54–56°; ir (Nujol) 1720 and 1655 $cm^{-1}$ (C=O); nmr ($CDCl_3$) $\delta$ 1.16 (t, 3, $J$ = 7.0 Hz, $CH_3$), 1.19 (t, 3, $J$ = 7.0 Hz, $CH_3$), 1.48 (d, 3, $J$ = 6.0 Hz, $CHCH_3$), 2.88 (q, 2, $J$ = 7.0 Hz, $NCH_2$), 3.16 and 3.63 (dq, 1, $J$ (*vic*) = $J$ (*gem*) = 7.0 Hz, NCHH– and NCHH–, respectively), 5.12 (q, 1, $J$ = 6.0 Hz, CH), 7.2–7.7 (m, 5, Ph); mass spectrum (70 eV) *m/e* 261 ($M^+$, calcd 261), 246 ($M^+ - Me$), 156 ($M^+ - PhCO$), 87 ($EtNNHEt^+$).

*Anal.* Calcd for $C_{14}H_{19}N_3O_2$: C, 64.34; H, 7.33; N, 16.08. Found: C, 64.27; H, 7.35; N, 16.08.

The urea **16** was identified with an authentic sample.

**Reaction of the Diaziridine 1b with the Isocyanate 10b.** The same treatment of the diaziridine **1b** (6.4 g, 50 mmol) and the isocyanate **10b** (2.7 g, 18 mmol) in refluxing benzene as in the above reaction gave 2.20 g (44%) of 1,2,5-triethyl-4-benzoyl-1,2,4-triazolidin-3-one (**15b**) and 1.40 g (39%) of the urea **16**. The triazolidinone **15b** was recrystallized from benzene–hexane to give colorless prisms: mp 101–102°; ir (Nujol) 1720 and 1650 $cm^{-1}$ (C=O); nmr ($CDCl_3$) $\delta$ 1.04 (t, 3, $J$ = 6.4 Hz, $CHCH_2CH_3$), 1.17 (t, 3, $J$ = 7.0 Hz, $NCH_2CH_3$), 1.19 (t, 3, $J$ = 7.0 Hz, $NCH_2CH_3$), 1.5 (m, 1, $CHCHHCH_3$), 2.0 (m, 1, $CHCHHCH_3$), 2.88 (q, 2, $NCH_2$), 3.10 and 3.67 (dq, 1, $J$ (*vic*) = 7.0, $J$ (*gem*) = 14.0 Hz, NCHH– and NCHH–, respectively), 4.85 (dd, 1, $CHCH_2$), 7.3–7.7 (m, 5, Ph); mass spectrum (70 eV) *m/e* 275 ($M^+$, calcd 275), 246 ($M^+ - Et$), 170 ($M^+ - PhCO$), 141 (246 – PhCO).

*Anal.* Calcd for $C_{15}H_{21}N_3O_2$: C, 65.43; H, 7.67; N, 15.26. Found: C, 65.26; H, 7.85; N, 15.54.

**Alkaline Hydrolysis of the Triazolidinone 15b.** To a solution of 1.0 g (36 mmol) of the triazolidinone **15b** in 15 ml of ethanol, 2 ml of 6 *N* potassium hydroxide solution was added and the mixture was refluxed for 3 hr. The mixture was concentrated and extracted with chloroform and dilute aqueous potassium hydroxide. The organic layer was dried ($Na_2SO_4$) and concentrated to give 0.50 g (95%) of 1,2,5-triethyl-1,2,4-triazolidin-3-one (**17**). The aqueous layer was acidified with concentrated hydrochloric acid and extracted ($CHCl_3$), dried ($Na_2SO_4$), and concentrated to afford 0.44 g (92%) of benzoic acid. The triazolidinone **17** was purified by sublimation: colorless plates; mp 46–48°; ir (KBr disk) 3190 (NH) and 1680 $cm^{-1}$ (C=O); nmr ($CDCl_3$) $\delta$ 0.92 (t, 3, $J$ = 6.6 Hz, $CH_3$), 1.09 (t, 3, $J$ = 6.9 Hz, $CH_3$), 1.15 (t, 3, $J$ = 7.0 Hz, $CH_3$), 1.49 (dq, 2, $J$ ($CH_3$) = 6.6, $J$ (CH) = 6.0 Hz, $CHCH_2$), 2.84 (q, 2, $J$ = 6.9 Hz, $NCH_2$), 2.9–3.9 (m, 2, $NCH_2$), 4.04 (t, 1, $CHCH_2$), 6.7 (broad s, 1, NH); the multiplet at 2.9–3.9 was similar to the pattern found for the *N*-methylene protons of the amide **3** and the last signal disappeared upon addition of deuterium oxide; mass spectrum (70 eV) *m/e* 171 ($M^+$, calcd 171).

**Acidic Hydrolysis of the Triazolidinone 15b.** To a solution of 600 mg (2.2 mmol) of the triazolidinone **15b** in 15 ml of ethanol, 1.5 ml of concentrated hydrochloric acid was added and the solution was refluxed for 9 hr. The solvent was removed *in vacuo* and extracted with ether and water. The ethereal layer was dried ($Na_2SO_4$) and concentrated to give 20 mg of 1,2-diethyl-5-phenyl-1,2,4-triazolin-3-one (**18**). The aqueous layer was made alkaline with aqueous sodium hydroxide and extracted (ether), dried ($Na_2SO_4$), and concentrated to afford 180 mg of **18**. The total yield was 43%. The triazolinone **18** was recrystallized from benzene to give colorless needles: mp 112–113°; ir (KBr disk) 1650 (C=O) and 1515 $cm^{-1}$ (C=N); nmr ($CDCl_3$) $\delta$ 1.08 (t, 3, $J$ = 7.2 Hz, $CH_3$), 1.28 (t, 3, $J$ = 7.2 Hz, $CH_3$), 3.94 (q, 2, $J$ = 7.2 Hz, $CH_2$), 3.97 (t, 2, $J$ = 7.2 Hz, $CH_2$), 7.3–7.8 (m, 5, Ph); mass spectrum (70 eV) *m/e* 217 ($M^+$, calcd 217), 202 ($M^+ - Me$), 189 ($M^+ - CO$ or $CH_2{=}CH_2$), 188 ($M^+ - Et$), 131 ($PhC{=}N{=}C{=}O^+$).

*Anal.* Calcd for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.41; H, 6.96; N, 19.20.

**Preparation of the 4-Acylsemicarbazide 19.** *N,N'*-Diethylhydrazine was prepared according to the procedure for the synthesis of *N,N'*-dimethylhydrazine using diethyl sulfate instead of dimethyl sulfate:[29] bp 82–87° (lit. bp 84–86°). To a solution of the hydrazine (1.5 g, 17 mmol) in 5 ml of ether, 1.9 g (13 mmol) of the isocyanate **10b** in 5 ml of ether was added dropwise over 20 min under a nitrogen atmosphere and the mixture was refluxed for 1 hr. After cooling, 550 mg (15%) of 1,2-diethyl-4-benzoylsemicarbazide (**19**) precipitated. Recrystallization of the precipitate from benzene–ethanol gave colorless needles: mp 171–172°; ir (Nujol) 3360 and 3180 (NH), 1683 and 1632 (C=O), and 1608 $cm^{-1}$ (NH); nmr ($CDCl_3$) $\delta$ 0.93 (t, 3, $J$ = 7.4 Hz, $CH_3$), 1.34 (t, 3, $J$ = 7.3 Hz, $CH_3$), 3.35 (q, 2, $J$ = 7.4 Hz, $NNCH_2$), 3.70 (q, 2, $J$ = 7.3 Hz, $CONCH_2$), 5.6 (broad, 2, 2 NH), 7.1–7.7 (m, 5, Ph); the broad singlet at $\delta$ 5.6 disappeared upon addition of deuterium oxide; mass spectrum (70 eV) *m/e* 235 ($M^+$, calcd 235), 217 ($M^+ - H_2O$), 202 (217 – Me), 192 ($M^+ - EtN$), 105 ($PhCO^+$).

*Anal.* Calcd for $C_{12}H_{17}N_3O_2$: C, 61.25; H, 7.28; N, 17.86. Found: C, 61.42; H, 7.38; N, 17.74.

**Cyclization of the 4-Acylsemicarbazide 19 to the Triazolinone 18.** Acidic treatment of the acylsemicarbazide **19** was done under similar conditions to those for the hydrolysis of the triazoli-

dinone **15b**. A solution of 400 mg (1.7 mmol) of **19** in 15 ml of ethanol containing 2 ml of 6 *N* hydrochloric acid was refluxed for 4 hr. Then the solution was made alkaline (aqueous sodium hydroxide), extracted ($CHCl_3$), dried ($Na_2SO_4$), and concentrated to give 132 mg (36%) of the triazolinone **18** and 30 mg (14%) of 1,2-diethylsemicarbazide which was formed by hydrolysis of **19**.

**Acknowledgments.** We thank Messrs. Toshihiro Tani and Kosaku Sugimoto for their assistance in the experiment and Mr. Yasuo Choki of Takeda Chemical Ind., Ltd., for his help in nmr measurements.

**Registry No.**—**1a**, 39169-68-1; **1b**, 39169-67-0; **1c**, 52225-94-2; **1d**, 52225-95-3; **1e**, 6794-94-1; **2**, 525-06-4; **3a**, 39169-70-5; **3b**, 39169-69-2; **3c**, 52225-96-4; **3d**, 52225-97-5; **4**, 52225-98-6; **7**, 6336-52-3; **9**, 52225-99-7; **10a**, 103-71-9; **10b**, 4461-33-0; **11**, 52225-74-8; **12**, 52225-75-9; **14**, 5040-62-0; **15a**, 52225-76-0; **15b**, 52225-77-1; **17**, 52225-78-2; **18**, 52225-79-3; **19**, 52225-80-6; **22a**, 44650-07-9; **22b**, 52225-81-7; **22e**, 2303-97-1; **22f**, 52225-82-8; **23**, 52225-83-9; **24**, 52225-84-0.

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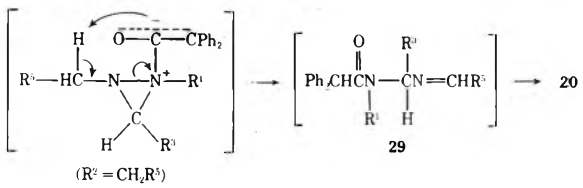
(30) The following mechanism leading to the intermediate **20** is also possible. This participation of an *N*-alkyl substituent in the reaction would be




compatible with the fact that the similarly acidic hydrogen on the ring carbon of an oxaziridine was not abstracted in the reaction with diphenylketene. The reactions with isocyanates can also be elucidated by the above mechanism including the abstraction of an $\alpha$ hydrogen on a N substituent. Thus further study of the mechanism is of future interest.

# Studies on Ketene and Its Derivatives. LXIII.[1] Reaction of Diketene with Azobenzenes

Tetsuzo Kato* and Masayuki Sato

*Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan*

Katsumi Tabei

*Tokyo College of Pharmacy, 3-20-1 Kitashinjuku, Shinjuku-Ku, Tokyo 160, Japan*

*Received December 27, 1973*

Irradiation of the solution of symmetric azobenzenes (**1a–k**) and diketene in chloroform resulted in the formation of 1:1 cycloadduct, 1,2-diarylhexahydropyridazine-3,5-dione (**2a–k**). Using asymmetric azobenzenes such as **1l–u**, the cycloaddition reaction occured stereoselectively to result in the formation of 1-(4-alkoxyphenyl)-2-arylhexahydropyridazine-3,5-dione (**2l–u**). The possible reaction mechanism is also discussed.

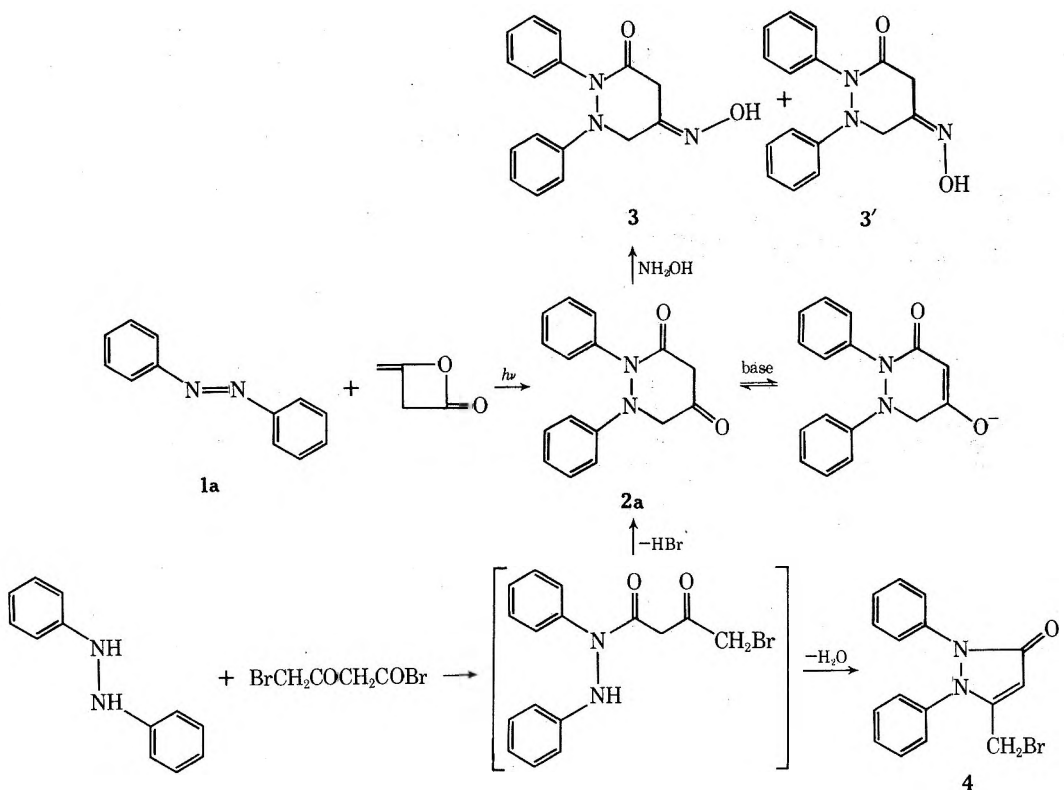
The cycloaddition of azo compounds with ketene is well known,[2] but reactions of azo compounds with diketene have not been reported. The present paper describes a study of reactions of diketene and azobenzenes to give 1,2-diarylpyridazinedione derivatives (**2**).

Refluxing of a solution of diketene and azobenzene (**1a**) in dry chloroform resulted in the recovery of starting materials; however, irradiation of the solution with stirring at room temperature gave rise to the 1:1 adduct (**2a**) in 62% yield. The ir spectrum of **2a** showed two carbonyl bands at 1746 and 1688 $cm^{-1}$ ascribable to ketone and amide group, respectively. The nmr spectrum ($CDCl_3$) showed two singlet signals at 3.35 (2 H, $COCH_2CO$) and 4.34 ppm (2 H, $NCH_2CO$).

Compound **2a** was insoluble in acid, and negative for the ferric chloride test. However, **2a** was enolized readily with base. In base the 1745-$cm^{-1}$ ir band disappeared and the amide carbonyl band shifted from 1688 to 1635 $cm^{-1}$. Reaction of **2a** with hydroxylamine afforded an oxime which from nmr data was a 1:1 mixture of stereoisomers (3 and 3′).

These data are consistent with the structure of **2a** as 1,2-diphenylhexahydropyridazine-3,5-dione, and a reference sample was obtained in 1.5% yield by condensation of hydrazobenzene with ω-bromoacetoacetyl bromide. The main product was 5-bromomethyl-1,2-diphenyl-3-pyrazolone (**4**) (Scheme I).

**Scheme I**




Ten symmetrical disubstituted azobenzenes (**1b–k**) were subjected to the same reaction. The corresponding 1,2-diarylhexahydropyridazine-3,5-dione derivatives (**2b–k**) were obtained in moderate yields with the exception of the dichloro- and 2,2′-dimethoxyazobenzenes (**1e,g,h**). Only the starting azo compounds were recovered in these cases. The results in hexane, dichloromethane, or excess diketene did not differ appreciably.

Although yields are not so high, the method is a convenient source for the preparation of the previously unknown 1,2-diarylhexahydropyridazinedione derivatives. The results are summarized in Table I.

The cycloaddition was carried out also with asymmetrical disubstituted azobenzenes such as 4-methoxy-4′-substituted azobenzenes (**1l–u**) (Table II). A single product corresponding to the 1:1 adduct (**2**) was isolated in each case in yields comparable to those with the symmetrical azobenzenes. Though two isomers are possible, the nmr spectra of the products (**2l–u**) indicate that the 4-methoxyphenyl group is attached to N-1 ($NCH_2CO$) rather than N-2 (NCO). A singlet or closely spaced multiplet for four aromatic protons is observed around 6.8 ppm, while another signal due to aromatic protons appears around 7.2–7.8 ppm as a multiplet. Comparison of the signal patterns of aromatic ring protons of **2l–u** with those of **2a–k** revealed that the characteristic sharp signals around 6.8 ppm seemed to be due to the 4-alkoxyphenyl group; namely, in the nmr spectra of **2a–k**, only **2j** and **2k** showed a four-proton singlet signal at 6.80 ppm (see Table I). Accordingly, signals around 6.8 ppm of **2l–u** should be due to 4-alkoxyphenyl ring protons.

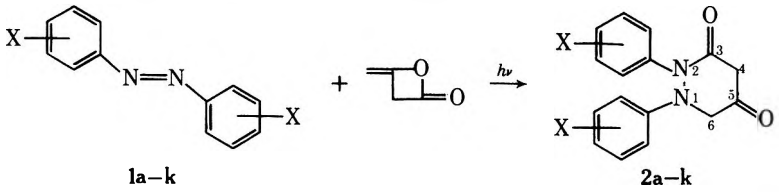
Moreover, it is known that signals of aminophenyl ring protons appear at higher field region than those of acylaminophenyl ring protons.[3] For instance, *p*-anisidine shows its ring protons at 6.68 and 6.73 ppm as an overlapped doublet signal. In contrast *p*-acetoanisidine shows a typical AB quartet signal at 6.77 ppm (2 H, $J$ = 9 Hz) related to the ring protons at the ortho position to the methoxy group, and at 7.36 ppm (2 H, $J$ = 9 Hz) to those at the ortho position to the acetamide group.

From the data described above, it is reasonably concluded that the 4-methoxyphenyl group is fixed to the 1 position of the pyridazine ring ($NCH_2CO$), and its ring protons appear as a characteristic singlet or overlapped doublet signal around 6.8 ppm.

Although **2** was not reduced by catalytic reduction, treatment of **2l** with sodium borohydride gave rise to the alcohol (**5l**) as an oil, which was dehydrated to give the tetrahydropyridazin-3-one (**6l**). Reaction of **2l** with acetyl chloride or tosyl chloride gave the enol esters, **7** or **8**, respectively (Scheme II). Heating of **2** and **5** with dilute acid or alkali gave a resinous product. Attempts to cleave the N–N bond of these pyridazine derivatives by catalytic hydrogenolysis were not successful.

The use of an nmr shift reagent with the tetrahydropyridazinone (**6o**) provided a further indication that the 4-alkoxyphenyl moiety is present at N-1. Namely, the nmr spectra of **6o** were measured after successive addition of $Eu(fod)_3$ and the field positions of the nmr lines ($\delta_E$) were plotted as a function of metal concentration (Figure 1). Since an amide group is a weak Lewis base, the observed $S$ values, the europium shift parameters, were rather small, but it was revealed that each proton resonance was affected

**Table I**
**Reaction of Diketene with Symmetric Azobenzenes**

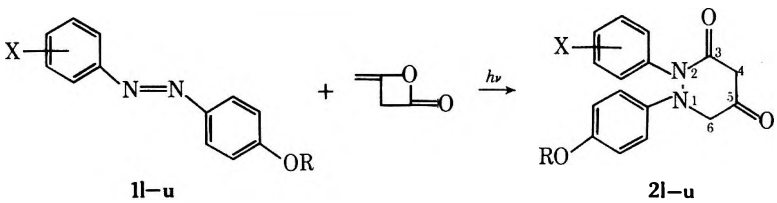


1a–k 2a–k

| 2[a] | X | Reaction conditions: Solvent[b] | Time, hr | Yield,[c] % | Mp, °C | Ir, $\nu_{max}$ ($CHCl_3$), $cm^{-1}$: Keto | Amide | Nmr, δ ($CDCl_3$), ppm: 4-$CH_2$ | 6-$CH_2$ | Aromatic |
|---|---|---|---|---|---|---|---|---|---|---|
| a | H | C | 48 | 62 | 148 | 1746 | 1688 | 3.35 | 4.34 | 6.8–7.9 (m, 10 H) |
| b | 2-$CH_3$ | C | 48 | 60 | 167 dec | 1739 | 1643 | 3.69 | 4.16 | 7.0–7.34 (m, 8 H) |
| c | 3-$CH_3$ | B | 72 | 46 | 170.5 dec | 1748 | 1687 | 3.36 | 4.34 | 6.78–7.65 (m, 8 H) |
| d | 4-$CH_3$ | C | 35 | 53 | 104.5 | 1745 | 1682 | 3.14 | 4.17 | 6.67 and 7.04 (AB q, 2 H, 2 H, $J$ = 9 Hz), 7.08 and 7.65 (AB q, 2 H, 2 H, $J$ = 9 Hz) |
| e | 2-Cl | C | 72 | | | | | | | |
| f | 3-Cl | C | 48 | 3 | 152.5 | 1750 | 1696 | 3.38 | 4.35 | 6.82–7.85 (m, 8 H) |
| g | 4-Cl | C | 72 | | | | | | | |
| h | 2-$OCH_3$ | C | 36 | | | | | | | |
| i | 3-$OCH_3$ | C | 36 | 27 | 145.5 | 1745 | 1686 | 3.38 | 4.33 | 6.40–7.50 (m, 8 H) |
| j | 4-$OCH_3$ | C | 24 | 63 | 144.5 | 1747 | 1681 | 3.35 | 4.28 | 6.80 (s, 4 H), 6.85 and 7.66 (AB q, 2 H, 2 H, $J$ = 8 Hz) |
| k | 4-OEt | C | 43 | 52 | 119 | 1743 | 1678 | 3.34 | 4.27 | 6.80 (s, 4 H), 6.80 and 7.66 (AB q, 2 H, 2 H, $J$ = 9 Hz) |

[a] Satisfactory analytical values (±0.30% for C, H, and N) were reported for 2a-k. [b] Solvents: C = chloroform, B = benzene. [c] Yields indicated do not reflect recovery of unreacted starting material.

**Table II**
**Reaction of Diketene with Asymmetric Azobenzenes**



1l–u 2l–u

| 2[a] | X | R | Reaction conditions: Solvent[b] | Time, hr | Yield,[c] % | Mp, °C | Ir, $\nu_{max}$ ($CHCl_3$), $cm^{-1}$: Keto | Amide | Nmr, δ($CDCl_3$), ppm: 4-$CH_2$ | 6-$CH_2$ | 1-Ar[d] | 2-Ar |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| l | H | $CH_3$ | B | 72 | 62 | 143 | 1742 | 1683 | 3.38 | 4.31 | 6.83 | 7.25–7.82 (m, 5 H) |
| m | 2-$CH_3$ | $CH_3$ | B | 48 | 36 | 135.5 | 1745 | 1676 | 3.50 | 4.33 | 6.90<br>6.91 | ~7.25 (m, 4 H) |
| n | 3-$CH_3$ | $CH_3$ | C | 24 | 32 | 81 | 1745 | 1686 | 3.35 | 4.28 | 6.81 | ~7.32 (m, 4 H) |
| o | 4-$CH_3$ | $CH_3$ | C | 24 | 44 | 143 | 1746 | 1682 | 3.34 | 4.28 | 6.81 | 7.15 and 7.67 (AB q, 2 H, 2 H, $J$ = 8 Hz) |
| p | 2-Cl | $CH_3$ | C | 48 | | | | | | | | |
| q | 3-Cl | $CH_3$ | C | 40 | 28 | 110 | 1746 | 1688 | 3.36 | 4.28 | 6.82 | 7.10–7.86 (m, 4 H) |
| r | 4-Cl | $CH_3$ | C | 48 | 55 | 138 | 1748 | 1685 | 3.37 | 4.30 | 6.82 | 7.32 and 7.81 (AB q, 2 H, 2 H, $J$ = 7 Hz) |
| s | 4-Br | $CH_3$ | C | 36 | 21 | 142 | 1747 | 1685 | 3.39 | 4.31 | 6.83 | 7.48 and 7.79 (AB q, 2 H, 2 H, $J$ = 7 Hz) |
| t | 4-$NO_2$ | $CH_3$ | C | 48 | | | | | | | | |
| u | H | $C_2H_5$ | B | 24 | 50 | 109.5 | 1744 | 1688 | 3.38 | 4.30 | 6.81 | 7.20–7.87 (m, 5 H) |

[a] Satisfactory analytical values (±0.30% for C, H, and N) were reported for 2l-u. [b] Solvents: B = benzene, C = chloroform. [c] Yields indicated do not reflect recovery of unreacted starting material. [d] Characteristic singlet or overlapped doublet signal (4 H).

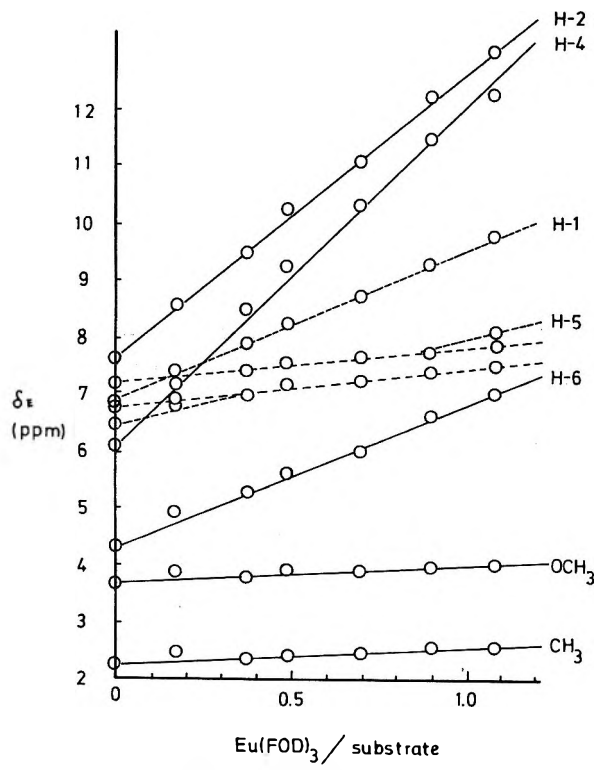
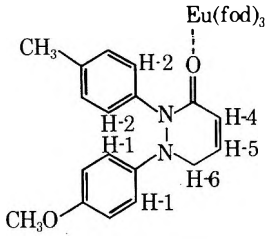



**Figure 1.** The relationship between chemical shifts and the molar ratio of Eu(fod)$_3$/substrate (**6o**).

by the contact shift to a different degree, and as shown in Table III, the relation between parameter $S$ and distance $r$

**Table III**
**$S^a$ and $r^b$ Values for Specified Hydrogens of 6o**



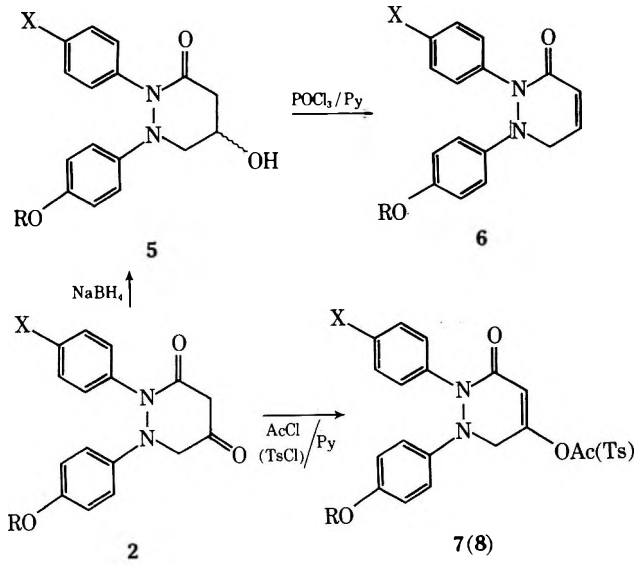

| $H_i$ | $S$ | $r$, Å | $K^c$ |
|---|---|---|---|
| 1 | 2.7 | 4.41 | 231.57 |
| 2 | 4.6 | 3.87 | 266.61 |
| 4 | 6.2 | 3.35 | 233.06 |
| 5 | 1.5 | 5.30 | 223.31 |
| 6 | 2.1 | 5.46 | 341.82 |

[a] Europium shift parameter, defined in the equation $\delta_E = \delta + S$ Eu(fod)$_3$/substrate. $\delta_E$ and $\delta$ (chemical shift in the uncomplexed substrate) are in parts per million relative to TMS. [b] Average distance between the hydrogen ($H_i$) and the metal ion (radius $Eu^{3+}$ = 0.95 Å) complexed with amide carbonyl group. [c] Paramagnetic shift ($\Delta\delta = \delta_E - \delta$) is dominated by the pseudo-contact interaction; $\Delta\delta_i = K/r_i^3$, where $K$ is assumed constant for a particular solution composition and temperature.[8]

from the center of the europium ion was fairly good except for H-6.

The signals centered at 6.10 (H-4) and 7.63 ppm (aromatic, H-2) showed the greatest shift, suggesting the closest protons to the metal ion in the complex. Other aromatic protons centered at 6.81–6.84 ppm (H-1) were affected

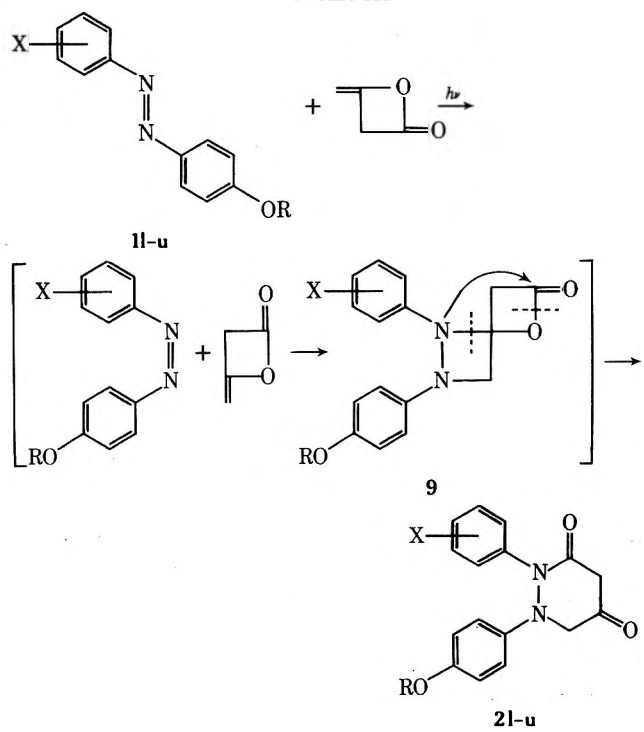
**Scheme II**




moderately with the contact shift. This fact is consistent with the structure of **6o** as 1-(4-methoxyphenyl)-2-(*p*-tolyl)tetrahydropyridazin-3-one, but not as the 1-(*p*-tolyl)-2-(4-methoxyphenyl) isomer.

Though details of the mechanism of the formation of the cycloadduct are not clear at present, a likely pathway is shown in Scheme III. It is already known that *trans*-azo-

**Scheme III**




benzene reacts with ketene only very slowly while the cis isomer reacts readily even at low temperature, and that *trans*-azobenzene is converted to the cis isomer by irradiation with uv light.[4] On the other hand, homolytic addition of the olefinic group of diketene gives a spiro compound; for instance, addition of a carbene generated from a diazo compound such as diazoacetophenone to the C=C double bond of diketene gave the spiro compound, 2-benzoyl-1-hydroxycyclopropaneacetic acid $\beta$-lactone.[5]

In this view, 1,2-cycloaddition of *cis*-azobenzene with the C=C double bond of diketene gives rise to a four-mem-

bered spiro adduct as an intermediate (**9**), which, on rearrangement, is converted to **2**.

## Experimental Section

Melting points were determined by a calibrated Yanagimoto melting point apparatus. Ir spectra were measured by a Jasco DS-301 spectrometer. Nmr spectra were measured on Hitachi Perkin-Elmer R-20 and Varian A-60 spectrometers in $CDCl_3$ solution, and reported as $\delta$ values (parts per million) relative to TMS. Uv spectra were measured by a Beckman DB-G spectrometer. Mass spectra were obtained on a Hitachi RMU-7L double-focusing mass spectrometer.

**Materials.** Symmetric azobenzenes used in the present experiment were prepared from the corresponding nitrobenzenes by alkaline reduction with zinc dust in methanol[6] or the Drynap reduction in methanol.[7] Asymmetric azobenzenes were also prepared from appropriately substituted anilines and phenol by diazo coupling followed by alkylation with dialkyl sulfate.

**General Procedure for Preparation of 1,2-Diarylhexahydropyridazine-3,5-diones (2).** A solution of **1** (0.025–0.05 mol) and diketene (0.5 mol) in dry $CHCl_3$ or benzene (80–120 ml) was irradiated with uv light while being stirred for 24–72 hr at room temperature. The light source was a Riko UVL-400HA water-cooled high-pressure mercury lamp (Pyrex filter) and the reaction vessel was equipped with a drying tube. After evaporation of excess diketene under reduced pressure, the reddish-brown tar was dissolved in benzene, and the benzene solution was then extracted with 5% NaOH. The alkaline solution was acidified with 10% HCl and extracted again with benzene. The benzene solution was washed with water and dried over $Na_2SO_4$. Evaporation of benzene gave a brown solid which was chromatographed over silica gel to give **2** as colorless to pale orange needles. Each product was recrystallized from benzene-hexane mixture or ethanol. The results are summarized in Tables I and II.

With use of a low-pressure mercury lamp, yields were rather low and the photopolymerization of diketene occurred prior to the cycloaddition reaction.

**Reaction of Hydrazobenzene with $\omega$-Bromoacetoacetyl Bromide.** A solution of $\omega$-bromoacetoacetyl bromide (13.5 g) in $CCl_4$ (100 ml) was added dropwise at 0° to a solution of hydrazobenzene (9.2 g) in $CHCl_3$ (200 ml). After stirring vigorously for 30 min, the reaction mixture was filtered and the residue was washed with $CHCl_3$. The filtrate and the $CHCl_3$ washing were combined and extracted with 5% NaOH. The alkaline solution was acidified with 10% HCl and then extracted with benzene. The benzene solution was washed with water and dried over $Na_2SO_4$.

Evaporation of the benzene gave **2a** as colorless needles (200 mg, 1.5%), mp 147°.

After extraction with 5% NaOH, the $CHCl_3$ layer was condensed to give a crystalline residue, which was purified by recrystallization to give colorless needles of **4**: mp 135°; yield 7.1 g (43%); ir ($CHCl_3$) 2980, 1660, 1595, 1490, 1380 $cm^{-1}$; nmr $\delta$ 4.15 (s, 2 H, $-CH_2Br$), 5.97 (s, 1 H, 4-CH=), ~7.46 ppm (m, 10 H, aromatic protons); mass spectrum *m/e* 330, 328 ($M^+$, base peak), 249, 183, 181, 144, 130, 104, 77.

*Anal.* Calcd for $C_{16}H_{13}BrN_2O$: C, 58.37; H, 3.98; N, 8.51. Found: C, 58.53; H, 3.88; N, 8.65.

**1,2-Diphenyltetrahydropyridazine-3,5-dione 5-Oxime (3a and 3a').** An EtOH solution of **2a** (500 mg in 30 ml) was treated with an aqueous solution of $NH_2OH \cdot HCl$ and $Na_2CO_3$ (140 and 210 mg in 20 ml). After the mixture was stirred for 1.5 hr at 60°, the solvent was evaporated under reduced pressure to afford a yellow oil which was then extracted with ether. The ether layer was washed with 5% NaOH and water and dried over $Na_2SO_4$. Evaporation of the ether gave the oxime, a mixture of **3a** and **3a'**, as colorless crystals (430 mg, 81%): mp 168–174°; ir ($CHCl_3$) 3550, 3000, 1670, 1645, 1510, 1360, 1200 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ 3.24 (s, 1.1 H, 4-$CH_2$ of **3a'**), 3.45 (s, 0.9 H, 4-$CH_2$ of **3a**), 4.52 (s, 0.9 H, 6-$CH_2$ of **3a**), 4.73 (s, 1.1 H, 6-$CH_2$ of **3a'**), 6.80–7.90 (m, 10 H, aromatic protons), 8.28–8.55 ppm (broad, 1 H, –OH, the signal disappeared upon addition of a small amount of $D_2O$); mass spectrum *m/e* 281 ($M^+$, base peak), 253, 236, 195, 183, 176, 131, 130, 119, 106, 105, 104, 93, 91, 78, 77.

*Anal.* Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.38; N, 14.94. Found: C, 68.29; H, 5.38; N, 14.50.

Attempts to isolate syn and anti isomers were not successful.

**1-(4-Methoxyphenyl)-2-phenyl-1,2,3,6-tetrahydropyridazin-3-one (6l).** To an EtOH solution of **2l** (3.2 g in 150 ml) was added $NaBH_4$ (450 mg) in small portions and the mixture was stirred for 3 hr at room temperature. After evaporation of EtOH, the residue was treated with water and then extracted with ether. The ether solution was washed with water and dried over $Na_2SO_4$. Evaporation of the ether gave a crude product which was then chromatographed over silica gel to afford a viscous oil (**5l**, 1.8 g, 56%): ir ($CHCl_3$) 3600, 3400, 2950, 1675, 1600, 1495, 1365 $cm^{-1}$; nmr $\delta$ 2.60 (m, 2 H, 4-$CH_2$), 3.20 (broad, 1 H, –OH, the signal disappeared upon addition of a small amount of $D_2O$), 3.34 (m, 1 H, 5-CH), 3.72 (s, 3 H, $-OCH_3$), 4.40 (m, 2 H, 6-$CH_2$), 6.82 (s, 4 H, *p*-methoxyphenyl ring protons), 7.20–7.85 ppm (m, 5 H, phenyl protons); mass spectrum *m/e* 298 ($M^+$), 207, 176, 136, 135 (base peak), 123, 120, 93, 85.

To a solution of **5l** (1.8 g) in dry pyridine (80 ml), $POCl_3$ (1.0 g) was added dropwise and the mixture was stirred for 3 hr at room temperature. After evaporation of the pyridine under reduced pressure, the residual tar was treated with ice water and then extracted with ether. The ether solution was washed with 10% HCl and water and dried over $Na_2SO_4$. Evaporation of the ether followed by chromatography over silica gel gave **6l** as colorless needles (600 mg, 36%): mp 95°; ir ($CHCl_3$) 2950, 2840, 1665, 1620, 1600, 1495, 1380, 1300 $cm^{-1}$; nmr $\delta$ 3.68 (s, 3 H, $-OCH_3$), 4.34 (q, 2 H, $J$ = 3 and 1 Hz, 6-$CH_2$), 6.08 (d, t, 1 H, $J$ = 9 and 1 Hz, 4-CH=), 6.52 (d, t, 1 H, $J$ = 9 and 3 Hz, 5-CH=), 6.82 and 6.87 (overlapped d, 2 H and 2 H, *p*-methoxyphenyl protons), 7.10–7.85 ppm (m, 5 H, phenyl protons); uv $\lambda_{max}$ (EtOH) 224 nm ($\epsilon$ 6860), 285 (2000); mass spectrum *m/e* 280 ($M^+$, base peak), 212, 189, 188, 158, 135, 122, 107, 78, 77.

*Anal.* Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.85; H, 5.80; 9.89.

**1-(4-Methoxyphenyl)-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridazin-3-one (6o).** Following the similar method described above, **2o** (2.5 g) was treated with $NaBH_4$ followed by dehydration with $POCl_3$ in dry pyridine to give **6o** (470 mg, 40%) as colorless needles: mp 102.5°; ir ($CHCl_3$) 3000, 2950, 2850, 1660, 1620, 1600, 1510, 1380, 1340, 1300, 1250 $cm^{-1}$; nmr $\delta$ 2.27 (s, 3 H, tolyl $CH_3$), 3.70 (s, 3 H, $-OCH_3$), 4.35 (q, 2 H, $J$ = 3 and 1 Hz, 6-$CH_2$), 6.10 (d, t, 1 H, $J$ = 9 and 1 Hz, 4-CH=), 6.50 (d, t, 1 H, $J$ = 9 and 3 Hz, 5-CH=), 6.81 and 6.84 (overlapped d, 2 H and 2 H, *p*-methoxyphenyl protons), 7.17 and 7.63 ppm (AB q, 4 H, $J$ = 8 Hz, *p*-tolyl protons); uv $\lambda_{max}$ (EtOH) 225 nm ($\epsilon$ 6700), 289 (2000); mass spectrum *m/e* 294 ($M^+$, base peak), 224, 201, 200, 174, 158, 149, 136, 121, 108, 93, 91, 77.

*Anal.* Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.54; H, 6.26; N, 9.32.

**1-(4-Ethoxyphenyl)-2-phenyl-1,2,3,6-tetrahydropyridazin-3-one (6u).** Following the above-cited method, **2u** (2.0 g) gave **6u** (400 mg, 42%) as pale yellow needles: mp 117°; ir ($CHCl_3$) 2980, 1662, 1615, 1595, 1480, 1380, 1340, 1295 $cm^{-1}$; nmr $\delta$ 1.32 (t, 3 H, $J$ = 7 Hz, ethoxy $CH_3$), 3.89 (q, 2 H, $J$ = 7 Hz, ethoxy $CH_2$), 4.32 (q, 2 H, $J$ = 3 and 1 Hz, 6-$CH_2$), 6.14 (d, t, 1 H, $J$ = 9 and 1 Hz, 4-CH=), 6.52 (d, t, 1 H, $J$ = 9 and 3 Hz, 5-CH=), ~6.80 (overlapped d, 4 H, *p*-ethoxyphenyl protons), 7.16–7.85 ppm (m, 5 H, phenyl protons); uv $\lambda_{max}$ (EtOH) 225 nm ($\epsilon$ 6700), 289 (2000); mass spectrum *m/e* 294 ($M^+$), 226, 189, 188, 172, 135, 122, 107, 91 (base peak), 77.

*Anal.* Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.52; H, 6.04; N, 9.30.

**5-Acetoxy-1-(4-methoxyphenyl)-2-phenyl-1,2,3,6-tetrahydropyridazin-3-one (7l).** To a solution of **2l** in dry pyridine (1.0 g in 50 ml), acetyl chloride (500 mg) was added dropwise and the mixture was stirred for 2 hr at room temperature. After evaporation of pyridine under reduced pressure, the residual oil was extracted with ether. The ether solution was washed with 5% NaOH, 10% HCl, and water, successively, and dried over $Na_2SO_4$. After evaporation of ether, the residual substance was chromatographed over silica gel followed by recrystallization from ethanol, giving **7l** (490 mg, 38%) as pale yellow needles: mp 86°; ir ($CHCl_3$) 3000, 1760, 1670, 1650, 1503, 1370, 1245, 1170, 1150 $cm^{-1}$; nmr $\delta$ 2.14 (s, 3 H, acetyl $CH_3$), 3.71 (s, 3 H, $-OCH_3$), 4.53 (s, 2 H, 6-$CH_2$), 6.03 (s, 1 H, 4-CH=), 6.83–6.85 (overlapped d, 2 H and 2 H, *p*-methoxyphenyl protons), 7.05–7.83 ppm (m, 5 H, phenyl protons); uv $\lambda_{max}$ (EtOH) 236 nm ($\epsilon$ 10,000), 290 (4200); mass spectrum *m/e* 338 ($M^+$), 296, 247, 227, 205, 174, 136, 135 (base peak), 120, 107, 93, 77.

*Anal.* Calcd for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.65; H, 5.31; N, 8.25.

**5-Acetoxy-1-(4-ethoxyphenyl)-2-phenyl-1,2,3,6-tetrahydropyridazin-3-one (7u).** Following the same method as mentioned above, **2u** (1.0 g) gave **7u** (680 mg, 60%) as colorless crystals: mp 129.5°; ir ($CHCl_3$) 2980, 1772, 1670, 1635, 1592, 1500, 1360, 1240, 1180, 1150 $cm^{-1}$; nmr $\delta$ 2.15 (s, 3 H, acetyl $CH_3$), 1.35 (t, 3 H,

$J$ = 7 Hz, ethoxy $CH_3$), 3.94 (q, 2 H, $J$ = 7 Hz, ethoxy $CH_2$), 4.54 (s, 2 H, 6-$CH_2$), 6.03 (s, 1 H, 4-CH=), 6.85 (overlapped d, 2 H and 2 H, *p*-ethoxyphenyl protons), 7.18–7.84 ppm (m, 5 H, phenyl protons); uv $\lambda_{max}$ (EtOH) 235 nm ($\epsilon$ 10,500), 290 (3550); mass spectrum *m/e* 352 ($M^+$), 310, 261, 242, 226, 219, 174, 150, 149, 148, 121 (base peak), 120, 93, 77.

*Anal.* Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.26; H, 5.79; N, 7.87.

**1-(4-Methoxyphenyl)-2-phenyl-5-(4-toluenesulfonyloxy)-1,2,3,6-tetrahydropyridazin-3-one (8l).** To a solution of **2l** in dry pyridine (1.2 g in 70 ml), TsCl (1.3 g) was added in small portions, and the mixture was stirred for 2 hr at room temperature. After evaporation of pyridine under reduced pressure, the resulting residue was extracted with benzene. The benzene solution was washed with 5% NaOH, 10% HCl, and water, successively, and dried over $Na_2SO_4$. After evaporation of benzene, the residual solid was dissolved in $CHCl_3$ and chromatographed over silica gel, affording enol tosylate **8l** (850 mg, 47%) as colorless crystals: mp 117°; ir ($CHCl_3$) 3000, 1660, 1640, 1600, 1510, 1500, 1387, 1360, 1248, 1192, 1185 $cm^{-1}$; nmr $\delta$ 2.44 (s, 3 H, tolyl $CH_3$), 3.77 (s, 3 H, $-OCH_3$), 4.50 (s, 2 H, 6-$CH_2$), 5.75 (s, 1 H, 4-CH=), 6.84 (overlapped d, 4 H, *p*-methoxyphenyl protons), 7.24 and 7.60 (AB q, 2 H and 2 H, $J$ = 7 Hz, *p*-tosyl protons), 7.14–7.82 (m, 5 H, phenyl protons); uv $\lambda_{max}$ (EtOH) 230 nm ($\epsilon$ 7100), 273 (3170); mass spectrum *m/e* 450 ($M^+$, base peak), 359, 328, 295, 225, 212, 162, 135, 120, 107, 91, 77.

*Anal.* Calcd for $C_{24}H_{22}N_2O_5S$: C, 63.99; H, 4.92; N, 6.22. Found: C, 64.00; H, 5.04; N, 5.97.

**Acknowledgment.** The authors express their deep thanks to Mrs. A. Sato and Mrs. C. Koyanagi for elemental analysis, Miss A. Ujiie and Mrs. E. Kawashima for the nmr spectra, and Mr. Y. Shida for mass spectra. A part of the expenses for the present work was defrayed by the Grant-in-Aid for Scientific Research from the Ministry of Education, Japan, which is gratefully acknowledged.

**Registry No.**—**1a,** 103-33-3; **1b,** 584-90-7; **1c,** 588-04-5; **1d,** 501-60-0; **1e,** 7334-33-0; **1f,** 15426-14-9; **1g,** 1602-00-2; **1h,** 613-55-8; **1i,** 6319-23-9; **1j,** 501-58-6; **1k,** 588-52-3; **1l,** 2396-60-3; **1m,** 29418-43-7; **1n,** 52148-10-4; **1o,** 29418-44-8; **1p,** 52148-11-5; **1q,** 52148-12-6; **1r,** 40473-79-8; **1s,** 24948-93-4; **1t,** 29418-59-5; **1u,** 7466-38-8; **2a,** 52148-13-7; **2b,** 52148-14-8; **2c,** 52148-15-9; **2d,** 52148-16-0; **2e,** 52148-17-1; **2f,** 52148-18-2; **2g,** 52148-19-3; **2h,** 52148-20-6; **2i,** 52148-21-7; **2j,** 52148-22-8; **2k,** 52148-23-9; **2l,** 52148-24-0; **2m,** 52148-25-1; **2n,** 52148-26-2; **2o,** 52148-27-3; **2p,** 52148-28-4; **2q,** 52148-29-5; **2r,** 52148-30-8; **2s,** 52148-31-9; **2t,** 52148-32-0; **2u,** 52148-33-1; **3a,** 52148-34-2; **3a′,** 52148-35-3; **4,** 52148-36-4; **5l,** 52148-37-5; **6l,** 52148-38-6; **6o,** 52148-39-7; **6u,** 52148-40-0; **7l,** 52148-41-1; **7u,** 52148-42-2; **8l,** 52148-43-3; diketene, 674-82-8; hydrazobenzene, 122-66-7; ω-bromoacetoacetyl bromide, 52148-44-4.

## References and Notes

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# Synthesis and Stereochemistry of Some 8-Substituted 2-Methyldecahydroisoquinolines

Ian W. Mathison* and Phillip H. Morgan†

*Department of Medicinal Chemistry, College of Pharmacy, University of Tennessee Medical Units, Memphis, Tennessee 38163*

*Received March 7, 1974*

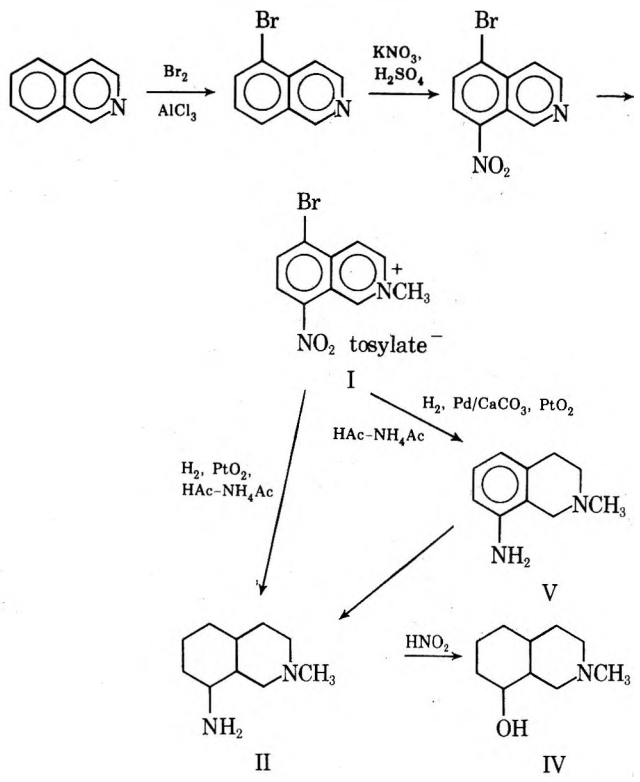
The synthesis and assignment of stereochemistry of three of the four possible diastereoisomers of the previously unreported 8-amino-2-methyldecahydroisoquinolines is reported. A one-step hydrogenolysis–catalytic hydrogenation of 5-bromo-8-nitro-2-methylisoquinolium tosylate was used to prepare the isomeric 8-amino-2-methyldecahydroisoquinolines. Separation of the diastereoisomers was achieved by the fractional crystallization of the corresponding acetamide derivatives and allowed the separation of the cis-8,9,10-H (30%, IIIa), trans-8,9,10-H (65%, IIIb), and cis-9,10,trans-8,9-H (1%, IIIc) isomers. Deamination with nitrous acid of the amines (obtained by hydrolysis of the acetamides) to the corresponding hydroxy compounds confirmed the equatorial stereochemistry of the 8 substituent in IIIb and IIIc. In the case of the amine obtained from IIIa, which possesses an intramolecular hydrogen bond and of necessity an axial substituent, high yields of the corresponding axial hydroxy compound were obtained on deamination. Owing to a conformational equilibrium this finding is not in conflict with the established high-yield conversions of equatorial amines to alcohols using nitrous acid. The isolation of alcohol IVc, as its methiodide derivative, completes the description of the four possible diastereoisomers of 8-hydroxy-2-methyldecahydroisoquinoline.

In a continuing study of the involvement of stereochemistry in the cardiovascular potencies of various derivatives of amino and hydroxy substituted decahydroisoquinolines[1] we report on the stereochemistry of 8-amino- and 8-hydroxy-2-methyldecahydroisoquinolines. Studies have been reported by Kimoto and Okamoto[2] on some 8-hydroxy-2-methyldecahydroisoquinolines; however, in comparing some of the melting point data with the present data, discrepancies are apparent. Elucidation of the conformation of the previously unreported 8-amino analogs is described.

The synthesis of 8-nitroisoquinoline (see Scheme I) was achieved by way of the bromination of isoquinoline using a swamping catalyst technique[3] to yield 5-bromoisoquinoline. Nitration using standard procedures gave good yields of the 5-bromo-8-nitroisoquinoline which was quaternized with methyl *p*-toluenesulfonate. The resulting salt (I) was then subjected to sequential reductions to produce the desired decahydroisoquinoline. The dehydrohalogenation of heterocycles is well documented[3] and using a base-supported palladium catalyst in addition to platinum oxide we

† The work reported constituted a segment of the dissertation submitted by Phillip H. Morgan to the University of Tennessee Medical Units in partial fulfillment of the Doctor of Philosophy degree requirements in Medicinal Chemistry.

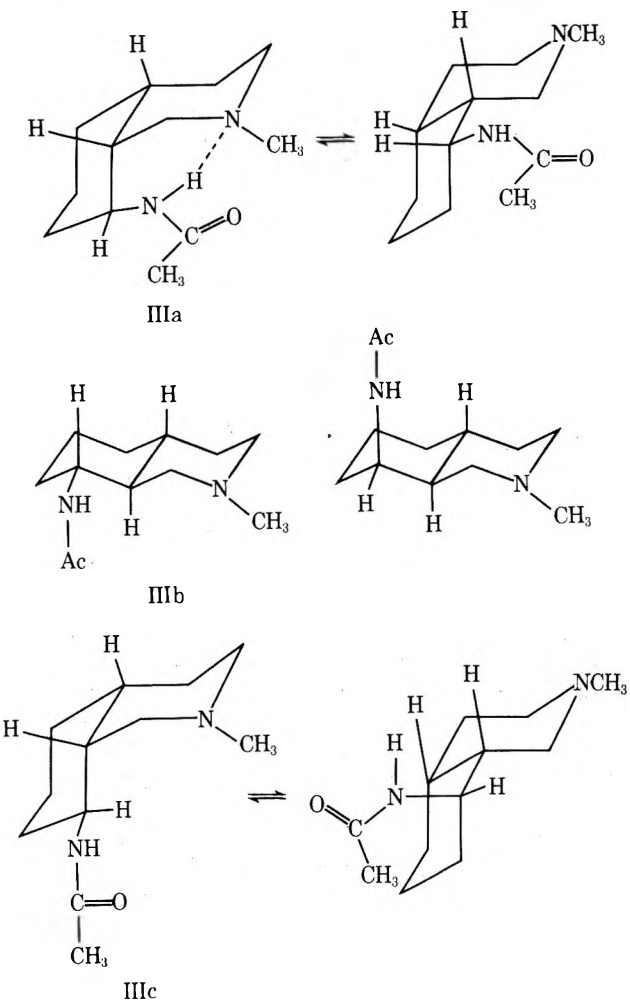
**Scheme I**
**Synthesis of 8-Amino- and 8-Hydroxy-2-methyldecahydroisoquinoline**




separation of isomers
*via* their acetamides (III)

were able to produce 8-nitro-2-methyl-1,2,3,4-tetrahydroisoquinoline. While further reduction of the tetrahydro compound using a platinum oxide–acid catalyzed hydrogenation in glacial acetic acid[1a] gave the desired 8-amino-2-methyldecahydroisoquinoline, a one-step reduction from the completely unsaturated to the fully reduced system was sought. Low-pressure reduction (72 hr) of I using various catalysts yielded the desired 8-amino-2-methyldecahydroisoquinolines. Gas–liquid chromatography of the oily product indicated the production of the isomers in the ratio 65 (IIIb):30 (IIIa):1 (IIIc). Separation of the various isomers was achieved by the fractional recrystallization of the corresponding acetamides. The infrared spectra of the purified acetamides were most informative as to the stereochemistry of one of the separated isomers (IIIa). The presence of an –NH stretching absorption at 3200 $cm^{-1}$ ($CH_2Cl_2$) which did not disappear on dilution indicated the presence of an intramolecular hydrogen bond.[4] Of the possible stereoisomers, only the cis-8,9,10-H isomer, having the acetamide grouping in the axial position, has the capability of forming such a bond (see Chart I). The equatorial nature of the 8 proton in IIIa (and thus an axial acetamide grouping) was obtained from its nmr spectrum. A narrow peak at $\delta$ 3.98 ($W_{1/2}$ = 14 Hz) established the equatorial nature of the 8 proton and the peak for the amide proton at $\delta$ 6.37 ($W_{1/2}$ = 75 Hz) indicated its participation in an intramolecular hydrogen bond. Hydrolysis of this acetamide with dilute acid yielded the corresponding amine, which on deamination with nitrous acid yielded the alcohol with retention of configuration in 85% yield. The high-yield production of alcohol in these deaminations occurs when the amine substituent is in an equatorial conformation.[5] We suggest that the high yields of the alcohol obtained with this axial amine are due to (a) nitrosation of the sterically

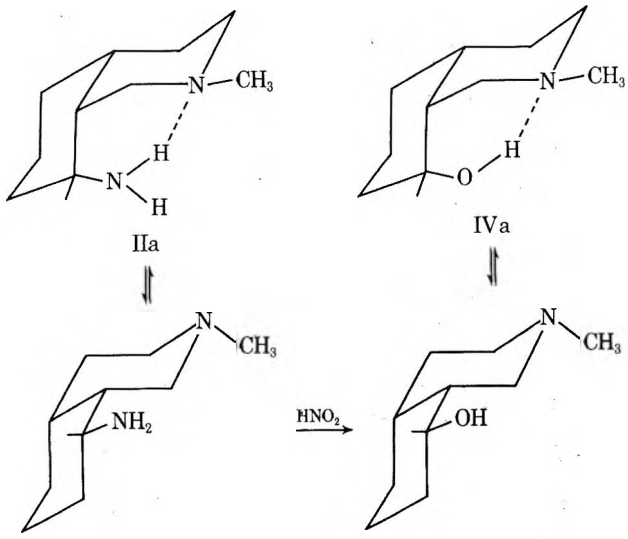
**Chart I**
**Possible Diastereoisomers of 8-Acetamido-2-methyldecahydroisoquinolines**




more favored equatorial amine (in equilibrium with the axial amine) thus giving the equatorial alcohol following the decomposition of the intermediate diazonium compound; (b) hydrolysis of the conformationally favored equatorial diazonium salt to yield the equatorial alcohol. Conformational preference of the diazonium grouping for the equatorial position was suggested by examination of the nmr of the nonintramolecularly hydrogen bonded quaternary salt (methiodide) of IVa. The narrow peak ($W_{1/2}$ = 10 Hz) for the equatorial 8 proton in IVa was not present in the spectrum of the quaternary salt but was replaced by a broader peak (which overlapped other signals) indicating its axial position and thus the more favored equatorial position for the 8 substituent. Since the diazonium salt intermediate would likewise not possess an intramolecular hydrogen bond, the diazonium group would be expected to occupy an equatorial position. The conformational equilibrium of the equatorial alcohol formed would provide for the isolation of the axial alcohol (see Chart II). The stereochemical assignment of the hydroxy compound produced by this sequence is consistent with these proposals. The alcohol (IVa) isolated from this deamination was shown to be identical with that reported by Kimoto[2b] [with the exception that our methiodide had mp 238–239° (lit.[2b] mp 229–231°)]. The nmr and ir characteristics indicated that both the amine and alcohol possessed an intramolecular hydrogen bond between the amine or hydroxyl grouping and the hetero nitrogen, thus confirming the presence of an axially substituted grouping.

The second acetamide (IIIb) isolated during the fraction-

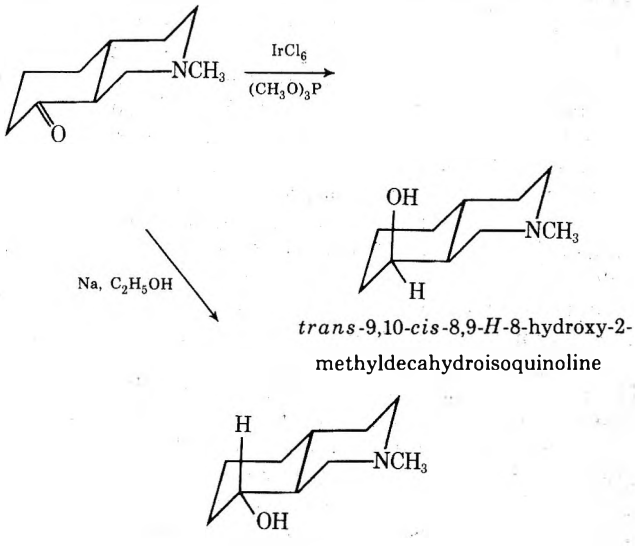
**Chart II**
**Deamination of**
*cis*-8,9,10-*H*-8-Amino-2-methyldecahydroisoquinoline




al crystallization required a more detailed study for its stereochemical elucidation. The equatorial conformation of the acetamide grouping was confirmed by the high yield of alcohol (IVb) following deamination of the corresponding solid amine (IIb). The infrared absorption of IVb at 1053 and 1013 $cm^{-1}$ provided spectral evidence for the equatorial position of the hydroxyl grouping. Although the spectral data were similar to those reported for *trans*-8,9,10-H-8-hydroxy-2-methyldecahydroisoquinoline[2b] the melting point of the isolated compound and its derivatives (analytically pure) differed by as much as 46° with those reported; it was therefore necessary to confirm the ring junction stereochemistry of our isolated alcohol, and thus the acetamide and amine, by unambiguous chemical means.

The oxidation of alcohols adjacent to a ring junction leads exclusively to the production of a trans ring junction ketone.[6] Stereoselective reduction of the ketone (see Scheme II) yields the axial or equatorial alcohol as desired; by this means alcohols of known stereochemistry were synthesized for comparison with alcohol IVb. Alcohol IVb was

**Scheme II**
**Selective Reduction of**
*trans*-9,10-*H*-2-Methyldecahydroisoquinol-8-one




*trans*-9,10-*cis*-8,9-*H*-8-hydroxy-2-methyldecahydroisoquinoline

*trans*-8,9,10-*H*-8 hydroxy-2-methyldecahydroisoquinoline (IVb)

oxidized by an Oppenauer procedure utilizing benzophenone and potassium *tert*-butoxide to yield *trans*-9,10-*H*-2-methyldecahydroisoquinol-8-one. Reduction of this ketone with sodium and alcohol yielded *trans*-8,9,10-*H*-8-hydroxy-2-methyldecahydroisoquinoline, which was shown to be identical with alcohol IVb. An alternate reduction of the ketone using chloroiridic acid and trimethyl phosphite yielded exclusively *trans*-9,10-*cis*-8,9-*H*-8-hydroxy-2-methyldecahydroisoquinoline comparable to the axial alcohol described by Kimoto and Okamoto.[2b]

The stereochemical characterization of the third acetamide, isolated in very small quantities, was made on the basis of its nmr spectrum. The wide $W_{1/2}$ (23 Hz) of the 8 proton ($\delta$ 4.38) indicated the presence of an equatorial acetamide grouping. Confirmation of the equatorial position of the substituent was obtained by hydrolysis of IIIc to its corresponding amine and subsequent deamination of the amine with nitrous acid. The alcohol obtained in high yield was converted to its methiodide derivative. Since one of the two possible equatorially substituted acetamides has been described (IIIb), and on the basis of our unambiguous synthesis of both trans-9,10-H isomers, with the limited quantities of material available our assignment for the cis ring junction stereochemistry, *i.e.*, *cis*-9,10,*trans*-8,9-*H*-8-acetamido-2-methyldecahydroisoquinoline, to IIIc would appear to be valid.

## Experimental Section

Melting points were determined on a Büchi melting point apparatus and are uncorrected. Infrared (ir) spectra were obtained using either a Perkin-Elmer Model 137 Infracord spectrophotometer or a Beckman Model IR-33 grating infrared spectrophotometer. Nuclear magnetic resonance (nmr) spectra were recorded on either a Varian Associates A-60A, a Hitachi Perkin-Elmer Model R-24, or a Jeolco Model C-60-HL nmr spectrometer, using tetramethylsilane (TMS) as an internal standard. Deuterium oxide exchange was routinely performed on all compounds possessing labile hydrogens. Nmr signals are reported using current conventions: br = broad, s = singlet, d = doublet, t = triplet, q = quadruplet, and m = multiplet. Half-band widths ($W_{1/2}$) are in hertz. Vapor phase chromatography (vpc) was carried out on a Varian Aerograph Model A-700 using helium as carrier gas and a column (20 ft × 0.75 in.) packed with 30% SE-30 on Chromosorb W. Combustion analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and Chemalytics, Inc., Tempe, Ariz. Analytical thin layer chromatography (tlc) was carried out on aluminum-supported, precoated tlc sheets of aluminum oxide (F-254, neutral Type E, layer thickness 0.20 mm) manufactured by E. Merck, Darmstadt, Germany. After development using $CHCl_3$–$CH_3OH$ (45:4), the analytical spots were visualized by spraying with Dragendorf's reagent. For column chromatography, aluminum oxide (Matheson Coleman and Bell, activated alumina, chromatographic grade, 80–200 mesh) or (Fisher, adsorption alumina, A-540, 80–200 mesh) was used after activation by heating at 150° for 12 hr. The solvents used for development and elution of the compounds from the column (2 × 20 cm) were benzene, benzene–ether, ether, ether–chloroform, chloroform, and chloroform–methanol.

**5-Bromoisoquinoline.** The swamping catalyst procedure outlined by Gordon and Pearson[3] was used for the preparation of 5-bromoisoquinoline from isoquinoline (200 g, 1.55 mol), anhydrous $AlCl_3$ (450 g, 3.4 mol), and liquid bromine (150 g, 0.94 mol). Modification of the original procedure was made in the addition of the bromine. This involved the use of an addition funnel placed on top of a steam-heated condenser attached to the reaction flask containing the viscous, molten $AlCl_3$–isoquinoline complex. Utilizing this apparatus, the bromine was vaporized prior to contacting the vigorously stirred complex. Following the 5-hr addition of the bromine, the mixture was stirred for a further 2 hr at 75° and the product was worked up by the reported procedure. The fractional distillation of the crude product, bp 95–97° (0.1 mm), yielded a clear liquid which solidified. Recrystallization from pentane afforded 5-bromoisoquinoline as white plates, 135 g (44%), mp 82–84° (lit.[3] mp 80–82°).

**5-Bromo-8-nitro-2-methylisoquinolinium *p*-Toluenesulfonate (I).** Nitration of 5-bromoisoquinoline according to the proce-

dure of Osborn, *et al.*,[6] gave a 93% yield of 5-bromo-8-nitroisoquinoline, mp 139–141° (lit.[3] mp 138–140°). Formation of the methyl *p*-toluenesulfonate salt was achieved by the treatment, with stirring, of the nitrobromo compound (315 g, 1.25 mol) dissolved in hot dimethylformamide (1200 ml) with 250 g (1.35 mol) of methyl *p*-toluenesulfonate for a period of 36 hr. After cooling in an ice bath, the reaction mixture was filtered, and the solid was washed with ether and acetone to yield I as a pale yellow solid, 435 g (80%), mp 252°.

*Anal.* Calcd for $C_{17}H_{15}BrN_2O_5S$: C, 46.48; H, 3.44; Br, 18.19; N, 6.38. Found: C, 46.63; H, 3.50; Br, 18.05; N, 6.34.

**8-Amino-2-methyl-1,2,3,4-tetrahydroisoquinoline (V).** A 25-g portion of salt I and an equal weight of ammonium acetate were dissolved in 200 ml of glacial acetic acid and hydrogenated at 40 psi for 12 hr over a mixed catalyst consisting of 8 g of palladium on $CaCO_3$ and 1 g of $PtO_2$. The exhausted catalyst was then filtered, and the filtrate was concentrated, made alkaline with $NH_4OH$, and extracted with ether. The dried ethereal extract was evaporated to yield a red oil which solidified on distillation and was recrystallized from ether-pentane to yield V as white needles in 50% yield, mp 62–63°.

*Anal.* Calcd for $C_{10}H_{14}N_2$: C, 74.03; H, 8.70; N, 17.27. Found: C, 73.96; H, 8.82; N, 17.10.

**8-Amino-2-methyldecahydroisoquinoline (II).** Ammonium acetate (2.5 g) and I (25 g) were dissolved in glacial acetic acid (200 ml) and hydrogenated at 40 psi for 72 hr over either (a) $PtO_2$ (2 g), Pd/C (5 g) in the presence of KOH (5 g), or (b) $PtO_2$ (2 g) in the presence of KOH (5 g), or (c) $PtO_2$ (2 g) as catalyst. The exhausted catalyst was then filtered, and the filtrate was concentrated on a rotary evaporator and made alkaline with $NH_4OH$. The resulting solution was extracted with ether, and the ether solution was dried and evaporated to leave a pale yellow oil. Vpc examination of this oil indicated the presence of two major components, IIb (65%) and IIa (30%), subsequently shown to be the *trans*-8,9,10-*H*- and *cis*-8,9,10-*H*-8-amino-2-methyldecahydroisoquinolines, respectively. An indeterminate amount of a third isomer (IIc) (a small shoulder on the major peak) was subsequently shown to be the cis-9,10,trans-8,9-H isomer. Approximately 5% of the 2-methyldecahydroisoquinolines was also seen at shorter retention times than those of the desired products. Separation of the isomer mixture of II by distillation was not possible and instability of the purified mixture was noted in the absence of solvent. The purified isomer mixture was derivatized to the corresponding acetamides immediately following distillation.

***cis*-8,9,10-*H*- and *trans*-8,9,10-*H*-8-Acetamido-2-methyldecahydroisoquinoline (IIIa and IIIb).** The freshly distilled 8-amino-2-methyldecahydroisoquinoline mixture (41 g, 0.24 mol) was dissolved in dry dimethylformamide (375 ml), cooled to 10°, and stirred. Acetic anhydride (50 g, 0.49 mol) dissolved in dry benzene (100 ml) was added over a 15-min period. Following the addition, the mixture was allowed to warm to room temperature and stirred for 24 hr. The solvents were then removed by rotary evaporation and the residual oil was dissolved in water, made alkaline with $NH_4OH$, and extracted with ether. Removal of the solvent from the dried ethereal extract yielded the crude mixture of the diastereoisomers (34 g, 66%). Several fractional recrystallizations of the isomeric mixture (150 g) from ethyl acetate or petroleum ether (bp 30–60°)–ether afforded pure *trans*-8,9,10-*H*-8-acetamido-2-methyldecahydroisoquinoline (IIIb) as white, felted needles (35 g): mp 192.5–194°; ir ($CHCl_3$) 3440 (free N–H stretch), 3300 $cm^{-1}$ (intermolecularly H-bonded N–H stretch); nmr ($CDCl_3$) $\delta$ 5.75 (br, 1, $W_{1/2}$ = 25 Hz, CONH), 3.68 (br, 1, $W_{1/2}$ = 23 Hz, CHNHAc), 2.27 (s, 3, $NCH_3$), and 1.98 ppm (s, 3, $COCH_3$).

*Anal.* Calcd for $C_{12}H_{22}N_2O$: C, 68.52; H, 10.55; N, 13.32. Found: C, 68.72; H, 10.26; N, 13.30.

The *cis*-8,9,10-H isomer (IIIa) was more soluble in the recrystallization solvent and was isolated as cuboid crystals by concentration of the mother liquors from which IIIb had been obtained. In some instances separation of IIIa, from the traces of IIIb still present, was achieved mechanically with tweezers. Recrystallization of IIIa from the same solvents as IIIb yielded pure *cis*-8,9,10-*H*-8-acetamido-2-methyldecahydroisoquinoline as cuboid crystals; mp 141–142°; ir ($CHCl_3$) 3440 (free N–H stretch), 3310 (intermolecularly H-bonded N–H stretch), and 3200 $cm^{-1}$ (intramolecularly H-bonded N–H stretch, did not disappear on dilution); nmr ($CDCl_3$) $\delta$ 6.37 (br, 1, $W_{1/2}$ = 75 Hz, –NHAc), 3.98 (br, 1, $W_{1/2}$ = 14 Hz, –CHNHAc), 2.27 (s, 3, $NCH_3$), and 1.96 ppm (s, 3, $COCH_3$).

*Anal.* Calcd for $C_{12}H_{22}N_2O$: C, 68.52; H, 10.55; N, 13.32. Found: C, 68.79; H, 10.62; N, 13.58.

A third isomer (IIIc) was isolated by hand picking its leaflet clusters from the mixture obtained when the petroleum ether–ether solvent was allowed to slowly evaporate. Recrystallization from ethyl acetate yielded 35 mg of pure *cis*-9,10,*trans*-8,9-*H*-8-acetamido-2-methyldecahydroisoquinoline: mp 154–157°; ir ($CHCl_3$) 3415 (free N–H stretch) and 3320 $cm^{-1}$ (intermolecularly H-bonded N–H stretch); nmr ($CDCl_3$) $\delta$ 5.57 (br, 1, $W_{1/2}$ = 25 Hz, –NHAc), 4.40 (br, 1, $W_{1/2}$ = 23 Hz, CHNHAc), 2.28 (s, 3, $NCH_3$), and 2.07 ppm (s, 3, $COCH_3$).

*Anal.* Calcd for $C_{12}H_{22}N_2O$: C, 68.52; H, 10.55; N, 13.32. Found: C, 68.57; H, 10.47; N, 13.14.

It should be noted that infrared dilution studies were carried out on all three isomers in dichloromethane solution. The peak at 3300–3320 $cm^{-1}$ corresponding to the intermolecularly H-bonded NH stretching frequency disappeared on dilution from 0.15 to 0.03 *M* concentration. For compound IIIa, however, the absorption at 3200 $cm^{-1}$ persisted throughout 0.15–0.01 *M* concentrations, indicative of an intramolecularly H-bonded N–H stretching frequency.[4]

**Hydrolysis of *cis*-8,9,10-*H*-8-Acetamido-2-methyldecahydroisoquinoline (IIIa) to *cis*-8,9,10-*H*-8-Amino-2-methyldecahydroisoquinoline (IIa).** A solution of IIIa (2.35 g, 0.011 mol) in 10% sulfuric acid (110 ml) was refluxed for 32 hr. The acidic solution, cooled in an ice bath, was made alkaline with concentrated sodium hydroxide solution and extracted with chloroform. The dried chloroform extract was evaporated on a rotary evaporator to yield *cis*-8,9,10-*H*-8-amino-2-methyldecahydroisoquinoline (IIa) as a straw-colored oil (1.86 g, 99%). The oil was quickly purged with nitrogen and stoppered to prevent formation of its solid carbonate which occurred when the amine was exposed to air. Attempts to crystallize the oil failed: ir ($CHCl_3$) 3375 (free N–H stretch), 3270 and 3160 (hydrogen-bonded N–H stretch), 1583 (N–H bending), and 1100 $cm^{-1}$ (C–N); nmr ($CDCl_3$) $\delta$ 2.28 (s, 3, $NCH_3$) and 1.37 ppm (s, 2, $NH_2$). The dihydrobromide salt was prepared and recrystallized from acetonitrile–ethyl acetate, mp 297–300°.

*Anal.* Calcd for $C_{10}H_{22}Br_2N_2$: C, 36.38; H, 6.72; Br, 48.41; N, 8.49. Found: C, 36.25; H, 6.67; Br, 48.37; N, 8.52.

**Hydrolysis of *trans*-8,9,10-*H*-8-Acetamido-2-methyldecahydroisoquinoline (IIIb) to *trans*-8,9,10-*H*-8-Amino-2-methyldecahydroisoquinoline (IIb).** A solution of IIIb (8 g, 0.038 mol) dissolved in 15% sulfuric acid solution (100 ml) was refluxed for 72 hr. The acidic reaction solution, cooled in an ice bath, was made alkaline with sodium hydroxide solution and extracted with chloroform. The dried chloroform extract was concentrated, giving 6.35 g of a straw-colored oil (98% yield) which formed tan crystals on standing of the pure *trans*-8,9,10-*H*-8-amino-2-methyldecahydroisoquinoline (IIb): mp 44–47°; ir ($CHCl_3$) 3370 (free N–H stretch), 3280 and 3150 (hydrogen-bonded N–H stretch), 1575 (N–H bending), and 1100 $cm^{-1}$ (C–N); nmr ($CDCl_3$) $\delta$ 2.30 (s, 3, $NCH_3$), and 1.21 ppm (s, 2, $NH_2$). The dihydrobromide salt was prepared and recrystallized from ethyl acetate–methanol–ether to give colorless, glassy crystals of *trans*-8,9,10-*H*-8-amino-2-methyldecahydroisoquinoline dihydrobromide, mp 256–258°.

*Anal.* Calcd for $C_{10}H_{22}Br_2N_2$: C, 36.38; H, 6.72; Br, 48.41; N, 8.49. Found: C, 36.24; H, 6.64; Br, 48.63; N, 8.30.

**Deamination with Nitrous Acid of *cis*-8,9,10-*H*-8-Amino-2-methyldecahydroisoquinoline (IIa) to *cis*-8,9,10-*H*-8-Hydroxy-2-methyldecahydroisoquinoline (IVa).** To a stirred solution of IIa (10 g, 0.06 mol) in glacial acetic acid (14.4 g, 0.24 mol) was added, dropwise, sodium nitrite (8.28 g, 0.12 mol) dissolved in water (65 ml).[7] This mixture was heated to 65°, and additional 2.88 g of acetic acid (20% excess in 20 ml of water) was added dropwise, and the resulting solution was heated for 3–4 hr. The reaction medium was made strongly alkaline with sodium hydroxide solution and refluxed for 2 hr. After cooling, the basic solution was extracted with chloroform. The chloroform extract was dried and concentrated, giving a viscous, straw-colored oil, which upon standing solidified to give 8.5 g of IVa, mp 68–75° (85% yield). Vpc indicated that the crude product contained 99% IVa and tlc showed one spot having an $R_f$ value of 0.653. Recrystallization of the solid from petroleum ether (bp 30–60°) gave 7.6 g (76% yield) of pure *cis*-8,9,10-*H*-8-hydroxy-2-methyldecahydroisoquinoline (IVa) as colorless, glassy prisms: mp 78–81° (lit.[2] mp 78–80°); ir ($CHCl_3$) 3660 (free O–H stretch), 3170 (hydrogen-bonded O–H stretch), 1057, 1014 $cm^{-1}$ (equatorial C–O); nmr ($CDCl_3$) $\delta$ 5.72 (br, 1, OH), 4.10 (br, 1, $W_{1/2}$ = 10 Hz, CHOH), and 2.25 ppm (s, 3, $NCH_3$). Two derivatives were prepared: the picrate, which was recrystallized from 95% ethanol, mp 183–184° (lit.[2a] mp 181–183°), and the methiodide, which was recrystallized from glyme–acetonitrile, mp 238–239° (lit.[2a] mp 229–231°).

**Deamination with Nitrous Acid of *trans*-8,9,10-*H*-8-Amino-2-methyldecahydroisoquinoline (IIb) to *trans*-8,9,10-*H*-8-Hydroxy-2-methyldecahydroisoquinoline (IVb).** *trans*-8,9,10-*H*-8-Amino-2-methyldecahydroisoquinoline (IIb, 6.2 g, 0.037 mol) was deaminated in a procedure identical with that described for the cis isomer. The viscous straw-colored oil (5.0 g) recovered from the chloroform extract was shown by vpc to contain 95.5% IVb and 4.5% olefins. Distillation of the oil *in vacuo* provided 3.41 g of *trans*-8,9,10-*H*-8-hydroxy-2-methyldecahydroisoquinoline (IVb), bp 92–96° (0.2 mm). Initial attempts to crystallize the oil failed; the hydrochloride salt was prepared and recrystallized from acetonitrile–ethyl acetate, giving 2.33 g (65%) of *trans*-8,9,10-*H*-8-hydroxy-2-methyldecahydroisoquinoline hydrochloride, mp 180–182°.

*Anal.* Calcd for $C_{10}H_{20}ClNO$: C, 58.38; H, 9.80; Cl, 17.23; N, 6.80. Found: C, 58.63; H, 10.01; Cl, 17.52; N, 6.71.

The hydrochloride salt was converted to the free base which, after standing overnight, crystallized to yield a tan, waxy solid, mp 50–53° (lit.[2] mp 84°). Attempts to recrystallize the material failed: ir ($CHCl_3$) 3610 (free O–H stretch), 3160 (hydrogen-bonded O–H stretch), and 1053 and 1013 $cm^{-1}$ (equatorial C–O[2b,6]); nmr ($CDCl_3$) $\delta$ 4.05 (s, 1, OH) (CHOH was masked by other alkyl protons from $\delta$ 2.7 to 3.5 ppm) and 2.25 ppm (s, 3, $NCH_3$).

Two derivatives were prepared as follows.

A picrate was recrystallized from 1-propanol, mp 196–198° (lit.[2a] mp 147–150°).

*Anal.* Calcd for $C_{16}H_{22}N_4O_8$: C, 48.24; H, 5.57; N, 14.06. Found: C, 48.30; H, 5.53; N, 13.74.

A methiodide was recrystallized from ethyl acetate–acetonitrile, mp 216–218° (lit.[2a] mp 235°).

*Anal.* Calcd for $C_{11}H_{22}INO$: C, 42.46; H, 7.13; I, 40.78; N, 4.50. Found: C, 42.64; H, 7.26; I, 41.00; N, 4.29.

**Oxidation of a Diastereoisomeric Mixture of 8-Hydroxy-2-methyldecahydroisoquinolines (IV) to *trans*-2-Methyldecahydroisoquinol-8-one.** The alcohol mixture (IV, 0.75 g, 0.0044 mol) was dissolved in benzene and refluxed in a flask equipped with a Dean-Stark trap for 15–30 min. To this solution was added potassium *tert*-butoxide (1.25 g, 0.011 mol) and benzophenone (4.05 g, 0.0222 mol). The mixture was purged with dry nitrogen and refluxed for 6 hr with a continuous stream of dry nitrogen slowly passing through the reaction flask. After cooling, the reaction medium was extracted with 10% hydrochloric acid solution. The acidic extract was made alkaline by slowly adding it to a cooled, stirred ammonium hydroxide solution, and the resulting basic solution was extracted with ether on a continuous extractor for 6 hr. The ethereal extract was washed twice with a saturated aqueous sodium chloride solution, dried, and concentrated to yield an oil (0.501 g, 67%). A hydrobromide salt was prepared which was recrystallized from ethyl acetate–acetonitrile to give 0.629 g (57%) of *trans*-2-methyldecahydroisoquinol-8-one hydrobromide, mp 217–219°. A methiodide derivative was prepared by dissolving the ketone in anhydrous diethyl ether, adding an excess of methyl iodide, and boiling off the excess reagent and solvent. The residual methiodide was washed with diethyl ether and recrystallized from ethyl acetate–acetonitrile, giving white, felted needles, mp 291–294°. A subsequent recrystallization from acetone–acetonitrile gave very small, white, glassy crystals of the pure methiodide, mp 295–297° (lit.[2a] mp 288–290°).

*Anal.* Calcd for $C_{11}H_{20}INO$: C, 42.73; H, 6.52; I, 41.04; N, 4.53. Found: C, 43.11; H, 6.72; I, 41.32; N, 4.44.

**Reduction[9] of *trans*-2-Methyldecahydroisoquinol-8-one to *trans*-9,10,*cis*-8,9-*H*-8-Hydroxy-2-methyldecahydroisoquinoline.** To a solution of the catalyst, chloroiridic acid ($H_2IrCl_6 \cdot 2H_2O$, 0.0517 g, 0.12 mmol) in 0.2 ml of concentrated hydrochloric acid was added trimethyl phosphite (0.75 ml) and this solution was combined with a solution of the ketone (0.318 g, 1.9 mmol) dissolved in 2-propanol (10 ml). The mixture was refluxed for 72 hr followed by a removal of the 2-propanol by rotary evaporation. The remaining acidic solution was washed twice with ether and slowly added to cold ammonium hydroxide. The resulting alkaline solution was extracted with ether on a continuous extractor for 12 hr, dried, and concentrated, giving an oil which solidified to yield 0.316 g (98%), mp 102–113°. Analytical tlc of the crude product showed only one spot ($R_f$ 0.56) indicating quantitative conversion of the trans ketone to the alcohol. The solid was recrystallized from petroleum ether (bp 30–60°) to give 0.225 g of pure *trans*-9,10,*cis*-8,9-*H*-8-hydroxy-2-methyldecahydroisoquinoline for a 73% overall yield; mp 114–115° (lit.[2a] mp 115°); ir ($CHCl_3$) 3615 (free O–H stretch), 3430, 3150 (hydrogen-bonded O–H stretch), and 992 $cm^{-1}$ (axial C–O); nmr ($CDCl_3$) $\delta$ 2.84 (br, 1, CHOH), 3.85 (br, 1, $W_{1/2}$ = 8 Hz, CHOH), and 2.30 ppm (s, 3, $NCH_3$). Two derivatives were prepared: a picrate, which was recrystallized from absolute ethanol, mp 242–243° (lit.[2a] mp 235°), and a methiodide, which was recrystallized from ethyl acetate–acetonitrile, mp 194–196° (lit.[2a] mp 183–185°).

**Reduction of *trans*-2-Methyldecahydroisoquinol-8-one to *trans*-8,9,10-*H*-8-Hydroxy-2-methyldecahydroisoquinoline.[10]** Small portions of sodium metal (1.1 g) were added to a refluxing solution of the ketone (0.182 g, 1.08 mmol) in 30 ml of absolute ethanol. The solution was allowed to reflux for 10 hr, a further 0.5 g of sodium metal was then added, and refluxing was continued for an additional 1 hr. After allowing the reaction mixture to cool, water (2 ml) was cautiously added to ensure the destruction of residual sodium metal. The ethanol was removed on a rotary evaporator and the residue was dissolved in water, made strongly alkaline, and extracted with ether on a continuous extractor for 12 hr. The ethereal extract was dried and concentrated to yield 0.141 g (80%) of an orange-colored oil. The C–O stretching bands in the ir of this oil indicated a high percentage of the desired trans-equatorial alcohol. Analytical tlc showed one major spot (approximately 90%), $R_f$ 0.520, representing the desired alcohol, and two minor spots (10% combined), consisting of unreacted ketone and the trans-axially substituted alcohol. The oil was chromatographed on alumina (10 g) and eluted with benzene, ether, and chloroform to yield 128 mg of pure *trans*-8,9,10-*H*-8-hydroxy-2-methyldecahydroisoquinoline (70% overall yield). A methiodide derivative was prepared (mp 215–218°) which, when mixed with the methiodide derived from the alcohol IVb, showed no melting point depression. The ir and nmr spectra of the alcohol prepared by the ketone reduction and the alcohol IVb were identical.

**Hydrolysis of *cis*-9,10,*trans*-8,9-*H*-8-Acetamido-2-methyldecahydroisoquinoline (IIIc) and Subsequent Deamination with Nitrous Acid of the Corresponding Amine.** *cis*-9,10,*trans*-8,9-*H*-8-Acetamido-2-methyldecahydroisoquinoline (IIIc, 20 mg) in 15% sulfuric acid (15 ml) was refluxed for 30 hr and the resulting amine was worked up in an identical manner with that described for the preparation of IIa from IIIa. The residual oil (~10 mg) was dissolved in glacial acetic acid (5 ml) and 5 ml of water was added. To this solution was added sodium nitrite (30 mg) dissolved in 15 ml of water and the resulting solution was heated to 60° for 1 hr. The solution was then made strongly alkaline with sodium hydroxide solution and refluxed for 2 hr. The product was obtained by extraction of the cooled solution with chloroform. The chloroform solution was dried over anhydrous sodium sulfate and the residue was refluxed with benzene using a Dean-Stark trap to ensure dryness. The crude oily residue (IVc) was dissolved in anhydrous ether (10 ml) and excess methyl iodide was added. The precipitated salt was recrystallized from methanol–ether to yield a very small quantity of rosette crystals of *cis*-9,10,*trans*-8,9-*H*-8-hydroxy-2-methyldecahydroisoquinoline methiodide, mp (hot-stage microscope) 237–241°.

**Acknowledgment.** The authors are indebted to Marion Laboratories, Inc., Kansas City, Mo., for their financial assistance in support of this work.

**Registry No.**—I, 52279-18-2; IIa, 52279-19-3; IIa dihydrobromide, 52341-52-3; IIb, 52341-53-4; IIb dihydrobromide, 52341-54-5; IIIa, 52279-20-6; IIIb, 52279-21-7; IIIc, 52279-22-8; IVa, 14788-35-3; IVb, 14788-37-5; IVb hydrochloride, 52279-23-9; IVb picrate, 52279-24-0; IVb methiodide, 14991-68-5; V, 14788-34-2; 5-bromoisoquinoline, 34784-04-8; *trans*-2-methyldecahydroisoquinol-8-one hydrobromide, 52279-25-1; *trans*-2-methyldecahydroisoquinol-8-one methiodide, 15778-55-9; *trans*-9,10,*cis*-8,9-*H*-8-hydroxy-2-methyldecahydroisoquinoline, 14788-36-4.

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# Chemistry of α-Nitro Sulfones. IV.[1] Functionalization at the Activated Carbon

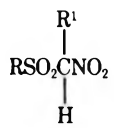
Job J. Zeilstra and Jan B. F. N. Engberts*

*Department of Organic Chemistry, The University, Zernikelaan, Groningen, The Netherlands*

*Received April 8, 1974*

Condensation reactions of nitromethyl *p*-tolyl sulfone (**1**) with formaldehyde and benzenesulfinic acid are described. A proposed rationalization of the reaction involves the intermediacy of the vinyl sulfone **6**. Some other aldehydes than formaldehyde may be used as well. The product derived from acetaldehyde can be reduced by sodium borohydride to 1-nitro-1-tosylpropane (**11**). Primary and secondary α-nitro sulfones undergo Michael-type addition reactions to certain activated carbon–carbon double bonds.

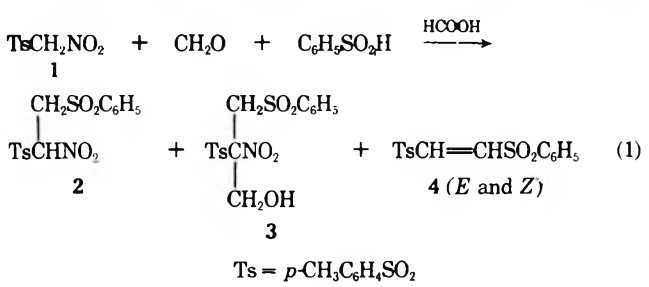
Electron-withdrawing substituents usually activate a neighboring C–H bond toward alkylation and condensation reactions.[2] However, several studies have demonstrated that the twofold activated C–H group in primary and secondary α-nitro sulfones (p$K_a$'s of about 6 in 50% ethanol–water[3]) often is only reluctantly—or indeed not at all—functionalized by means of these types of reaction.[4,5] This is noteworthy since rather similar systems like α-nitro esters,[6] nitroacetonitrile,[7] bis(phenylsulfonyl)methane,[8] and bis(alkylsulfonyl)methanes[9] easily react with aldehydes to give alcohols, alkenes, or bisadducts; moreover, nitroalkanes can also condense with, for instance, *C*-nitroso compounds[10] and benzofuroxan.[11] With these results in mind and in continuation of our studies on α-nitro sulfones,[1,3,12] we have probed further into the propensity of α-nitro sulfones for functionalization at the activated carbon atom.



$R^1$ = H, alkyl, aryl

## Results and Discussion

Under a variety of conditions and in the presence of either basic or acidic catalysts, nitromethyl *p*-tolyl sulfone (**1**) did not react with a series of aliphatic or aromatic aldehydes,[13] or with nitrosobenzene, *p*-dimethylaminonitrosobenzene, and benzofuroxan. However, when **1** was allowed to react with formaldehyde and benzenesulfinic acid in refluxing 90% aqueous formic acid, three types of condensation products (**2**, **3**, and **4**) could be isolated in yields depending on the conditions used (eq 1, Table I). The conversion of **1** into **2** is reminiscent of the condensation of carbon acids like indole or β-naphthol with formaldehyde and sulfinic acids.[14] Neither **2** nor **3** could be converted into **4** by refluxing in formic acid. Instead, starting material and partially esterified **3** were the only materials isolated. Surprisingly, an excess of benzenesulfinic acid effected the transformation of **3** into **4** in a yield of 31%. Since sulfinic acids are fairly strong reducing agents,[15] we presume that a reduction process induced by the sulfinic acid is part of the reaction.



Ts = *p*-$CH_3C_6H_4SO_2$

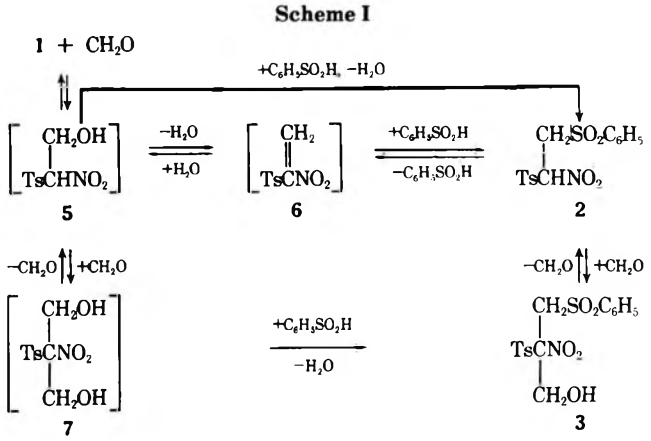
**Table I**
**Condensation Products from 1 (Equation 1)**

| Formaldehyde, equiv[a] | Benzenesulfinic acid, equiv[a] | Reaction temp, °C | Reaction time, min | Yield, % product |
|---|---|---|---|---|
| 1 | 1 | 100 | 13 | 31 (**2**), 6 (**3**)[b] |
| 3 | 2 | 100 | 13 | 8 (**2**), 28 (**3**) |
| 1 | 1 | 70 | 90 | 20 (**2**)[c] |
| 3 | 2 | 50 | 180 | 93 (**3**) |
| 3 | 1 | 50 | 180 | 89 (**3**) |
| 3 | 2 | 100 | 180 | 42 (**4**) |

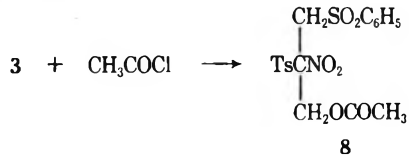
[a] Relative to 1 equiv of **1**. [b] 44% recovery of **1**. [c] 60% recovery of **1**.

At the moment no clear-cut choice can be made between the several reaction pathways conceivable for the production of **2** and **3** from **1** (Scheme I). The intermediacy of hy-

**Scheme I**



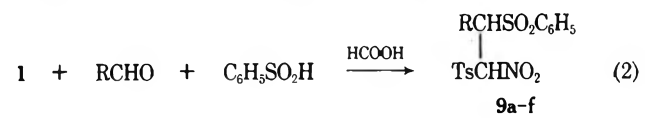
droxymethyl phenyl sulfone, the adduct of benzenesulfinic acid to formaldehyde, is highly unlikely in view of the steric and field effects of the sulfonyl moiety which will prevent SN2 displacement of the hydroxyl substituent.[16] In addition, entry to **3** *via* **7** is implausible for steric reasons (*vide infra*). In regard to the formation of **2** from **5**, we favor an elimination–addition mechanism over nucleophilic substitution of the OH group in **5** by sulfinate anion. The resistance of **3** to further coupling with benzenesulfinic acid may be understood on this basis, because no vinyl sulfone can be generated from **3**. However, steric hindrance may also be invoked to explain the absence of further conversion. The importance of this factor may be judged from the observation that refluxing of **3** for 2 hr with pure thionyl chloride did not effect substitution of the hydroxyl moiety. Acylation of **3** could only be achieved by refluxing with acetyl chloride for 3 hr. The products formed upon treatment



**8**

of **3** with base suggest that the reactions proposed in Scheme I are reversible processes. Thus, **2** was obtained from **3** by using 5% aqueous sodium hydroxide.[17] When **2** was subjected to further reaction with base, **1** was formed in high yield. This reaction most likely involves the vinyl sulfone **6** as an intermediate; this idea receives support from the well-known sulfinate elimination from β-nitroethyl sulfones in dilute alkali.[18] Addition of water to **6**, which is highly susceptible to nucleophilic addition,[19] will afford **5**. Subsequent β-elimination of formaldehyde from the labile **5**, also induced by base, then leads to the conjugated base of **1**. The great ease of this reaction may well explain our inability to isolate addition products from the reaction of primary and secondary α-nitro sulfones with aldehydes.[13]

The condensation according to eq 1 is not restricted to formaldehyde. With several aliphatic and aromatic aldehydes the corresponding condensation products could also be obtained (eq 2, Table II). However, the success of



(2)

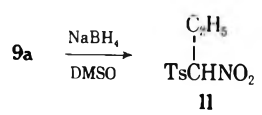
**9a–f**

the reaction clearly depends on the nature of the carbonyl component, since the starting materials were recovered almost quantitatively when butyraldehyde, isobutyraldehyde, *p*-methoxybenzaldehyde, or ketones were used. In the case of *p*-nitrobenzaldehyde and using prolonged reaction times, the disulfonylalkene **10** was formed as the major

$$TsCH{=}C(C_6H_4NO_2\text{-}p)SO_2C_6H_5$$

**10** (*E* and *Z*)

product. The condensation given in eq 2 may be of considerable synthetic utility, since we found that **9a** may be reduced to **11** by treatment with sodium borohydride in DMSO. This reaction constitutes a useful and facile alter-



**11**

native synthesis of secondary α-nitro sulfones starting from the readily available **1**. Most probably the reduction proceeds *via* a vinyl sulfone intermediate by analogy with similar reductions of β-substituted nitroalkanes in which nitroalkenes are initially formed.[20]

**Table II**
**Condensation Products from 1 (Equation 2)**

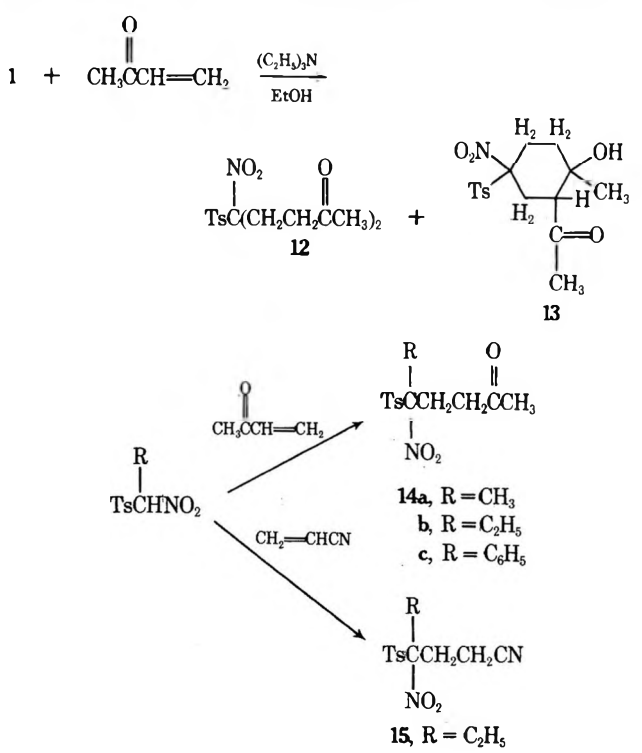
| Compd | R | Reaction time, hr | Reaction temp, °C | Yield, % |
|---|---|---|---|---|
| **9a** | $CH_3$ | 3 | 50 | 85 |
| **9b** | $C_2H_5$ | 3 | 50 | 39 |
| **9c** | $p$-$CH_3C_6H_4$ | 15 | 70 | 11[a] |
| **9d** | $C_6H_5$ | 15 | 70 | 85 |
| **9e** | $p$-$ClC_6H_4$ | 15 | 70 | 53 |
| **9f** | $p$-$NO_2C_6H_4$ | 1 | 70 | 24 |
| **10** | $p$-$NO_2C_6H_4$ | 15 | 70 | 66 |

[a] 53% recovery of **1**.

Attempts to condense secondary α-nitro sulfones like **11** with formaldehyde and benzenesulfinic acid were unsuccessful, lending support to the idea that an unsaturated sulfone, formed *via* initial addition of **11** to the aldehyde, is a key intermediate in the condensation reaction. The more severe steric requirements, as compared with the corresponding reaction with **1**, may also contribute to inertness of **11**.

We have so far also not been able to isolate Mannich bases from the reaction of α-nitro sulfones with formaldehyde and amines, using either basic or acidic conditions (normally in acetic acid rather than formic acid to avoid the Leuckart reaction).[21] In one case we have isolated **7** (*cf.* Scheme I) from the reaction of **1** with formaldehyde and diethylamine in an acidic medium after chromatography of the complex reaction mixture. Since **7** was absent in the crude products (nmr analysis) and **7** cannot be prepared from **1** and formaldehyde, the possibility remains that **7** originates from decomposition of a labile Mannich base derived from **1** during purification.

Finally we report that both primary and secondary α-nitro sulfones can undergo Michael-type addition reactions, using a catalytic amount of triethylamine. With **1** and an excess of methyl vinyl ketone, the bisadduct **12** is obtained besides the intramolecular aldol condensation product **13**. Conditions may be varied so that **13** becomes the sole product of the reaction. As anticipated, secondary



α-nitro sulfones afforded monoaddition products. Under comparable conditions, **1** does not add to methyl cinnamate and **11** fails to react with benzalacetone. These observations contrast sharply with the known smooth addition of ethyl nitroacetate to the above carbonyl compounds.[22] More severe steric demands in the reactions of **1** and **11** may well contribute to this striking difference in reactivity.

## Experimental Section

Elemental analyses were carried out in the Analytical Department of this laboratory under the supervision of Mr. W. M. Hazenberg and Mr. A. F. Hamminga. Melting points were determined using a Mettler FP1 melting point apparatus with a Mettler FP52 microscope attachment. Nmr spectra were recorded on a Varian A-60 spectrometer, using TMS (δ 0) as an internal standard. Ir spectra were measured with a Perkin-Elmer instrument, Model 257. Mass spectra were taken on a AEI MS-9 double-focusing mass spectrometer.

The α-nitro sulfones were prepared according to our previously described method[1] or according to the method of Truce, *et al.*[23] The other chemicals were commercial products and were adequately purified before use.

**Attempted Condensations with 1.** These include the following: (1) with formaldehyde: in EtOH–$NH_3$, 3 hr at 50°; in refluxing HCOOH, 10–30 min; in HCOOH, 3 hr at 50°; (2) with benzaldehyde: in EtOH with a catalytic amount of $MeNH_2$ or $K_2CO_3$, reflux, 10 min; without solvent, catalytic amount of $MeNH_2$, reflux, 2 hr; in benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid, azeotropic distillation over anhydrous Cu(II)$SO_4$, 15 hr; (3) with nitrosobenzene: in HCOOH–$H_2O$ (2:1), 1 hr at 50°; in HCOOH, 1 hr at 50°; (4) with *p*-dimethylaminonitrosobenzene: in EtOH–$H_2O$ in the presence of $K_2CO_3$, reflux, 30 min; in MeOH–$K_2CO_3$, 10 min at 25°; (5) with benzofuroxan: in EtOH in the presence of $NH_3$, 20 min at 0° or reflux for 1 hr; in HCOOH, 3 hr at 50°. In all cases **1** was recovered unchanged, usually in high yield. No evidence could be obtained for the formation of the desired condensation products.

**1-Nitro-1-(*p*-tolylsulfonyl)-2-(phenylsulfonyl)ethane (2).** A solution of **1** (2.15 g, 10 mmol), sodium benzenesulfinate (1.64 g, 10 mmol), and 1 ml of 36% aqueous formaldehyde in 28 ml of 90% formic acid was refluxed for 13 min. After dilution with water, the mixture was extracted with $CH_2Cl_2$ (200 ml). The $CH_2Cl_2$ extract was washed with water and dried over $Na_2SO_4$. Removal of the solvent *in vacuo* gave an oil which crystallized after adding some ethanol. Recrystallization from ethanol furnished 1.15 g (31%) of **2**: mp 143.6–144.7°; nmr ($CDCl_3$) δ 2.50 (s, 3 H, aryl $CH_3$), 4.0–4.3 (m, 2 H, $CH_2SO_2$), 5.35 and 5.49 (2 d, 1 H, $J$ = 3 Hz, $CHNO_2$), 7.3–8.1 ppm (m, 9 H, aryl protons); ir (KBr) 1570, 1300–1350, 1150 $cm^{-1}$.

*Anal.* Calcd for $C_{15}H_{15}NO_6S_2$: C, 48.77; H, 4.10; N, 3.80; S, 17.36. Found: C, 48.88; H, 4.14; N, 3.86; S, 17.24.

The filtrate was concentrated and allowed to stand at 0° in a refrigerator. The solid that separated was recrystallized from ethanol to give 0.94 g of **1** (44%), mp 115.0–116.0°. After standing for 3 days an additional solid precipitated. Recrystallization from benzene–*n*-hexane yielded 0.51 g of **3** (6%), mp 167.9–169.3° (*vide infra*).

**2-Nitro-2-(*p*-tolylsulfonyl)-3-(phenylsulfonyl)propanol-1 (3).** A solution of **1** (2.15 g, 10 mmol), sodium benzenesulfinate (3.28 g, 20 mmol), and 3 ml of 36% aqueous formaldehyde in 28 ml of 90% formic acid was stirred for 3 hr at 50°. After standing at 0° for 15 hr, the separated solid was filtered off, dried *in vacuo*, and recrystallized from benzene–*n*-hexane to give 3.48 g of **3**. A second portion of **3** (0.25 g) was obtained after dilution of the mother liquor with water and subsequent cooling at 0°, total yield 3.73 g (93%) of **3**: mp 168.4–169.5; nmr ($CDCl_3$) δ 2.49 (s, 3 H, aryl $CH_3$), 2.89 (br s, 1 H, OH), 4.40 (d, 2 H, $J$ = 4 Hz, $SO_2CH_2$), 4.63 (s, 2 H, $CH_2OH$), 7.2–8.1 ppm (m, 9 H, aryl protons); ir (KBr) 3540, 1550, 1280–1340, 1150 $cm^{-1}$.

*Anal.* Calcd for $C_{16}H_{17}NO_7S_2$: C, 48.11; H, 4.29; N, 3.51; S, 16.05. Found: C, 48.04; H, 4.32; N, 3.47; S, 16.03.

**Reaction of 3 with NaOH.** Sulfone **3** (2.00 g, 5 mmol) was dissolved in 30 ml of 5% aqueous NaOH kept under an atmosphere of nitrogen. After stirring for 5 min at room temperature, the solution was filtered, cooled to 5°, acidified with acetic acid, and extracted with 150 ml of $CH_2Cl_2$. The extract was washed with water and dried over $Na_2SO_4$. Recrystallization of the solid, obtained after removal of the solvent *in vacuo*, yielded 0.92 g (50%) of **2**, mp 140.3–142.3°.

**Reaction of 2 with NaOH.** A solution of 0.74 g (2 mmol) of **2** in 10 ml of 10% aqueous NaOH was refluxed under nitrogen for 15 hr. After cooling to 5° and acidification with acetic acid, solid material was obtained that was recrystallized from ethanol to afford 0.35 g (81%) of **1**, mp 114.9–115.8°.

**1-(*p*-Tolylsulfonyl)-2-(phenylsulfonyl)ethene (4).** A solution of **1** (2.15 g, 10 mmol), sodium benzenesulfinate (3.28 g, 20 mmol), and 3 ml of 36% aqueous formaldehyde in 28 ml of 90% aqueous formic acid was refluxed for 3 hr. Work-up was carried out as described for **2**. Crude **4** was recrystallized from ethanol, yield 1.34 g (42%): mp 182.0–196.5° (*E* and *Z* isomers); nmr ($CDCl_3$) δ 2.50 (s, 3 H, aryl $CH_3$), 7.3–8.1 ppm (unresolved multiplet, 11 H, aryl and vinyl protons); ir (KBr) 1320, 1150 $cm^{-1}$.

*Anal.* Calcd for $C_{15}H_{14}O_4S_2$: C, 55.88; H, 4.38; S, 19.89. Found: C, 55.80, H, 4.42; S, 19.83.

**2-Nitro-2-(*p*-tolylsulfonyl)propane-1,3-diol (7).** A solution of **1** (2.15 g, 10 mmol), diethylamine (1.60 g, 22 mmol), and 3 ml of 36% aqueous formaldehyde in 20 ml of formic acid was stirred for 2 hr at 50°. The solution was diluted with water and extracted with 200 ml of $CH_2Cl_2$. The $CH_2Cl_2$ extract was washed with water, dried over $Na_2SO_4$, and evaporated to dryness. The residue was purified by chromatography on silica gel, using a mixture of $CH_2Cl_2$ and EtOAc with increasing concentrations of EtOAc as the eluent. Recrystallization from benzene afforded 0.55 g of pure **7** (20%): mp 100.0–105.5°; nmr ($CDCl_3$) δ 2.50 (s, 3 H, aryl $CH_3$), 3.20 (t, 2 H, $J$ = 7 Hz, OH), 4.3–4.7 (m, 4 H, $CH_2O$), 7.3–7.9 ppm (m, 4 H, aryl protons); ir (KBr) 3480, 1550, 1350–1300, 1150 $cm^{-1}$; mol wt (osmotically) 287 ± 10; mass spectrum *m/e* 275 ($M^+$).

*Anal.* Calcd for $C_{10}H_{13}NO_6S$: C, 43.64; H, 4.76; N, 5.09; S, 11.65. Found: C, 43.67; H, 4.71; N, 4.90; S, 11.64.

**2-Nitro-2-(*p*-tolylsulfonyl)-3-(phenylsulfonyl)propyl Acetate (8).** A solution of **3** (1.50 g, 3.75 mmol) in 15 ml of acetyl chloride was refluxed for 3 hr. Evaporation to dryness and crystallization from EtOH gave 1.61 g of **8** (97%): mp 135.2–135.5°; nmr ($CDCl_3$) δ 2.00 (s, 3 H, $CH_3C{=}O$), 2.50 (s, 3 H, aryl $CH_3$), 4.30 and 4.60 (2 d, 2 H, $J$ = 15 Hz, $SO_2CH_2$), 4.92 and 5.12 (2 d, 2 H, $J$ = 13 Hz, $CH_2O$), 7.3–8.1 ppm (m, 9 H, aryl protons); ir (KBr) 1740, 1560, 1340–1180, 1210, 1150 $cm^{-1}$.

*Anal.* Calcd for $C_{18}H_{19}NO_8S_2$: C, 48.95; H, 4.35; N, 3.18; S, 14.57. Found: C, 49.00; H, 4.30; N, 3.02; S, 14.42.

**1-Nitro-1-(*p*-tolylsulfonyl)-2-(phenylsulfonyl)propane (9a).** A solution of **1** (2.15 g, 10 mmol), acetaldehyde (0.97 g, 22 mmol), and sodium benzenesulfinate (1.80 g, 11 mmol) in 28 ml of 90% aqueous formic acid was stirred under nitrogen for 3 hr at 50°. After crystallization in a refrigerator and subsequent filtration, the crystals were dried *in vacuo* and recrystallized from EtOH–$H_2O$, yielding 3.26 g of **9a** (85%): mp 159.2–161.2°; nmr ($CDCl_3$) δ 1.75 (d, 3 H, $J$ = 7 Hz, $CH_3CH$), 2.50 (s, 3 H, aryl $CH_3$), 4.2–4.6 (m, 1 H, $CH_3CH$), 5.80 (d, 1 H, $J$ = 10 Hz, $O_2NCH$), 7.3–8.1 ppm (m, 9 H, aryl protons). Refluxing of a solution of **9a** in EtOH caused epimerization, mp 122–156°. The 1:1 mixture of epimers gave additional absorptions in the nmr spectrum: δ 1.69 (d, 1 H, $J$ = 7 Hz, $CH_3CH$), 6.20 ppm (d, 1 H, $J$ = 1.5 Hz, $O_2NCH$).

*Anal.* Calcd for $C_{16}H_{17}NO_6S_2$: C, 50.12; H, 4.47; N, 3.66; S, 16.72. Found: C, 50.23; H, 4.43; N, 3.55; S, 16.76.

**1-Nitro-1-(*p*-tolylsulfonyl)-2-(phenylsulfonyl)butane (9b)** was prepared as described for **9a** starting from 1.28 g (22 mmol) of propionaldehyde. The reaction mixture was allowed to stand in a refrigerator for several days and was subsequently filtered to remove the crystals. These crystals were dried *in vacuo* and recrystallized from EtOH to give 1.54 g of **9b** (39%): mp 136–153°; nmr ($CDCl_3$) δ 1.20 (t, 3 H, $J$ = 7 Hz, $CH_3CH_2$), 2.2–2.6 (m, 2 H, $CH_3CH_2$), 2.50 (s, 3 H, aryl $CH_3$), 4.1–4.5 (m, 1 H, $CH_2CH$), 6.03 (d, 1 H, $J$ = 10 Hz, $O_2NCH$), 7.3–8.0 ppm (m, 9 H, aryl protons); ir (KBr) 1560, 1330, 1150 $cm^{-1}$.

*Anal.* Calcd for $C_{17}H_{19}NO_6S_2$: C, 51.37; H, 4.82; N, 3.53; S, 16.13. Found: C, 51.14; H, 4.72; N, 3.49; S, 16.15.

**1-Nitro-1-(*p*-tolylsulfonyl)-2-(phenylsulfonyl)-2-(*p*-tolyl)ethane (9c).** A solution of **1** (2.15 g, 10 mmol), *p*-methylbenzaldehyde (2.64 g, 22 mmol), and sodium benzenesulfinate (1.80 g, 11 mmol) in 28 ml of 90% aqueous formic acid was stirred under nitrogen for 15 hr at 70°. The reaction mixture was allowed to stand in a refrigerator for several days. Crystals separated, which were removed by filtration and dried *in vacuo*. Recrystallization from EtOH gave 0.50 g of pure **9c** (11%): mp 166.9–178.2° dec; nmr ($CDCl_3$) δ 2.31 (s, 3 H, aryl $CH_3$), 2.44 (s, 3 H, aryl $CH_3$ of Ts), 5.18 (d, 1 H, $J$ = 12 Hz, $SO_2CH$), 6.48 (d, 1 H, $J$ = 12 Hz, $O_2NCH$), 6.9–7.6 ppm (m, 13 H, aryl protons); ir (KBr) 1570, 1350–1290, 1150 $cm^{-1}$.

*Anal.* Calcd for $C_{22}H_{21}NO_6S_2$: C, 57.50; H, 4.61; N, 3.05; S, 13.94. Found: C, 57.34; H, 4.64; N, 2.97; S 13.97.

The mother liquor was diluted with water and extracted with $CH_2Cl_2$. The extract was washed with water, dried over $Na_2SO_4$, and evaporated to dryness. Crystallization of the residue from EtOH gave 1.13 g of 1 (53%), mp 115.5–116.1°.

**1-Nitro-1-(*p*-tolylsulfonyl)-2-(phenylsulfonyl)-2-phenylethane (9d)** was prepared from 2.32 g (22 mmol) of benzaldehyde following the procedure given for **9c.** Recrystallization from (EtOAc–DMSO)–*n*-hexane gave 4.08 g of pure **9d** (85%): mp 208.8° dec; nmr (DMSO-$d_6$) $\delta$ 2.40 (s, 3 H, aryl $CH_3$), 5.59 (d, 1 H, $J$ = 12 Hz, $SO_2CH$), 7.0–8.0 ppm (m, 14 H, 13 aryl protons + $O_2NCH$); ir (KBr) 1560, 1350–1290, 1150 $cm^{-1}$.

*Anal.* Calcd for $C_{21}H_{19}NO_6S_2$: C, 56.62; H, 4.30; N, 3.15; S, 14.41. Found: C, 56.34; H, 4.62; N, 3.00; S, 14.50.

**1-Nitro-1-(*p*-tolylsulfonyl)-2-(phenylsulfonyl)-2-(*p*-chlorophenyl)ethane (9e)** was prepared from *p*-chlorobenzaldehyde (2.87 g, 22 mmol) according to the procedure given for **9c.** Recrystallization from acetone–DMSO–water gave 2.55 g of pure **9e** (53%): mp 192.1–193.5° dec; nmr (acetone-$d_6$) $\delta$ 2.47 (s, 3 H, aryl $CH_3$), 5.48 (d, 1 H, $J$ = 13 Hz, $SO_2CH$), 7.0–7.7 ppm (m, 14 H, 13 aryl protons + $O_2NCH$); ir (KBr) 1560, 1350–1280, 1150 $cm^{-1}$.

*Anal.* Calcd for $C_{21}H_{18}ClNO_6S_2$: C, 52.55; H, 3.78; Cl, 7.39; N, 2.92; S, 13.36. Found: C, 52.78; H, 3.80; Cl, 7.40; N, 2.88; S, 13.40.

**1-Nitro-1-(*p*-tolylsulfonyl)-2-(phenylsulfonyl)-2-(*p*-nitrophenyl)ethane (9f).** A solution of 1 (2.15 g, 10 mmol), *p*-nitrobenzaldehyde (3.32 g, 22 mmol), and sodium benzenesulfinate (1.80 g, 11 mmol) in 28 ml of 90% aqueous formic acid was stirred under nitrogen for 1 hr at 70°. After cooling to 35° the separated solid was filtered off. Drying of this material *in vacuo* and recrystallization from acetone–water gave 1.16 g of pure **9f** (24%): mp 193.4–196.7° dec; nmr (acetone-$d_6$) $\delta$ 2.45 (s, 3 H, aryl $CH_3$), 5.70 (d, 1 H, $J$ = 12 Hz, $SO_2CH$), 7.2–8.1 ppm (m, 14 H, 13 aryl protons + $O_2NCH$); ir (KBr) 1560, 1520, 1350–1310, 1150 $cm^{-1}$.

*Anal.* Calcd for $C_{21}H_{18}N_2O_8S_2$: C, 51.42; H, 3.70; N, 5.72; S, 13.09. Found: C, 51.44; H, 3.71; N, 5.55; S, 12.77.

**1-(Phenylsulfonyl)-1-(*p*-nitrophenyl)-2-(*p*-tolylsulfonyl)ethene (10).** The same solution of starting materials as used for the preparation of **9f** was stirred under nitrogen for 15 hr at 70°. Cooling to room temperature and filtration of the solid gave a powder. Drying of this powder *in vacuo* and recrystallization from acetone–water gave 1.85 g of pure **10** as light-yellow needles. The mother liquor was diluted with water and extracted with $CH_2Cl_2$ (200 ml). The $CH_2Cl_2$ extract was washed with water, dried over $Na_2SO_4$, and evaporated to dryness. Crystallization of the residue from acetone–water gave another 1.06 g of **10,** total yield 2.92 g (66%): mp 224.3–230.4°; nmr (DMSO-$d_6$) $\delta$ 2.45 (s, 3 H, aryl $CH_3$), 7.0–8.3 ppm (m, 14 H, 13 aryl protons + 1 vinyl proton); ir (KBr) 1520, 1350–1280, 1150 $cm^{-1}$.

*Anal.* Calcd for $C_{21}H_{17}NO_6S_2$: C, 56.88; H, 3.86; N, 3.16; S, 14.45. Found: C, 56.94; H, 3.75; N, 13.12; S, 14.37.

**Reduction of 9a with $NaBH_4$.** To a stirred solution of **9a** (1.91 g, 5 mmol) in 25 ml of anhydrous DMSO (under nitrogen) was slowly added $NaBH_4$ (0.80 g, 20 mmol) at room temperature. After 3 hr the solution was acidified with acetic acid and diluted with water. The resulting solution was extracted with 150 ml of $CH_2Cl_2$, and the $CH_2Cl_2$ extract washed with water, dried over $Na_2SO_4$ and evaporated to dryness. The residue was diluted with EtOH and allowed to stand in the refrigerator, after which the solid was filtered and recrystallized from EtOH, yield 0.91 g of 11 (75%), mp 66.0–67.2° (lit.[1] mp 67.0–67.5°).

**5-Nitro-5-(*p*-tolylsulfonyl)-2,8-nonanedione (12).** A solution of 1 (2.15 g, 10 mmol), methyl vinyl ketone (1.54 g, 22 mmol), and 0.2 ml of triethylamine in a mixture of 10 ml of EtOH and 10 ml of $CH_2Cl_2$ was stirred for 1 hr at room temperature. After acidification with acetic acid, followed by evaporation *in vacuo* of the $CH_2Cl_2$ and part of the EtOH, the solution was allowed to stand in the refrigerator. Crystals separated which were filtered off. Recrystallization from EtOH gave 0.64 g of pure **12** (18%): mp 122.7–123.4°; nmr ($CDCl_3$) $\delta$ 2.17 (s, 6 H, $CH_3C{=}O$), 2.50 (s, 3 H, aryl $CH_3$), 2.4–3.0 (m, 8 H, $CH_2$), 7.3–7.9 ppm (m, 4 H, aryl protons); ir (KBr) 1710, 1550, 1350–1270, 1150 $cm^{-1}$.

*Anal.* Calcd for $C_{16}H_{21}NO_6S$: C, 54.07; H, 5.96; N, 3.94; S, 9.02. Found: C, 53.90; H, 6.01; N, 3.86; S, 8.93.

**1-Methyl-2-acetyl-4-nitro-4-(*p*-tolylsulfonyl)-1-cyclohexanol (13).** A solution of 1 (2.15 g, 10 mmol), methyl vinyl ketone (1.54 g, 22 mmol), and 0.2 ml of triethylamine in 15 ml of EtOH was refluxed for 5 hr. After acidification with acetic acid the solution was allowed to stand in the refrigerator. The separated crystals were filtered off. Recrystallization from acetone–water gave 2.89 g of pure **13** (81%): mp 188.4–188.5°; nmr ($CDCl_3$) $\delta$ 1.17 (s, 3 H, $CH_3$), 2.30 (s, 3 H, $CH_3C{=}O$), 1.3–3.0 (m, 7 H, ring H), 3.83 (d, 1 H, $J$ = 2 Hz, OH), 7.3–7.8 ppm (m, 4 H, aryl protons); ir (KBr) 3420, 1690, 1550, 1370–1260, 1150 $cm^{-1}$; mol wt (osmotically) 354 ± 11; mass spectrum *m/e* 340 ($M^+ - CH_3$), 312 ($M^+$ – acetyl), 249 ($M^+$ – tolyl), 200 ($M^+$ – Ts).

*Anal.* Calcd for $C_{16}H_{21}NO_6S$: C, 54.07; H, 5.96; N, 3.94; S, 9.02. Found: C, 54.19; H, 5.97; N, 3.77; S, 8.84.

**5-Nitro-5-(*p*-tolylsulfonyl)-2-hexanone (14a).** According to the procedure followed for the preparation of **13,** 1-nitro-1-(*p*-tolylsulfonyl)ethane (2.29 g, 10 mmol) was treated with methyl vinyl ketone (0.77 g, 11 mmol) for 30 min, yield 2.80 g (94%) of **14a:** mp 119.0–119.1° (from EtOH); nmr ($CDCl_3$) $\delta$ 1.90 (s, 3 H, $CH_3$), 2.18 (s, 3 H, $CH_3C{=}O$), 2.50 (s, 3 H, aryl $CH_3$), 2.59 (s, 2 H, $CH_2C{=}O$), 7.3–7.9 ppm (m, 4 H, aryl protons); ir (KBr) 1710, 1550, 1350–1290, 1150 $cm^{-1}$.

*Anal.* Calcd for $C_{13}H_{17}NO_5S$: C, 52.16; H, 5.72; N, 4.68; S, 10.71. Found: C, 52.10; H, 5.78; N, 4.61; S, 10.64.

**5-Nitro-5-(*p*-tolylsulfonyl)-2-heptanone (14b).** According to the procedure given for the preparation of **13,** 1-nitro-1-(*p*-tolylsulfonyl)propane (2.43 g, 10 mmol) was treated with methyl vinyl ketone (0.77 g, 11 mmol) for 30 min, yield 3.06 g (98%) of **14b:** mp 84.2–84.4° (from EtOH); nmr ($CDCl_3$) $\delta$ 0.98 (t, 3 H, $J$ = 8 Hz, $CH_3CH_2$), 2.20 (s, 3 H, $CH_3C{=}O$), 2.50 (s, 3 H, aryl $CH_3$), 2.0–3.0 (m, 6 H, $CH_2$), 7.2–7.9 ppm (m, 4 H, aryl protons); ir (KBr) 1720, 1550, 1350–1280, 1150 $cm^{-1}$.

*Anal.* Calcd for $C_{14}H_{19}NO_5S$: C, 53.66; H, 6.11; N, 4.47; S, 10.23. Found: C, 53.78; H, 6.08; N, 4.28; S, 10.25.

**5-Nitro-5-(*p*-tolylsulfonyl)-5-phenyl-2-pentanone (14c).** According to the procedure given for the preparation of **13,** $\alpha$-nitrobenzyl *p*-tolyl sulfone (2.91 g, 10 mmol) was treated with methyl vinyl ketone (0.77 g, 11 mmol) for 2 hr, yield 3.41 g (94%) of **14c:** mp 105.4–106.1° (from EtOH); nmr ($CDCl_3$) $\delta$ 2.10 (s, 3 H, $CH_3C{=}O$), 2.33 (s, 3 H, aryl $CH_3$), 2.3–3.4 (m, 4 H, $CH_2$), 7.0–7.6 ppm (m, 9 H, aryl protons); ir (KBr) 1720, 1550, 1350–1280, 1150 $cm^{-1}$.

*Anal.* Calcd for $C_{18}H_{19}NO_5S$: C, 59.82; H, 5.30; N, 3.88; S, 8.87. Found: C, 59.44; H, 5.36; N, 3.80; S, 8.72.

**1-Cyano-3-nitro-3-(*p*-tolylsulfonyl)pentane (15).** According to the procedure given for the preparation of **13,** 1-nitro-1-(*p*-tolylsulfonyl)propane (2.43 g, 10 mmol) was treated with acrylonitrile (0.58 g, 11 mmol) for 1 hr, yield 1.85 g (62%) of **15:** mp 83.8–85.5° (from EtOH); nmr ($CDCl_3$) $\delta$ 0.97 (t, 3 H, $J$ = 7 Hz, $CH_3CH_2$), 2.26 (q, 2 H, $J$ = 7 Hz, $CH_3CH_2$), 2.50 (s, 3 H, aryl $CH_3$), 2.6–3.0 (m, 4 H, $CH_2$), 7.2–7.9 ppm (m, 4 H, aryl protons); ir (KBr) 2260, 1550, 1350–1280, 1150 $cm^{-1}$.

*Anal.* Calcd for $C_{13}H_{16}N_2O_4S$: C, 52.69; H, 5.44; N, 9.45; S, 10.82. Found: C, 52.58; H, 5.49; N, 9.35; S, 10.73.

**Registry No.—1,** 51351-89-4; **2,** 52260-52-3; **3,** 52358-28-8; (*E*)-**4,** 52260-53-4; (*Z*)-**4,** 52260-54-5; **7,** 52341-43-2; **8,** 52341-44-3; **9a** epimer A, 52260-55-6; **9a** epimer B, 52260-56-7; **9b,** 52260-57-8; **9c,** 52260-58-9; **9d,** 52260-59-0; **9e,** 52260-60-3; **9f,** 52260-61-4; (*E*)-**10,** 52260-62-5; (*Z*)-**10,** 52260-63-6; **12,** 52260-64-7; **13,** 52260-65-8; **14a,** 52260-66-9; **14b,** 52260-67-0; **14c,** 52260-68-1; **15,** 52341-45-4; formaldehyde, 50-00-0; sodium benzenesulfinate, 873-55-2; benzaldehyde, 100-52-7; nitrosobenzene, 586-96-9; *p*-dimethylaminonitrosobenzene, 138-89-6; benzofuroxan, 480-96-6; acetyl chloride, 75-36-5; acetaldehyde, 75-07-0; propionaldehyde, 123-38-6; *p*-methylbenzaldehyde, 104-87-0; *p*-chlorobenzaldehyde, 104-88-1; *p*-nitrobenzaldehyde, 555-16-8; methyl vinyl ketone, 78-94-4; 1-nitro-1-(*p*-tolylsulfonyl)ethane, 51351-86-1; 1-nitro-1-(*p*-tolylsulfonyl)propane, 42759-54-6; $\alpha$-nitrobenzyl *p*-tolyl sulfone, 21272-79-7; acrylonitrile, 107-13-1.

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# Free-Radical Chain Isomerization of *N*-Vinylsulfonamides

W. R. Hertler

*Contribution No. 2144 from the Central Research Department, E. I. du Pont de Nemours and Co., Inc., Wilmington, Delaware 19898*

*Received May 7, 1974*

Several new *N*-vinylsulfonamides were synthesized and photochemically or thermally caused to isomerize to β-sulfonylvinylamines. The chain length for the isomerization of *N*-methyl-*N*-(α-styryl)-*p*-toluenesulfonamide photoinitiated by benzoin methyl ether is estimated to be 1430.

The irradiation of certain *N*-vinylsulfonamides with high energy electrons was reported to induce a free-radical chain reaction leading to the formation of β-sulfonylvinylamines.[1] The same transformation was found to occur upon photolysis or thermolysis of an azonitrile initiator in the presence of an *N*-vinylsulfonamide.[2] This paper details our study of the generality of the photo- and thermal rearrangement of *N*-vinylsulfonamides and describes the synthesis of several new *N*-vinylsulfonamides.

Stacey, Sauer, and McKusick[1] proposed the mechanism shown in Scheme I for the radiation-induced rearrangement of *N*-methyl-*N*-vinylbenzenesulfonamide to *N*-methyl-2-benzenesulfonylvinylamine. Certain *N*-vinylsulfonamides were found to undergo electron-induced topotactic rearrangement in the crystalline state.

**Scheme I**

Initiation

$$C_6H_5SO_2N(CH_3)CH{=}CH_2 \longrightarrow R\cdot$$
(1)

$$R\cdot + 1 \longrightarrow C_6H_5SO_2N(CH_3)\dot{C}HCH_2R$$

$$\downarrow$$

$$C_6H_5SO_2\cdot + CH_3N{=}CHCH_2R$$

Propagation

$$C_6H_5SO_2\cdot + 1 \longrightarrow C_6H_5SO_2N(CH_3)\dot{C}HCH_2SO_2C_6H_5$$

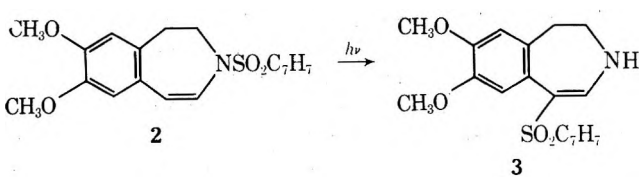
$$\downarrow$$

$$C_6H_5SO_2\cdot + CH_3N{=}CHCH_2SO_2C_6H_5$$

$$\downarrow$$

$$CH_3NHCH{=}CHSO_2C_6H_5$$

More recently, Graftieaux and Gardent[3] reported the light-induced rearrangement of 3-*p*-toluenesulfonyl-7,8-dimethoxy-4,5-dihydro-3*H*-benzazepine-3 (**2**) to the sulfone, **3**. A mechanism involving homolytic S–N scission with recombination of the radicals in a solvent cage was suggested; however, no evidence was presented to rule out a Stacey–Sauer–McKusick chain mechanism.



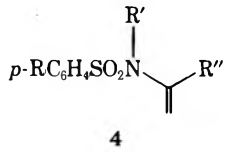

**2** **3**

**Table I**
***N*-Vinylsulfonamides, *p*-RC$_6$H$_4$SO$_2$NR′C(R″)=CH$_2$**

| Compd | R | R′ | R″ |
|---|---|---|---|
| 5[1] | $CH_3$ | $CH_3$ | H |
| 6 | $CH_3O$ | $CH_3$ | H |
| 7[4] | $CH_3$ | $CH_3$ | $C_6H_5$ |
| 8 | $CH_3$ | *p*-$CH_3OC_6H_4$ | $C_6H_5$ |
| 9 | $CH_3$ | $CH_3$ | *p*-$CH_3OC_6H_4$ |
| 10 | Br | $CH_3$ | $C_6H_5$ |
| 11 | $CH_3$ | $CH_3$ | *p*-$BrC_6H_4$ |
| 12 | $CH_3O$ | $CH_3$ | $C_6H_5$ |
| 13 | $CH_3$ | *p*-$(CH_3)_2NC_6H_4$ | $C_6H_5$ |
| 14 | $CH_3$ | $C_2H_5$ | $CH_3$ |
| 15 | H | $C_2H_5$ | $CH_3$ |

## Results

**Synthesis.** Three general methods were used for the preparation of the *N*-vinylsulfonamides of general formula **4**. The literature[4] reaction of acetylene with an *N*-alkylarenesulfonamide was used for the preparation of **4** where R″ = H. For the preparation of *N*-(α-styryl)sulfonamides (**4**, R″ = aryl), the procedure[1] outlined in eq 1 was used, and the procedure of eq 2 was used to prepare *N*-2-(alkenyl)sulfonamides (**4**, R″ = alky). The *N*-vinylsulfonamides prepared by these procedures are listed in Table I. The properties of the new *N*-vinylsulfonamides are summarized in Table II, and the properties of some of the intermediates are summarized in Table III.



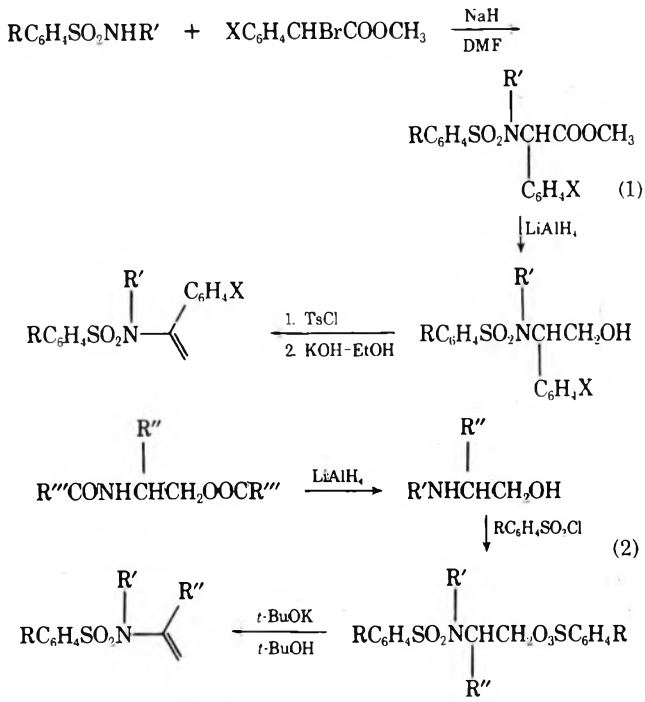

**4**

The reaction sequence of eq 1 does not appear to be entirely general for the preparation of *N*-(α-styryl)sulfonamides as evidenced by an interesting anomalous reaction which was found to occur in attempting to carry out the first step (eq 1) when R = $CH_3$, R′ = isopropyl, and R″ =

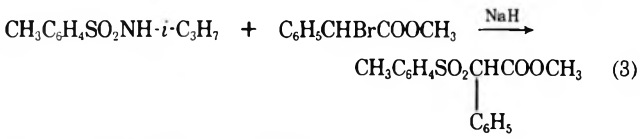
**Table II**
**Properties of *N*-Vinylsulfonamides**

| Compd[a] | Mp, °C (recrystn solvent) | Method of synthesis[b] | Nmr, δ (60 MHz, $CDCl_3$), ($H_3$)–N–($H_1$, $H_2$) |
|---|---|---|---|
| 6 | liq, bp ~112 (0.005 mm) | A | 4.08–4.45 (m, $H_1$, $H_2$), 6.81–7.80 (m, $H_3$) |
| 8 | 78–81 (ethanol) | B | 5.19 ($H_1$), 5.42 ($H_2$) |
| 9 | 79–82 (ether–hexane) | B | 4.79 ($H_1$), 5.33 ($H_2$) |
| 10 | 76.5–78 (methanol) | B | 4.91 ($H_1$), 5.40 ($H_2$) |
| 11 | 108–109 (methanol) | B | 4.85 (d, $H_1$, $J_{12}$ = 1 Hz), 5.43 (d, $H_2$, $J_{12}$ = 1 Hz) |
| 12 | 86.5–88.5 (methanol) | B | 4.85 ($H_1$), 5.39 ($H_2$) |
| 13 | 131.5–133.5 (ethanol) | B | 5.19 ($H_1$), 5.44 ($H_2$) |
| 14 | 64.5–68 (heptane) | C | 4.75 ($H_1$), 5.05 ($H_2$) |
| 15 | liq, bp 97–103° (0.05 mm) | C | 4.69 ($H_1$), 5.03 (q, $H_2$, $J_{2CH_3}$ = 1 Hz) |

[a] Satisfactory analytical data (±0.4% for C, H, N) were reported for all new compounds listed in the table with the exception of 14 and 15 (N): Ed. [b] Method A is described in ref 4. Method B is described in eq 1. Method C is described in eq 2.



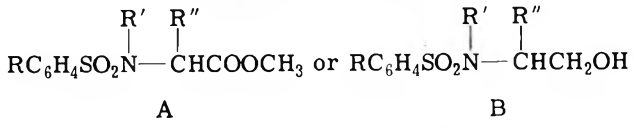

H. Instead of obtaining the sulfonamido ester, a sulfone was obtained in low yield along with isopropylamine (eq 3).




Apparently, the steric hindrance at the nitrogen atom of the sulfonamide caused the reaction to follow the anomalous course. The same sulfone was formed when *N*-methyl-*p*-toluenesulfonamide was allowed to react with methyl-α-chlorophenyl acetate and sodium hydride. The amount of sulfone found to accompany the desired sulfonamide ester in various other preparations seemed to increase when the substitution on the α-halo ester would be expected to increase the acidity of the tertiary hydrogen atom.

**Photoinitiated Isomerization of *N*-Vinylsulfonamides.** Several photoinitiators commonly used for photopolymerizations were found to be useful in photoinitiation of the isomerization of *N*-vinylsulfonamides to β-sulfonylvinylamines. The initiators examined were benzoin methyl ether, Michler's ketone–benzophenone, benzophenone–isopropyl alcohol, and a hexaarylbiimidazole-2-mercaptobenzoxazole. The irradiation experiments are summarized in Table IV. From the relatively small doses required to produce substantial rearrangement, it is apparent that rearrangement proceeds by a mechanism involving a chain reaction. The benzoin methyl ether initiated isomerization of **7** in benzene solution was determined to have a chain length of 1430 assuming a quantum efficiency of 0.2 for dissociation of benzoin methyl ether, which is the value measured (at 366 mμ) by Pappas and Chattopadhyay[5] for formation of α,α′-diisopropoxybibenzyl from benzoin isopropyl ether. The photorearrangement of the *N*-vinylsulfonamides is strongly inhibited by oxygen consistent with a free-radical chain mechanism. The introduction of an alkyl substituent to the vinyl group of the *N*-vinylsulfonamide greatly facilitates the photoinitiated rearrangement as can be seen by comparing (Table IV) the rearrangement of **14** with **5** and **6**.

**Table III**
**Properties of Intermediates (A and B) in Synthesis of *N*-Vinylsulfonamides[a]**




| Type of intermediate | R, R′, R″ same as in compound | Mp, °C (recrystn solvent) |
|---|---|---|
| A | 7 | 87.5–88.5 (ether) |
| A | 9 | 104.5–105.5 (ether) |
| A | 10 | 98–100 (ether–hexane) |
| A | 11 | 112.5–113.5 (methanol) |
| A | 12 | 104–107 (methanol) |
| A | 13 | 114–119 (methanol) |
| B | 12 | 97–99 (ether–hexane) |
| B | 13 | 192–195 dec (methanol) |

[a] Satisfactory analytical data (±0.4% for C, H, N) were reported for all new compounds listed in the table: Ed.

**Thermal Rearrangement of *N*-Vinylsulfonamides.** When *N*-vinylsulfonamides are heated above the melting point in the presence of air, they undergo rearrangement to β-sulfonylvinylamines. The thermal rearrangement is less facile in an inert atmosphere such as nitrogen. Perhaps oxidation produces an unstable intermediate which serves to

**Table IV**
**Photoinitiated Isomerization of *N*-Vinylsulfonamides**

| Compd (wt in mg) | Initiator[a] (wt in mg) | Conditions and dose[b] | % rearrangement[c] |
|---|---|---|---|
| 5 (400) | BME (20) | $N_2$, 94°, <1.5 J/cm$^2$ (C arc) | 10 |
| 6 (200) | BME (10) | $N_2$, rt, ~1.5 J/cm$^2$ (C arc) | 20–33 |
| 7 (300) | BME (30), 0.5 ml of $CH_3CN$ | $N_2$, 180 mJ/cm$^2$ (366 mμ) | 18 |
| 7 (300) | BME (30), 0.5 ml of $C_6H_6$ | $N_2$, 180 mJ/cm$^2$ (366 mμ) | 26[d] |
| 7 (150) | $Ph_2CO$ (0.1 *M*), 0.963 ml of *i*-PrOH, 0.188 ml of $C_6H_6$ | $N_2$, 720 mJ/cm$^2$ (366 mμ) | 27 |
| 7 (150) | CDM HABI (1), 0.25 ml of $C_6H_6$ | $N_2$, 720 mJ/cm$^2$ (366 mμ) | 11 |
| 7 (150) | CDM HABI (0.25), 2MBO (0.025), 0.25 ml of $C_6H_6$ | $N_2$, 720 mJ/cm$^2$ (366 mμ) | 60 |
| 7 (75) | BME (7.5), 0.13 ml of $CDCl_3$ | $N_2$, 540 mJ/cm$^2$ (366 mμ) | 50 |
| 7 (75) | BME (7.5), 0.13 ml of $CDCl_3$ | Air, 540 mJ/cm$^2$ (366 mμ) | 0 |
| 10 (150) | BME (15), 0.25 ml of $C_6H_6$ | Air, 180 mJ/cm$^2$ (366 mμ) | 0 |
| 10 (150) | BME (15), 0.25 ml of $C_6H_6$ | $N_2$, 180 mJ/cm$^2$ (366 mμ) | 19 |
| 12 (150) | BME (15), 0.25 ml of $C_6H_6$ | $N_2$, 180 mJ/cm$^2$ (366 mμ) | 38 |
| 12 (150) | BME (15), 0.25 ml of $C_6H_6$ | Air, 180 mJ/cm$^2$ (366 mμ) | 11 |
| 13 (150) | BME (15), 0.15 ml of $C_6H_6$, 0.15 ml of MeCN | $N_2$, 720 mJ/cm$^2$ (366 mμ) | 0 |
| 14 (150) | BME (16), 0.25 ml of $C_6H_6$ | $N_2$, 720 mJ/cm$^2$ (366 mμ) | 41 |
| 14 (150) | BME (15), 0.25 ml of $C_6H_6$ | Air, 720 mJ/cm$^2$ (366 mμ) | 8–14 |

[a] BME, benzoin methyl ether; CDM HABI, 2-*o*-chlorophenyl-4,5-di-*m*-methoxyphenylimidazole dimer; 2MBO, 2-mercaptobenzoxazole. [b] The 366-mμ exposures were carried out in rectangular 1-cm. Pyrex cells using a filtered high pressure Hg lamp at a dose rate of about 100 μW/cm$^2$. The carbon arc exposures were carried out with a Bausch and Lomb 4.5-A carbon arc. At the photoinitiator concentrations used, much more than 99% of the incident light at 366 mμ was absorbed. [c] Degree of rearrangement is determined by nmr. [d] Assuming a quantum efficiency of 0.2 for BME initiation (see ref 5), this corresponds to 1430 isomerizations per initiating radical.

**Table V**
**Thermal Rearrangement of *N*-Vinylsulfonamides[a]**

| Compd | Conditions (hr, temp in °C, atm) | % rearrangement |
|---|---|---|
| 7 | 1, 95, air | 35 |
| 7 | 1, 95, $N_2$ | 0 |
| 8 | 1.5, 95, air | 0 |
| 9 | 1, 95–99, air | 19 |
| 10 | 1, 95, air | 17 |
| 11 | 1, 114, air | 44 |
| 11 | 1, 116, $N_2$ | 34 |
| 12 | 1, 95–100, air | 29 |
| 12 | 1, 95–99, $N_2$ | 16.5 |
| 13 | 4, 133, air | 100 |
| 14 | 1, 95–99, air | 0 |

[a] The extent of rearrangement was estimated by nmr using the spectra of the starting material and the product as standards.

initiate the rearrangement. The thermal rearrangement of *N*-vinylsulfonamides is summarized in Table V. The products of rearrangement were obtained on a preparative scale by heating the *N*-vinylsulfonamides above the melting point with azobisisobutyronitrile initiator either in air or nitrogen. The properties of the resulting β-sulfonylvinylamines are summarized in Table VI.

## Experimental Section

***N*-Methyl-*N*-vinyl-*p*-methoxybenzenesulfonamide (6). Method A.** A mixture of 15 g of *N*-methyl-*p*-methoxybenzenesulfonamide, 40 ml of benzene, and 0.595 g of powdered potassium hydroxide was heated at 160° in a 240-cc Hastalloy shaker bomb under 220–305 psi of acetylene for 16 hr. The resulting mixture was filtered, and the filtrate was washed twice with 10% aqueous sodium hydroxide and once with water. After the mixture dried, the solvent was removed *in vacuo*, and the residue was distilled in a short-path column at ~112° (0.005 mm) to give 8.4 g of *N*-methyl-*N*-vinyl-*p*-methoxybenzenesulfonamide as a viscous liquid (see Table II).

***N*-Methyl-*N*-(α-styryl)-*p*-bromobenzenesulfonamide (10). Method B.** To a slurry of 345 ml of anhydrous dimethylformamide and 11.5 g of a 50% dispersion of sodium hydride in mineral oil was added 55.4 g of *N*-methyl-*p*-bromobenzenesulfonamide. The mixture was stirred for 2 hr at which time the hydrogen evolution had ceased. The mixture was then cooled in an ice bath at 10° and treated with 50.8 g of methyl α-bromophenylacetate. The mixture was stirred at room temperature for 1 hr. The resulting solution was poured into ice water and extracted twice with benzene. The benzene extracts were combined and washed twice with water, once with 1% aqueous sodium hydroxide, and twice with water. The benzene solution was dried over Drierite and evaporated *in vacuo* to give 72.3 g of oil. Cooling while scratching with hexane caused crystallization to occur. Filtration gave 55.9 g of solid. Recrystallization from ether–hexane gave 33.8 g of crystals of *N*-methyl-*N*-(α-carbomethoxybenzyl)-*p*-bromobenzenesulfonamide, mp 94.5–97.5°. An additional recrystallization raised the melting point to 98–100°.

*Anal.* Calcd for $C_{16}H_{16}NBrO_4S$: C, 48.1; H, 4.05; N, 3.52. Found: C, 47.6, 47.8; H, 3.96, 4.09; N, 3.39, 3.30.

To a stirred slurry of 1.85 g of lithium aluminum hydride and 125 ml of tetrahydrofuran cooled in an ice bath was added a solution of 33 g of *N*-methyl-*N*-(α-carbomethoxybenzyl)-*p*-bromobenzenesulfonamide in 83 ml of tetrahydrofuran at a rate such that the temperature remained near 28°. The mixture was stirred at room temperature for 1.25 hr, treated with an additional 0.2 g of lithium aluminum hydride, and stirred for 0.75 hr. The mixture was cooled, treated with 15 ml of water and stirred for 30 min. The mixture was filtered, and the filtrate was evaporated *in vacuo* to 27.2 g of oil. This residue was treated with 50 ml of 10% sodium hydroxide and sufficient ethanol to give a homogeneous solution at the reflux. After refluxing for 1 hr, the mixture was concentrated *in vacuo* to remove ethanol and was then treated with water and ether. The ether extract was washed twice with water, dried, and evaporated to 16.5 g of *N*-methyl-*N*-[α-(hydroxymethyl)benzyl]-*p*-bromobenzenesulfonamide as a viscous oil which could not readily be crystallized.

To a stirred solution of 18 g of *p*-toluenesulfonyl chloride in 80 ml of pyridine was added dropwise with warming a solution of 16.5

**Table VI**
**Rearrangement Products of *N*-Vinylsulfonamides[a]**

| Conditions[b] | Mp, °C (recrystn solvent) | Comments |
|---|---|---|
| **6** (1 g)<br>AIBN (50 mg)<br>2.5 hr, 90°, $N_2$ | 132.5–135.5 (ethyl acetate) | Nmr δ 2.71 (d, $J$ = 5 Hz, $NCH_3$) |
| **8** (1 g)<br>AIBN (40 mg)<br>2 hr, 95°, air | Glass | $\epsilon_{3200\ A}^{benzene}$ 7500, no **8** remained |
| **10** (1 g)<br>AIBN (15 mg)<br>2 hr, 95°, air | 155–156.5 (ethyl acetate–heptane) | Nmr δ 2.71 (d, $J$ = 5 Hz, $NCH_3$), 4.70 (vinyl H) |
| **11** (750 mg)<br>AIBN (15 mg)<br>3.5 hr, 100°, air | 117–119 (benzene–heptane) | Nmr δ 2.65 (d, $J$ = 5 Hz, $NCH_3$), 4.66 (vinyl H) |
| **12** (1 g)<br>AIBN (10 mg)<br>3 hr, 95–100°, air | 94.5–97.5 (ether–heptane) | Nmr δ 2.70 (d, $J$ = 5 Hz, $NCH_3$), 4.70 (vinyl H) |
| **13** (750 mg)<br>AIBN (15 mg)<br>1.5 hr, 135°, $N_2$ | 103–107 | $\epsilon_{3550\ A}^{ether}$ 10,100 (sh, tail to 4700 Å)<br>Nmr suggests isomeric mixture |
| **14** (700 mg)<br>AIBN (15 mg)<br>3 hr, 95–104°, air | 88–91 (cyclohexane) | Nmr [two isomers (2:1)] δ 4.53 and 4.98 (vinyl H trans and cis to N) |

[a] Satisfactory analytical data (±0.4% for C, H, N) were reported for all new compounds listed in this table with the exception of the entry for 14: Ed. [b] AIBN, azobisisobutyronitrile.

g of *N*-methyl-*N*-[α-(hydroxymethyl)benzyl]-*p*-bromobenzenesulfonamide in 60 ml of pyridine over a period of 15 min. The temperature was maintained at ~40° during the addition. The resulting solution was stirred overnight at room temperature, cooled to 10°, and treated with a few pieces of ice. After 15 min, the solution was poured into a mixture of ice and hydrochloric acid. The resulting gummy precipitate was collected by filtration, dissolved in benzene, washed twice with water, dried over Drierite, and evaporated *in vacuo* to give 25.6 g of *N*-methyl-*N*-(α-phenyl-β-*p*-toluenesulfonoxyethyl)-*p*-bromobenzenesulfonamide as a viscous oil.

A mixture of 25.6 g of *N*-methyl-*N*-(α-phenyl-β-*p*-toluenesulfonoxyethyl)-*p*-bromobenzenesulfonamide, 115 ml of ethanol, and 13 g of potassium hydroxide was stirred for 2 hr at reflux under nitrogen. The resulting gummy precipitate was extracted with ether–hexane. The extract was washed twice with water, dried, and evaporated to 14 g of oil. Recrystallization from methanol gave 8.66 g of crystals of *N*-methyl-*N*-(α-styryl)-*p*-bromobenzenesulfonamide: mp 73.5–76° (a second recrystallization from methanol raised the melting point to 76.5–78°); nmr ($CDCl_3$) δ 3.09 ($NCH_3$), 4.91 (vinyl H cis to phenyl), 5.40 (vinyl H cis to N), 7.23–7.75 (aromatic).

*Anal.* Calcd for $C_{15}H_{14}NSO_2Br$: C, 51.1; H, 4.00; N, 4.00; Br, 22.7. Found: C, 50.7; H, 3.96; N, 3.78; Br, 22.0.

***N*-Ethyl-*N*-2-propenyl-*p*-toluenesulfonamide (14). Method C.** To a stirred slurry of 40 g of lithium aluminum hydride in 750 ml of tetrahydrofuran was added a solution of 110 g of 2-acetamidopropyl acetate (prepared by the reaction of acetic anhydride with 2-amino-1-propanol) in 250 ml of tetrahydrofuran at a rate such that gentle reflux was maintained. Stirring at reflux was continued for 9 hr. The mixture was cooled in ice, treated with 100 ml of water, stirred for 1.5 hr, and filtered. The filtrate was dried with Drierite and evaporated *in vacuo* to 54.2 g of liquid. Distillation gave 34.2 g of *N*-ethyl-*N*-β-hydroxyisopropylamine, bp 60–67° (7–38 mm).

*Anal.* Calcd for $C_5H_{13}NO$: C, 58.2; H, 12.7; N, 13.6. Found: C, 58.6; H, 12.7; N, 13.5.

To a stirred solution of 15.2 g of *N*-ethyl-*N*-β-hydroxyisopropylamine in 300 ml of pyridine was added a solution of 89 g of *p*-toluenesulfonyl chloride in 250 ml of pyridine at a rate such that the temperature remained at 40–45°. After stirring overnight at room temperature, the solution was cooled to 10°, treated with a few pieces of ice, and after 20 min poured into excess ice and hydrochloric acid. The resulting gum was collected by decantation, dissolved in ether, washed with dilute hydrochloric acid and water, dried, and evaporated to 28.6 g of amber oil. Recrystallization from ether-hexane gave 18.2 g of crystals of *N*-ethyl-*N*-(3-*p*-toluenesulfonoxy-2-propyl)-*p*-toluenesulfonamide.

A mixture of 14 g of potassium *tert*-butoxide, 100 ml of *tert*-butyl alcohol, and 17 g of *N*-ethyl-*N*-(3-*p*-toluenesulfonoxy-2-propyl)-*p*-toluenesulfonamide was stirred at reflux under nitrogen for 1 hr, cooled, diluted with ice water, and extracted with ether. The ether extract was washed twice with water, dried, and evaporated to a crystalline residue. Recrystallization from heptane gave 6.8 g of crystals of *N*-ethyl-*N*-2-propenyl-*p*-toluenesulfonamide: mp 64.5–68°; nmr ($CDCl_3$) δ 1.16 (triplet, $J$ = 7 Hz, $CH_3$ of $C_2H_5$), 1.89 (vinyl $CH_3$), 2.44 (aromatic $CH_3$), 3.42 (quartet, $J$ = 7 Hz, $CH_2N$), 4.75 (vinyl H cis to $CH_3$), 5.05 (vinyl H cis to N), 7.24–7.80 (aromatic).

*Anal.* Calcd for $C_{12}H_{17}NO_2S$: C, 60.4; H, 7.15; N, 5.86. Found: C, 60.0; H, 7.28; N, 5.40.

**Methyl 2-*p*-Toluenesulfonyl-2-phenylacetate.** A mixture of 300 ml of dimethylformamide, 9.6 g of 50% sodium hydride dispersed in mineral oil, 42.5 g of *N*-isopropyl-*p*-toluenesulfonamide, and 45.8 g of methyl-α-bromophenyl acetate was stirred for 3 hr at 45°. The mixture was poured into ice water and extracted with ether. The ether extract was washed with water three times, dried, and evaporated *in vacuo* to 61 g of oil. Crystallization from heptane and then from methanol gave 14.7 g of methyl-2-(*p*-toluenesulfonyl)-2-phenyl acetate: mp 114–117° (an additional recrystallization from methanol raised the melting point to 124–126°); nmr ($CDCl_3$) δ 2.41 (aromatic $CH_3$), 3.75 ($COOCH_3$), 5.08 (tertiary CH), 7.13–7.58 (aromatic).

*Anal.* Calcd for $C_{16}H_{16}O_4S$: C, 63.1; H, 5.30; N, 0.00; S, 10.5; mol wt, 304. Found: C, 63.2; H, 5.30; N, <0.03; S, 10.7; mol wt, 304 (mass spectrum)

The mass spectrum of the product showed, in addition to the parent peak (*m/e* 304), a large peak at *m/e* 149 corresponding to loss of $C_6H_5CHCOOCH_3$.

The same product was obtained from the reaction of *N*-methyl-*p*-toluenesulfonamide with methyl α-chlorophenylacetate and sodium hydride in dimethylformamide. Methylamine was evolved from the reaction mixture.

**Registry No.**—**6**, 52260-06-7; **8**, 52260-07-8; **9**, 52260-08-9; **10**, 52260-09-0; **11**, 52260-10-3; **12**, 52260-11-4; **13**, 52260-12-5; **14**, 52260-13-6; **15**, 52260-14-7; *N*-methyl-*p*-methoxybenzenesulfon-

amide, 7010-86-8; *N*-methyl-*p*-bromobenzenesulfonamide, 703-12-8; methyl α-bromophenylacetate, 3042-81-7; *N*-methyl-*N*-(α-carbomethoxybenzyl)-*p*-bromobenzenesulfonamide, 52260-15-8; 2-acetamidopropyl acetate, 52260-16-9; *N*-ethyl-*N*-β-hydroxyisopropylamine, 24417-04-7; *p*-toluenesulfonyl chloride, 98-59-9; methyl 2-*p*-toluenesulfonyl-2-phenylacetate, 33829-52-6; *N*-isopropyl-*p*-toluenesulfonamide, 21230-07-9.

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# Steric and Electrostatic Interactions in Reactions of Carbohydrates. III.[1] Direct Displacement of the C-2 Sulfonate of Methyl 4,6-*O*-Benzylidene-3-*O*-methyl-2-*O*-methylsulfonyl-β-D-gluco- and -mannopyranosides[2]


Momčilo Miljković,* Miodrag Gligorijević, and Djordje Glišin

*Department of Biological Chemistry, The Milton S. Hershey Medical Center of The Pennsylvania State University, Hershey, Pennsylvania 17033*


*Received April 3, 1974*


Heating of an *N,N*-dimethylformamide solution of methyl 4,6-*O*-benzylidene-3-*O*-methyl-2-*O*-methylsulfonyl-β-D-glucopyranoside (2) and methyl 4,6-*O*-benzylidene-3-*O*-methyl-2-*O*-methysulfonyl-β-D-mannopyranoside (4) with potassium benzoate resulted in direct displacement of the C-2 sulfonyloxy group giving the corresponding D-manno- (14, 62%) and D-gluco (13, 70%) derivatives. Methyl 4,6-*O*-benzylidene-3-*O*-methyl-2-*O*-methylsulfonyl-α-D-glucopyranoside (1) gave, under the same experimental conditions, only very small amount (~3%) of a product which could be the product of direct displacement (15), whereas methyl 4,6-*O*-benzylidene-3-*O*-methyl-2-*O*-methylsulfonyl-α-D-mannopyranoside (3) did not undergo direct displacement at all. The greater reactivity of 4 *vs.* 2 and the unreactivity of 1 and 3 toward the direct nucleophilic displacement was rationalized in terms of torsional strain and electrostatic and steric nonbonding interactions in the corresponding transition states.


In connection with some other work we became interested in direct displacement of the C-2 sulfonyloxy group of pyranosides. Our previous findings that the stereochemical course of the addition of $CH_3Li$, $CH_3MgX$, and $NaBH_4$ to the C-2 and C-4 carbonyl carbon atom strongly depended upon the anomeric configuration of the corresponding hexopyranosiduloses[1,3] suggesting that the torsional strain and nonbonding steric and electrostatic interactions in the corresponding transition states are the decisive factors in determining the stereochemical course of these reactions, prompted us to investigate the possible relationship between the anomeric configuration and the reactivity of a C-2 sulfonyloxy group of hexopyranosides toward direct displacement.

Except for displacement of the *p*-tolylsulfonyl group of methyl 4,6-*O*-benzylidene-3-deoxy-2-*O*-*p*-tolylsulfonyl-α-D-*ribo*-hexopyranoside with azide,[4] direct displacement of a C-2 sulfonyloxy group of a furanoside or a pyranoside ring with a charged nucleophile has not been yet reported. The use of an uncharged nucleophile, *e.g.*, hydrazine, did result in displacement of the C-2 sulfonate in both furanoside[5-7] and pyranoside[8] rings. The unreactivity of the C-2 sulfonyloxy group toward displacement with charged nucleophiles was attributed to the electron-withdrawing effect of the anomeric carbon atom and to the unfavorable dipolar interaction in the transition state.[9-13] The greater reactivity of uncharged nucleophiles is displacement of the sulfonyloxy group at the C-2 carbon atom was ascribed to the reversal of polarity of one of the polar bonds in the transition state resulting in a dipolar attractive force.[11] Although some speculations on the reactivity of a C-2 sulfonyloxy group of β-D-glycopyranosides having the C-1 aglycon group equatorially oriented have been entertained,[11] direct displacement of the C-2 sulfonate of a β-D-glycopyranoside was not thus far attempted.

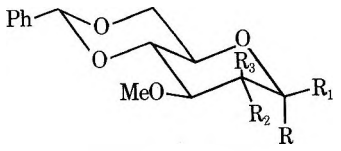
The following substrates were chosen for our study: methyl 4,6-*O*-benzylidene-3-*O*-methyl-2-*O*-methylsulfonyl-α-D-glucopyranoside (1),[3] methyl 4,6-*O*-benzylidene-3-*O*-methyl-2-*O*-methylsulfonyl-β-D-glucopyranoside (2), methyl 4,6-*O*-benzylidene-3-*O*-methyl-2-*O*-methylsulfonyl-α-D-mannopyranoside (3), and methyl 4,6-*O*-benzylidene-3-*O*-methyl-2-*O*-methylsulfonyl-β-D-mannopyranoside (4).

It is known[14,15] that the reactivity of a sulfonyloxy group directly attached to a six-membered ring (cyclohexane or glycopyranoside) toward direct displacement with a nucleophile will generally depend upon (a) gound-state energy (conformational free-energy) of the substrate and (b) energy of the corresponding transition state.

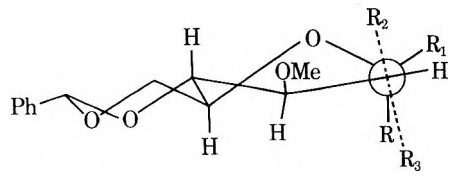
Whereas the ground state energy of α- and β-D-glucopyranosides 1 and 2 and α-D-mannopyranoside 3 should not be significantly different, the conformational free-energy of β-D-mannopyranoside 4, should be considerably higher due to the unfavorable dipolar interaction between the axially oriented C-2 methylsulfonyloxy group and the $C_1$–$O_1$ and the $C_1$–$O_5$ dipoles. Consequently, the activation energy for direct displacement of the C-2 sulfonyloxy group of β-D-mannopyranoside 4 should be lower than for displacement of the C-2 sulfonyloxy group of α- and β-D-glucopyranosides 1 and 2, and α-D-mannopyranoside 3.

However, as has been already stated, the reactivity of a sulfonyloxy group toward direct displacement does not depend solely upon the ground state energy of a substrate, but also upon the transition state energy level, *i.e.*, torsional strain, nonbonded steric and electrostatic interactions between the approaching nucleophile and/or leaving sulfonate and other substituents of a six-membered pyranoside ring.

Thus, the "axial" attack of a charged nucleophile to the C-2 atom of 1 (α-D-glucopyranoside) resulting in transition



1, R = $CH_3O$; $R_1$ = $R_3$ = H; $R_2$ = $CH_3SO_3$
2, R = $R_3$ = H; $R_1$ = $CH_3O$; $R_2$ = $CH_3SO_3$
3, R = $CH_3O$; $R_1$ = $R_2$ = H; $R_3$ = $CH_3SO_3$
4, R = $R_2$ = H; $R_1$ = $CH_3O$; $R_3$ = $CH_3SO_3$
9, R = $CH_3O$; $R_1$ = $R_3$ = H; $R_2$ = OH
10, R = $R_3$ = H; $R_1$ = $CH_3O$; $R_2$ = OH
11, R = $CH_3O$; $R_1$ = $R_2$ = H; $R_3$ = OH
12, R = $R_2$ = H; $R_1$ = $CH_3O$; $R_3$ = OH
13, R = $R_3$ = H; $R_1$ = $CH_3O$; $R_2$ = $C_6H_5COO$
14, R = $R_2$ = H; $R_1$ = $CH_3O$; $R_3$ = $C_6H_5COO$
15, R = $CH_3O$; $R_1$ = $R_2$ = H; $R_3$ = $C_6H_5COO$
16, R = $CH_3O$; $R_1$ = $R_3$ = H; $R_2$ = $C_6H_5COO$



5, R = $CH_3O$; $R_1$ = H; $R_2$ = nucleophile; $R_3$ = $CH_3SO_3$
6, R = H; $R_1$ = $CH_3O$; $R_2$ = nucleophile; $R_3$ = $CH_3SO_3$
7, R = $CH_3O$; $R_1$ = H; $R_2$ = $CH_3SO_3$; $R_3$ = nucleophile
8, R = H; $R_1$ = $CH_3O$; $R_2$ = $CH_3SO_3$; $R_3$ = nucleophile

state **5**, will give rise, owing to the flattening of the pyranoside ring, to a strong torsional strain and electrostatic interaction between the leaving C-2 methylsulfonyloxy and the axially oriented C-1 methoxy group. The "axial" attack of a charged nucleophile to the C-2 atom of **2** (β-D-glucopyranoside) resulting in transition state **6**, where the negatively charged nucleophile approaches the C-2 atom from a direction bisecting $C_1$–$O_1$ and $C_1$–$O_5$ torsional angle, will be subjected to dipolar interactions between the approaching nucleophile and the $C_1$–$O_1$ and the $C_1$–$O_5$ dipoles. The "equatorial" attack of a charged nucleophile to the C-2 atom of **3** (α-D-mannopyranoside) resulting in transition state **7** will give rise, due to the flattening of the pyranoside ring, to a strong torsional strain and electrostatic interaction between the approaching nucleophile and the axially oriented C-1 methoxy group. Finally, the "equatorial" attack of a charged nucleophile to the C-2 atom of **4** (β-D-mannoyranoside) resulting in transition state **8**, will be free both from torsional strain and dipolar interactions. In addition to the above mentioned interactions, the formation of transition states **5**, **6**, **7** and **8** will also give rise to much weaker nonbonded steric interactions between the approaching nucleophile and the axially oriented hydrogen atoms. Thus, in transition states **5** and **6** there will be in each one 1,3-nonbonded steric interaction between the nucleophile and the C-4 hydrogen atom, whereas in transition states **7** and **8**, there will be in each one 1,4-nonbonded steric interaction between the nucleophile and the C-5 hydrogen atom.

The already mentioned dipolar interactions between the axially oriented C-2 methylsulfonyloxy group and the $C_1$–$O_1$ and the $C_1$–$O_5$ dipoles in **4** should facilitate the formation of the transition state **8** due to electrostatic and steric relief.

The uncharged nucleophiles (*e.g.*, hydrazine) should be more effective for direct displacement of the C-2 sulfonyloxy group of **2** since there will be no electrostatic repulsion between the approaching neutral nucleophile and the $C_1$–$O_1$ and the $C_1$–$O_5$ dipoles in transition state **6**. However, there should be little or no difference in reactivity of charged and uncharged nucleophiles in direct displacement of the C-2 sulfonyloxy group of **1**, **3**, and possibly **4**.

Taking into consideration the ground-state energy levels of **1**, **2**, **3** and **4** and the energy levels of SN2 transition states **5**, **6**, **7** and **8**, the following order of reactivity of the C-2 sulfonyloxy group toward direct displacement with a (charged or uncharged) nucleophile could be expected: 3 > 2 ≫ 1 and **4**.

The results of our investigation are reported in this paper.

The C-2 sulfonates **1**–**4** were synthesized by mesylation of methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-glucopyranoside (**9**),[16] methyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-glucopyranoside (**10**),[16] methyl4,6-*O*-benzylidene-3-*O*-methyl-α-D-mannopyranoside (**11**), and methyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-mannopyranoside (**12**)[1] with methylsulfonyl chloride in pyridine. Methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-mannopyranoside **11** was synthesized by catalytic hydrogenation of methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose using platinum on carbon (10%) as the catalyst.

Heating of an *N*,*N*-dimethylformamide solution of **4** with potassium benzoate at reflux for 8 hr resulted in smooth displacement of the C-2 sulfonyloxy group.[17] In addition to small amount of starting material **4** (8%), the only product which could be isolated from the reaction mixture was methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-3-*O*-methyl-β-D-glucopyranoside (**13**, 70%). The structure of **13** was deduced from comparison (mmp, ir and nmr spectra) with an authentic sample, obtained by benzoylation of methyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-glucopyranoside (**10**) with benzoyl chloride in pyridine.

Refluxing of an *N*,*N*-dimethylformamide solution of **2** with potassium benzoate resulted also in displacement of the C-2 methylsulfonyloxy group giving, in addition to a small amount of starting material **2** (7%), methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-3-*O*-methyl-β-D-mannopyranoside (**14**, 62%); however, the reaction was considerably slower (120 hr). The structure of **14** has been proven by comparison with an authentic sample (ir and nmr spectra) obtained by benzoylation of methyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-mannopyranoside (**12**) with benzoyl chloride in pyridine.

Refluxing of an *N*,*N*-dimethylformamide solution of **1** with potassium benzoate for 120 hr afforded, in addition to starting material **1** (77.5%), an extremely small amount of a product (3.5%) which on the basis of comparison with an authentic sample synthesized by benzoylation of **11** with benzoyl chloride in pyridine (ir and nmr spectra) could be methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-3-*O*-methyl-α-D-mannopyranoside (**15**).

Refluxing of an *N*,*N*-dimethylformamide solution of **3** with potassium benzoate for 120 hr afforded in addition to small amount of unidentified products the starting material **3** (29%) as the only isolable product. The expected direct displacement product, *i.e.*, methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-3-*O*-methyl-α-D-glucopyranoside (**16**), could not be found among the unidentified products.

The above experimental results strongly indicate that the reactivity of the C-2 sulfonyloxy group of a glycopyranosyl-2-sulfonate toward direct displacement depends chiefly upon the anomeric configuration, since the torsional strain and dipolar interactions between an approaching nucleophile or leaving sulfonate and the C-1 alkoxy group in the transition state are the most important factors in these reactions. The belief that the observed "unreactivity" of the C-2 sulfonyloxy group toward direct displacement may be a consequence of the electron-withdrawing effect of the

anomeric carbon atom, a conclusion, which was probably based on unsuccessful attempts to effect the direct displacement of the C-2 sulfonyloxy group of α-anomers of D-glycopyranosides, seems thus to have no justification.

## Experimental Section

**General.** The silica gel used for all column chromatography was E. Merck (Darmstadt, Germany) silica gel, grain size <0.08 mm. The melting points are uncorrected. Optical rotations were determined with a Cary 60 spectropolarimeter in a 1.0-cm cell. The ir spectra were recorded with a Perkin-Elmer infrared spectrophotometer Model 267; the nmr spectra were recorded with a Varian T-60 spectrometer using tetramethylsilane as the internal standard. Chemical shifts (δ) are expressed in parts per million.

**Methyl 4,6-*O*-Benzylidene-3-*O*-methyl-2-*O*-methylsulfonyl-β-D-mannopyranoside (4).** To a pyridine solution (10 ml) of **12** (210 mg, 0.71 mmol) methanesulfonyl chloride (0.21 ml, 2.71 mmol) was added and the reaction mixture was kept at room temperature for 45 min. The excess of methanesulfonyl chloride was destroyed by adding methanol, and solvents were evaporated *in vacuo*. The crude reaction product was chromatographed on silica gel. Elution with 95:5 benzene–2-propanol afforded pure crystalline **4** (196 mg, 73%). An analytical sample was obtained by recrystallizing **4** from acetone–isopropyl ether: mp 182–182.5°; $[\alpha]^{27}D$ −79° (c 1.0, $CHCl_3$); ir ($CHCl_3$) 1350 and 1170 $cm^{-1}$ (asymmetric and symmetric $SO_2$ stretch); nmr ($CDCl_3$) δ 7.6–7.2 (m, 5, phenyl), 5.61 (s, 1, methine H from benzylidene group), 5.16 (br d, $J_{1,2} \leq 1$ and $J_{2,3}$ = 3.0 Hz, 1, H-2), 4.54 (br s, $J_{1,2} \leq 1$ Hz, 1, H-1), 4.5–3.2 (m, 5, H-3, H-4, H-5, H-6, H′-6), 3.57 (s, 6, C-1 and C-3 methoxy groups), 3.15 (s, 3, methyl from C-2 methylsulfonyl group).

*Anal.* Calcd for $C_{16}H_{22}O_8S$: C, 51.33; H, 5.92; S, 8.57. Found: C, 51.51; H, 6.08; S, 8.67.

**Reaction of Methyl 4,6-*O*-Benzylidene-3-*O*-methyl-2-*O*-methylsulfonyl-β-D-mannopyranoside (4) with Potassium Benzoate in Refluxing *N,N*-Dimethylformamide.** An *N,N*-dimethylformamide solution (10 ml) containing **4** (196 mg, 0.52 mmol) and potassium benzoate (225 mg, 1.4 mmol) was heated at reflux for 8 hr. The solvent was then removed *in vacuo* and the residue was chromatographed on silica gel (20 g). Elution with 98:2 benzene–2-propanol gave two fractions. The first fraction (140 mg, 67%) was pure **13**, whereas the second fraction (30 mg) was a mixture of starting material **4**, product **13**, and two unidentified products. After rechromatography of the second fraction on silica gel (5 g) and elution with 98:2 benzene–2-propanol an additional amount (7 mg) of pure **13**, in addition to a small amount (5 mg) of unidentified product and starting material **4** (17 mg; 8%) was isolated. Therefore the total amount of product **13** isolated from the reaction was 147 mg (70%). The compound **13** was identified as methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-3-*O*-methyl-β-D-glucopyranoside by comparison (mixture melting point, ir and nmr spectra) with an authentic sample obtained by benzoylation of methyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-glucopyranoside (**10**) with benzoyl chloride in pyridine.

**Methyl 2-*O*-Benzoyl-4,6-*O*-benzylidene-3-*O*-methyl-β-D-glucopyranoside (13).** To a pyridine solution (5 ml) of **10** (117 mg; 0.39 mmol), benzoyl chloride (0.1 ml, 0.8 mmol) was added and the reaction mixture was kept at room temperature for 18 hr. The residue (282 mg) obtained after removal of pyridine *in vacuo* was chromatographed on silica gel (25 g). Elution with 98:2 benzene-2-propanol gave pure **13** (148 mg; 93%). Analytical sample was obtained by recrystallization from acetone–isopropyl ether: mp 146°; $[\alpha]^{27}D$ −9° (c 1.0, $CHCl_3$); ir ($CHCl_3$) 1723 and 1265 $cm^{-1}$ (C=O and C—O stretch, benzoate); nmr ($CDCl_3$) δ 8.2–7.1 (m, 10, two phenyl groups), 5.56 (s, 1, methine H from benzylidene group), 5.23 (br t, $J_{1,2} \approx J_{2,3}$ = 7.0 Hz, 1, H-2), 4.56 (d, $J_{1,2}$ = 7.0 Hz, 1, H-1), 3.50 and 3.45 (two s, 6, C-1 and C-3 methoxy groups).

*Anal.* Calcd. for $C_{22}H_{24}O_7$: C, 65.99; H, 6.04. Found: C, 66.11; H, 6.00.

**Methyl 4,6-*O*-Benzylidene-3-*O*-methyl-2-*O*-methylsulfonyl-β-D-glucopyranoside (2).** A pyridine solution (5 ml) containing **10** (100 mg; 0.33 mmol) and methanesulfonyl chloride (0.25 ml, 3.2 mmol) was kept at room temperature for 5 hr. The excess of methanesulfonyl chloride was destroyed by adding methanol (1 ml). Benzene was then added and solvents were removed *in vacuo*. The residue was extracted with 4:1 benzene–ethyl acetate, the extract was evaporated *in vacuo*, and the crude product was chromatographed on silica gel (30 g). Elution with 4:1 benzene–ethyl acetate gave pure **2** (133 mg, 89%) as white crystalline material. Analytical sample was obtained by recrystallization from chloroform–isopropyl ether: mp 126.5° $[\alpha]^{27}D$ −56° (c 1.0, $CHCl_3$); ir ($CHCl_3$) 1370 and 1180 (asymmetric and symmetric $SO_2$ stretch); nmr ($CDCl_3$) δ 7.5–7.1 (m, 5, phenyl), 5.53 (s, 1, methine H from benzylidene group), 3.60 and 3.53 (two s, 6, C-1 and C-3 methoxy groups), 3.07 (s, 3, methyl from C-2 methylsulfonyl group).

*Anal.* Calcd for $C_{16}H_{22}O_8S$: C, 51.33; H, 5.92; S, 8.57. Found: C, 51.19; H, 6.01; S, 8.44.

**Reaction of Methyl 4,6-*O*-Benzylidene-3-*O*-methyl-2-*O*-methylsulfonyl-β-D-glucopyranoside (2) with Potassium Benzoate in Refluxing *N,N*-Dimethylformamide.** An *N,N*-dimethylformamide solution (20 ml) containing **2** (164 mg, 0.44 mmol) and potassium benzoate (352 mg, 2.2 mmol) was heated at reflux for 120 hr. The reaction mixture was, after cooling to room temperature, diluted with chloroform and the precipitate was filtered off. The filtrate was evaporated *in vacuo* and the crude product (224 mg) was chromatographed on silica gel (three times). Elution with 99:1 benzene-2-propanol and 9:1 benzene–ethyl acetate afforded, in addition to some starting material **2** (27 mg, 7%), pure **14** (110 mg, 62%) as an amorphous solid. Compound **14** was identified as methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-3-*O*-methyl-β-D-mannopyranoside by comparison (ir and nmr spectra) with an authentic sample obtained by benzoylation of methyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-mannopyranoside (**12**) with benzoyl chloride in pyridine.

**Methyl 2-*O*-Benzoyl-4,6-*O*-benzylidene-3-*O*-methyl-β-D-mannopyranoside (14).** To a pyridine solution (2 ml) of **12** (126 mg, 0.43 mmol) benzoyl chloride (1.0 ml, 8.6 mmol) was added and the reaction mixture was kept at room temperature overnight. Pyridine was then evaporated *in vacuo* and the residue was chromatographed on silica gel (30 g, elution with 98:2 benzene–2-propanol) and $Al_2O_3$[10 g, activity II; elution with hexane (10 ml), 1:1 hexane–benzene (100 ml), and benzene (100 ml)]. The pure **14** thus isolated (135 mg, 79%) was an amorphous solid: $[\alpha]^{27}D$ −112° (c 1.0, $CHCl_3$); ir ($CHCl_3$) 1715 and 1265 $cm^{-1}$ (C=O and C—O stretch, benzoate); nmr ($CDCl_3$) δ 8.2–7.2 (m, 10, two phenyl groups), 5.83 (q, $J_{1,2}$ = 1.1 and $J_{2,3}$ = 3.2 Hz, 1; H-2), 5.63 (s, 1, methine H from benzylidene group), 4.58 (d, $J_{1,2}$ = 1.1 Hz, 1, H-1), 4.5–3.6 (m, 5, H-3, H-4, H-5, H-6, H′-6), 3.47 and 3.43 (two s, 6, C-1 and C-3 methoxy groups).

*Anal.* Calcd for $C_{22}H_{24}O_7$: C, 65.99; H, 6.04. Found: C, 66.16; H, 6.05.

**Reaction of Methyl 4,6-*O*-Benzylidene-3-*O*-methyl-2-*O*-methylsulfonyl-α-D-glucopyranoside (1) with Potassium Benzoate in Refluxing *N,N*-Dimethylformamide.** An *N,N*-dimethylformamide solution (10 ml) of 1[3] (132 mg, 0.35 mmol) and potassium benzoate (238 mg, 1.5 mmol) was heated at reflux for 120 hr. After cooling to room temperature, the reaction mixture was diluted with chloroform. The precipitate was filtered off and then dissolved in water. The water solution was extracted with chloroform, the chloroform extract was dried over anhydrous $MgSO_4$ and the chloroform extract, combined with filtrate, was evaporated *in vacuo*. The crude product (192 mg) was chromatographed on silica gel (10 g). Elution with 98:2 benzene–2-propanol afforded two fractions. The first fraction (5 mg, 3.5%) could be the product of direct displacement, *i.e.*, methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-3-*O*-methyl-α-D-mannopyranoside (**15**): ir ($CHCl_3$) 1715 and 1265 $cm^{-1}$ (C=O and C—O stretch, benzoate); nmr ($CDCl_3$) δ 8.2–7.2 (m, 10, two phenyl groups), 5.68 (s, 1, methine H from benzylidene group), 5.60 (unresolved m, 1, H-2), 4.85 (d, $J_{1,2}$ = 1.4 Hz, 1, H-1), 3.47 and 3.44 (two s, 6, C-1 and C-3 methoxy groups). The second fraction (102 mg, 77.5%) was, according to ir and nmr spectra, the starting material **1**.

**Methyl 4,6-*O*-Benzylidene-3-*O*-methyl-α-D-mannopyranoside (11).** An ethyl acetate solution (16 ml) of methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose (565 mg, 1.92 mmol) was hydrogenated at the atmospheric pressure using 10% Pt on carbon as the catalyst (136 mg). After 2 hr the absorption of hydrogen ceased and the catalyst was then filtered off, washed with several portions of ethylacetate and the filtrate was evaporated *in vacuo*. The residue was chromatographed on silica gel (60 g). Elution with 95:5 benzene–2-propanol gave three fractions. The first fraction (160 mg; 28%) was pure methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-mannopyranoside (**11**) (an amorphous solid), whereas the third fraction (263 mg, 46%) was pure crystalline methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-glucopyranoside (**9**). The second fraction (73 mg), being a mixture of **9** and **11**, was rechromatographed on silica gel (15 g) using 95:5 benzene–2-propanol as eluent, whereby additional amounts of pure **11** (32 mg, 5.6%) and pure **9** (38 mg, 6.7%) were obtained. Thus the total amounts of pure **9** and **11** isolated after catalytic hydrogena-

tion of methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose were 301 mg (52.9%) of **9** and 192 mg (33.7%) of **11** (the gluco:manno ratio being thus 1.57:1). The analytical sample of **11**, an amorphous solid showed an $[\alpha]^{27}D$ +76° (c 1.0, $CHCl_3$); ir ($CHCl_3$) 3560 (broad peak) and 3470 (shoulder) (OH) nmr ($CDCl_3$) δ 7.6–7.3 (m, 5, phenyl), 5.58 (s, 1, methine H from benzylidene group), 4.77 (d, $J_{1,2}$ = 1.4 Hz, 1, H-1), 4.4–3.6 (m, 6, H-2, H-3, H-4, H-5, H-6 and H′-6), 3.53 and 3.37 (two s, 6, C-1 and C-3 methoxy groups), 2.65 (d, $J$ = 1.4 Hz, 1, OH).

*Anal.* Calcd for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80. Found: C, 61.05; H, 7.00.

**Methyl 4,6-*O*-Benzylidene-3-*O*-methyl-2-*O*-methylsulfonyl-α-D-mannopyranoside (3).** To a pyridine solution of **11** (87 mg; 0.29 mmol) methanesulfonyl chloride (0.100 ml, 0.59 mmol) was added and the reaction mixture was kept at room temperature for 2 hr. The excess of methanesulfonyl chloride was destroyed by methanol and the solvents were evaporated *in vacuo*. The residue was chromatographed on silica gel (20 g). Elution with 97:3 benzene–2-propanol afforded pure crystalline **3** (105 mg, 95%). An analytical sample was obtained by recrystallizing **3** from acetone: mp 185–186°; $[\alpha]^{27}D$ +22° (c 0.7, $CHCl_3$); ir ($CHCl_3$) 1363 and 1170 $cm^{-1}$ (asymmetric and symmetric $SO_2$ stretch); nmr ($CDCl_3$) δ 7.6–7.2 (m, 5 phenyl), 5.62 (s, 1, methine H from benzylidene group), 5.0 (m, 1, H-2), 4.90 (d, $J_{1,2} \leq 1$ Hz, 1, H-1), 4.4–3.8 (m, 5, H-3, H-4, H-5, H-6, and H′-6), 3.56 and 3.40 (two s, 6, C-1 and C-3 methoxy groups), 3.13 (s, 3, methyl from C-2 methylsulfonyl group).

*Anal.* Calcd for $C_{16}H_{22}O_8S$: C, 51.33; H, 5.92; S, 8.57. Found: C, 51.39; H, 5.90; S, 8.79.

**Reaction of Methyl 4,6-*O*-Benzylidene-3-*O*-methyl-2-*O*-methylsulfonyl-α-D-mannopyranoside 3 with Potassium Benzoate in Refluxing *N,N*-Dimethylformamide.** An *N,N*-dimethylformamide solution (10 ml) containing **3** (202 mg, 0.54 mmol) and potassium benzoate (202 mg, 1.26 mmol) was heated at reflux for 120 hr. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel (30 g). Elution with 2:1 benzene–ethyl acetate afforded four fractions. The third fraction was pure starting material **3** (59 mg, 29%), whereas the other three fractions were unidentified products of decomposition of **3** under the given experimental conditions.

**Methyl 2-*O*-Benzoyl-4,6-*O*-benzylidene-3-*O*-methyl-α-D-mannopyranoside (15).** To a pyridine solution of **11** (81 mg, 0.27 mmol) benzoyl chloride (0.100 ml, 0.59 mmol) was added and the reaction mixture was kept at room temperature for 2 hr. The pyridine was removed *in vacuo* and the residue was chromatographed on silica gel (20 g). Elution with 98:2 benzene–2-propanol gave slightly impure **15** (111 mg). The rechromatography on slica gel (16 g) and elution with 98:2 benzene–2-propanol afforded pure **15** (110 mg; 100%) as an amorphous solid: $[\alpha]^{27}D$ −48° (c 1.0, $CHCl_3$); ir ($CHCl_3$) 1720 and 1265 $cm^{-1}$ (C=O and C—O stretch, benzoate); nmr ($CDCl_3$) δ 8.2–7.2 (m, 10, phenyl), 5.68 (s, 1, methine H from benzylidene group), 5.61 (m, 1, H-2), 4.85 (d, $J_{1,2} \leq 1$ Hz, 1, H-1), 4.5–3.7 (m, 5, H-3, H-4, H-5, H-6, and H′-6), 3.46 and 3.43 (two s, 6, C-1 and C-3 methoxy groups).

*Anal.* Calcd for $C_{22}H_{24}O_7$: C, 65.99; H, 6.04. Found: C, 66.18; H, 6.20.

**Registry No.**—**1**, 51016-19-4; **2**, 52260-45-4; **3**, 52260-46-5; **4**, 52260-47-6; **10**, 35775-68-9; **11**, 52260-48-7; **12**, 51364-57-9; **13**, 52260-49-8; **14**, 52260-50-1; **15**, 52260-51-2; methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose, 29774-59-2.

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# Use of Carbon-13 and Proton Magnetic Resonance Studies for the Determination of Glycosylation Site in Nucleosides of Fused Nitrogen Heterocycles


Phoebe Dea,*[1] Ganapathi R. Revankar, Richard L. Tolman, Roland K. Robins, and Martin P. Schweizer

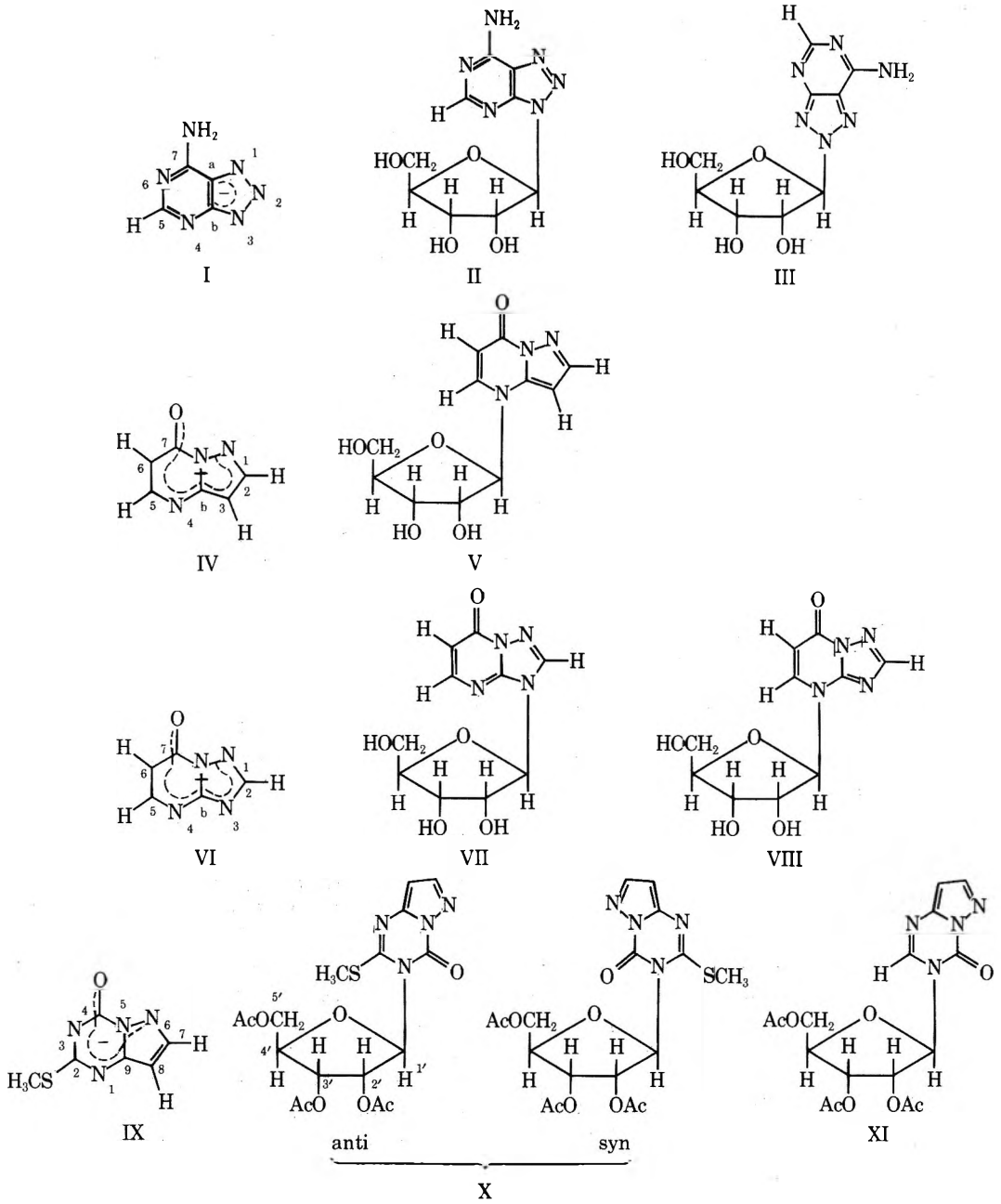
*ICN Pharmaceuticals, Inc., Nucleic Acid Research Institute, Irvine, California 92664*


*Received July 1, 1974*


Several selected fused nitrogen heterocyclic systems, 7-amino-*v*-triazolo[4,5-*d*]pyrimidine (I), pyrazolo[1,5-*a*]pyrimidin-7-one (IV), *s*-triazolo[1,5-*a*]pyrimidin-7-one (VI), and 2-methylthiopyrazolo[1,5-*a*]-*s*-triazin-4-one (IX), and their *N*-ribofuranosides have been studied with respect to the effect of N-ribosylation on the carbon-13 chemical shifts of the neighboring carbons. Large upfield α shifts and small downfield β shifts were observed in the nucleoside when compared to the base anion, thereby providing a convenient general method for the assignment of the glycosylation site in complex fused nitrogen heterocyclic systems.


Recently, several nmr studies in this laboratory have demonstrated the potential use of carbon-13 nuclear magnetic resonance spectroscopy as a general unequivocal method for the assignment of glycosylation site in both five- and six-membered nitrogen heterocycles.[2,3] The assignments were based upon the use of previously reported α- and β-substitution shifts observed in other heterocyclic systems when the neutral species is compared with the anionic form.[4–6] These shift parameters were first described by Pugmire and Grant from studies on the azines and their charged species,[4,5] where nitrogen protonation resulted in an upfield shift for the α carbon and downfield shifts were

**Chart I**




observed for the $\beta$ and $\gamma$ carbon atoms when compared to the free base. From the results of their theoretical calculations on these systems, the observed $\alpha$-substitution shifts have been explained on the basis of a decrease in bonding between N–$C_\alpha$ while $\beta$ and $\gamma$ shifts are the result of charge polarization effects.

Our carbon-13 nmr results on several five- and six-membered nitrogen heterocycles have indicated that N-protonation and N-ribosylation result in similar $\alpha$ and $\beta$ shifts. In view of the success using these substitution parameters in determinations of the preferred positions of the labile protons in the simple azines as well as benzimidazole, various purines and other fused-ring heteroaromatic systems,[6,7] we have extended our carbon-13 nmr studies to examination of the effect of ribosylation on the chemical shifts of neighboring carbon atoms in several selected fused nitrogen heterocycles. In these systems, the existence of the second ring provides an opportunity to examine long-range cross-ring effects as well as the unusual characteristics of the bridgehead carbons.

## Results and Discussion

**A. 7-Amino-*v*-triazolo[4,5-*d*]pyrimidine (I).** To determine whether the effect of N-ribosylation in the fused-ring heterocycles is similar to the previously studied five- and six-membered rings, we have chosen to examine the carbon-13 chemical shifts of 7-amino-3-$\beta$-D-ribofuranosyl-*v*-triazolo[4,5-*d*]pyrimidine (II, Chart I) and 7-amino-2-$\beta$-D-ribofuranosyl-*v*-triazolo[4,5-*d*]pyrimidine (III) and have compared their chemical shifts to those of the anion of 7-amino-*v*-triazolo[4,5-*d*]pyrimidine (I). The glycosylation site in these two nucleosides had previously been assigned from uv spectra.[8] The carbon-13 chemical shifts are summarized in Table I. The $C_5$ and $C_7$ carbons are assigned based on the splitting patterns observed in the proton coupled spectra. The chemical shifts of the $C_a$ and $C_b$ carbons are found to be similar to those reported for adenosine.[9]

In this series of compounds the $C_b$ carbon is $\alpha$ to the glycosylation site in II but is $\beta$ to the glycosylated nitrogen in III. A corresponding upfield shift of 6.8 ppm was observed

**Table I**
**Comparison of Carbon-13 Chemical Shifts for the Various Fused Nitrogen Heterocyclic Systems (See Chart I)**

| Compd | Chemical shift, δ ppm[a] $C_2$ | $C_3$ | $C_5$ | $C_6$ | $C_7$ | $C_a$ | $C_b$ |
|---|---|---|---|---|---|---|---|
| I | | | 155.8 | | 158.9 | 124.0 | 152.4 |
| II | | | 153.0 | | 154.0 | 121.1 | 145.6 |
| III | | | 153.7 | | 154.4 | 122.9 | 153.5 |
| $\Delta\delta_{I-II}$ | | | +2.8 | | +4.9 | +2.9 | +6.8 |
| $\Delta\delta_{I-III}$ | | | +2.1 | | +4.5 | +1.1 | −1.1 |
| IV | 151.3 | 92.9 | 141.2 | 91.7 | 159.4 | | 151.7 |
| V | 142.8 | 96.6 | 138.1 | 93.8 | 156.0 | | 141.4 |
| $\Delta\delta_{IV-V}$ | +8.5 | −3.7 | +3.1 | −2.1 | +3.4 | | +10.3 |
| VI | 152.5 | | 154.1 | 97.2 | 160.1 | | 158.3 |
| VII | 140.8 | | 153.3 | 104.0 | 156.8 | | 149.6 |
| VIII | 151.6 | | 138.9 | 100.2 | 155.4 | | 143.1 |
| $\Delta\delta_{VI-VII}$ | +11.7 | | +0.8 | −6.8 | +3.3 | | +8.7 |
| $\Delta\delta_{VI-VIII}$ | +0.9 | | +15.2 | −3.0 | +4.7 | | +15.2 |

| | $C_7$ | $C_8$ | $C_2$ | $C_4$ | $C_9$ | $C_{1'}$ | $C_{2'}$ | $C_{3'}$ | $C_{4'}$ | $C_{5'}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| IX | 143.0 | 92.8 | 150.6 | 167.1 | 151.0 | | | | | |
| X | 147.0 | 98.1 | 146.0 | 156.6 | 142.9 | 90.6 | 72.2 | 68.7 | 78.8 | 62.3 |
| XI | 148.8[b] | 102.0 | 148.5[b] | 153.3[b] | 145.8[b] | 91.4 | 74.6 | 70.9 | 80.9 | 63.8 |
| $\Delta\delta_{IX-X}$ | −4.0 | −5.3 | +4.6 | +10.5 | +8.1 | | | | | |
| $\Delta\delta_{IX-XI}$ | −5.8 | −9.2 | +2.1 | +12.8 | +5.2 | | | | | |
| $\Delta\delta_{X-XI}$ | | | | | | −0.8 | −2.1 | −2.4 | −2.2 | −1.5 |

[a] Chemical shifts measured from DMSO-$d_6$, converted to TMS scale using $\delta_{TMS} = \delta_{DMSO} + 39.5$ ppm. [b] Assignments tentative owing to low signal to noise ratio in the proton-coupled spectrum.

for the $C_b$ resonance in II whereas a downfield shift of 1.1 ppm was observed for III when compared to the $C_b$ chemical shift in I (Table I). The substitution parameters observed here are very similar to the previously reported α- and β-protonation parameters of +9.04 and −1.59 ppm, respectively, for the five-membered azines[5] and the corresponding values of +7.8 and −4.4 ppm reported for the six-membered azines.[4] It must be noted in the case of III that the change in chemical shift of $C_b$ is actually an average of β and γ positional effects. Furthermore, the $C_a$ carbon of II and III which is β and γ to the respective glycosylation site shows upfield shifts of 2.9 and 1.1 ppm. This is similar to the reversal in trend noted by Pugmire, *et al.*,[6] at the bridgehead positions in some methylpurines.

We also note that the long-range cross-ring effects are not preserved for the γ carbons. Upfield shifts of 2.1 and 2.8 ppm for $C_5$ and 4.5 and 4.9 ppm for $C_7$ were observed rather than the downfield γ shifts reported in other simpler systems.

**B. Pyrazolo[1,5-*a*]pyrimidin-7-one (IV).** Evidence that glycosylation in pyrazolo[1,5-*a*]pyrimidin-7-one (IV) occurs at the $N_4$ position was first obtained by comparing the pmr spectrum of this nucleoside (V) with those of several related heterocycles. It has been observed that N-methylation results in an increase in the coupling constant between protons on neighboring carbons. Some of our results are summarized in Table II. We note that in cases where methylation occurs at the $N_1$ position, the $H_{2-3}$ coupling constants are of the order of 3.5 Hz, whereas methylation at $N_4$ results in smaller couplings of 2.0 Hz.[10] Since ribosylation or methylation is expected to produce very similar inductive effects, the fact that the observed $J_{H_{2-3}}$ in *N*-β-D-ribofuranosylpyrazolo[1,5-*a*]pyrimidin-7-one is only 2.0 Hz leads to the conclusion that $N_4$ is the glycosylation site.

Confirmation of this assignment was derived from the following carbon-13 nmr studies. The proton splitting pattern in the carbon-13 spectrum enables one to distinguish the $C_7$ and $C_b$ carbons where the large carbon-13–proton coupling is absent, since there are no protons directly attached. The carbonyl carbon is assigned to the resonance furthest downfield in the spectrum. The specific assignment of the remaining $C_2$, $C_3$, $C_5$, and $C_6$ carbons in the heterocycle or the nucleoside is not possible from the proton-coupled spectra alone, since they all exhibit identical proton splitting patterns. From chemical shift considerations, it is expected that the $C_2$ and $C_5$ carbons should occur considerably more downfield compared to the $C_3$ and $C_6$ carbons. The specific assignments of these carbons were achieved using off-resonance proton decoupling techniques. The results are summarized in Table I.

**Table II**
**Some Typical Changes in Proton Coupling Constants as a Result of N-Methylation**

| Compd | $J_H$ |
|---|---|
| 1,5-Dimethylpyrazolo[1,5-*a*]pyrimidin-7-one | 3.55 |
| 1,2-Dimethylpyrazol-3-one | 3.50 |
| 4,5-Dimethylpyrazolo[1,5-*a*]pyrimidin-7-one | 2.05 |
| 5-Methyl-4-β-D-ribofuranosylpyrazolo-[1,5-*a*]-pyrimidin-7-one | 2.00 |
| 4-β-D-Ribofuranosylpyrazolo[1,5-*a*]pyrimidin-7-one | 2.00 |

The two carbons adjacent to the glycosylation site $N_4$ are $C_b$ and $C_5$. When the carbon-13 shifts of the nucleoside are compared with those of the anion of the heterocycle, a large upfield shift of 10.3 ppm was observed for $C_b$ and a smaller but also upfield shift of 3.1 ppm was observed for $C_5$. The two β carbons $C_3$ and $C_6$ also exhibit the usual downfield shifts of 3.7 and 2.1 ppm, respectively. The γ shifts for $C_2$

and $C_7$, however, are upfield, being 8.5 and 3.4 ppm, again showing a reversal in trend in the long-range inductive effects.

**C. *s*-Triazolo[1,5-*a*]pyrimidin-7-one (VI).** There are three possible glycosylation sites in *s*-triazolo[1,5-*a*]pyrimidin-7-one, namely, $N_1$, $N_3$, and $N_4$. Although the attachment of the $\beta$-D-ribofuranosyl moiety in position 1 could not be ruled out absolutely from uv data, tentative assignments of the 3- and 4-$\beta$-D-ribofuranosyl isomers had been reported based on comparisons of the uv spectra[11] with those of the corresponding $N_3$ and $N_4$ methyl derivatives.[10,11]

The carbon-13 chemical shifts obtained for the two nucleosides of this series are presented in Table I, along with the carbon-13 chemical shifts of the heterocycle anion for comparison. The carbonyl resonance was assigned to the most downfield signal from chemical shift considerations and $C_b$ can be assigned from the proton-coupled spectrum, since it is the only other carbon with no directly bonded protons. The $C_5$ and $C_6$ resonances in both nucleosides can be distinguished from the $C_2$ resonance by a small geminal coupling arising from the adjacent proton. The upfield resonance is assigned to the $C_6$ carbon by comparison with the chemical shifts of related compounds.

The possibility that glycosylation had occurred at $N_1$ can be eliminated from the positive $\beta$ shift of 3.3 and 4.7 ppm observed for $C_7$ for nucleosides VII and VIII, respectively, when compared to the carbon shifts of the base anion. The nucleoside VII exhibits large upfield shifts of 11.7 and 8.7 ppm for the $C_2$ and $C_b$ carbon resonances, whereas the $C_5$ resonance remains essentially unchanged. These $\alpha$ shifts confirm that this nucleoside is 3-$\beta$-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (VII). In the case of the 4 isomer VIII, there is little change in the chemical shift for the $C_2$ carbon when compared to the base anion, but both $C_b$ and $C_5$ resonances move upfield by 15.2 ppm and both of these carbons are adjacent to the glycosylation site. The $C_6$ resonance exhibits a downfield $\beta$ shift of 3.0 ppm. The $\gamma$ shifts in both nucleosides are again inconsistent with the downfield shifts reported for other simpler ring systems, being +0.8 ppm for $C_5$ and +3.3 ppm for $C_7$ in the 3 isomer, and +0.9 and +4.7 ppm for the $C_2$ and the carbonyl carbon in the 4 isomer, respectively.

**D. 2-Methylthiopyrazolo[1,5-*a*]-*s*-triazin-4-one (IX).** The pyrazolotriazine heterocycle (IX) also provides three possible sites for glycosylation, *i.e.*, $N_1$, $N_3$, and $N_6$. We have examined the carbon-13 spectra of the base anion (IX), the corresponding nucleoside (X), and the dethiated derivative of the nucleoside (XI). All pertinent carbon-13 nmr data are summarized in Table I. The assignment of the various carbon resonances in the heterocycle is based on comparison of the proton coupled and decoupled spectra. The $C_7$ and $C_8$ carbon resonances can be identified from large carbon-13 proton couplings. Since carbons bonded to nitrogen atoms are generally known to be appreciably deshielded relative to benzene while $\beta$ carbons are shielded,[12] the 50-ppm difference between these two resonances strongly supports the assignment of the lower field signal to the $C_7$ carbon $\alpha$ to the nitrogen. The most downfield resonance in the spectrum is assigned to the carbonyl, $C_4$. The remaining $C_2$ and $C_9$ resonances can be unequivocally assigned by examining their proton splitting patterns in the undecoupled spectra. The $C_2$ resonance appears as a singlet while $C_9$ appears as a doublet, split by the vicinal $H_7$ proton.

In the nucleoside spectrum, $C_7$, $C_8$, and $C_4$ carbons are assigned in a similar manner. The $C_9$ resonance is again identified as a closely spaced doublet in the proton coupled spectrum, but the splitting pattern for the $C_2$ resonance cannot be distinguished owing to the overlap with one leg of the $C_7$ doublet. However, the $C_2$ carbon can be assigned to the only remaining downfield resonance. The chemical shifts of the ribose carbons are assigned by comparison with previously reported spectra.[13]

When the chemical shifts of the base carbons of the nucleoside X were compared to those of the triazine anion, large upfield shifts were noted for three carbons, namely, $C_2$, $C_4$, and $C_9$, the shifts being 4.6, 10.5, and 8.1 ppm, respectively. Using the previously reported large positive shifts observed in other heterocyclic systems upon comparison of a neutral species with an anionic form, we can eliminate $N_6$ as the site of glycosylation because of the negative $\alpha$ shift (−4.0 ppm) at $C_7$ but it is not possible to establish whether $N_1$ or $N_3$ is the glycosylation site from these chemical shift data alone.

Let us first consider the case where the ribose is attached at the $N_3$ position. Examination of molecular models reveals that the anti conformation [for purposes of discussion here, the anti glycosidic conformation refers to the range of torsional angles about the glycoside bond such that the 4-keto is directed away from the furanose ring (see Chart I)] is impossible, since the $SCH_3$ substituent is too bulky to go over the ribose ring. In the syn conformation, the 4-keto group of the base would be located over the ribose ring. The presence of the keto group over the ring as occurs in 6-methylcytidine and other 2,6-dioxopyrimidine nucleosides has been shown[14] to result in C–H bond polarization whereby the $C_{2'}$ is observed to shift upfield by 2–2.5 ppm while the $H_{2'}$ and $H_{3'}$ protons shift downfield by 0.2 and 0.1 ppm, respectively. We have therefore examined the carbon-13 ribose chemical shifts and have compared them to those of the dethiated nucleoside XI where the bulky $SCH_3$ group is absent and the ribose is expected to be free to rotate round the glycosyl bond. Our results (Table I) indicate that all the ribose carbon resonances in X are upfield compared to the dethiated analog (XI). In particular, the $C_{2'}$ and $C_{3'}$ carbons in X were shifted upfield by 2.1 and 2.4 ppm, respectively. In the $^1H$ nmr spectra, the $H_{2'}$ and $H_{3'}$ in X occur at −5.90 and −5.66 ppm, respectively, whereas those for XI appear at −5.58 and −5.52 ppm. Therefore, the carbon shifts were observed to change in opposite directions to the proton shifts of the directly bonded hydrogens, indicating the presence of a carbonyl group over the ring in X. Both the carbon-13 and proton chemical shift data indicate that the nucleoside X exists predominantly in the syn conformation whereas the nucleoside XI exists predominantly in the anti conformation. In order to account for the presence of the keto group over the ring, the ribose must be attached to the $N_3$ position, since the keto group would be too far away to exert any effect on the ribose shifts if the ribosylation had occurred at $N_1$. The large positive $\alpha$ shifts observed in $C_2$ and $C_4$ are also consistent with this structure. As has been observed in all of the nucleosides examined in this study, a positive $\gamma$ shift is noted at $C_9$ (8.1 ppm).

In summary, carbon-13 nmr study of the four heterocyclic series have shown that large upfield $\alpha$ shifts and the small downfield $\beta$ shifts are preserved in these complex fused-ring systems. The only exception observed in the $\beta$ shift is in the case of 7-amino-2-$\beta$-D-ribofuranosyl-*v*-triazolo[4,5-*d*]pyrimidine (III), where a bridgehead carbon is involved. The $\gamma$ shifts in these systems, however, are entirely inconsistent with past observations in other fused nitrogen heterocycles, namely, the *N*-methylpurines.[6] The $\gamma$ carbons in the nucleosides all exhibit upfield rather than downfield shifts and a wide range of magnitudes are observed. Nonetheless, in most heterocyclic systems, measurement of the $\alpha$ and $\beta$ shifts alone are sufficient to estab-

lish the glycosylation site. This study shows that carbon-13 nmr can readily be applied for structural assignments of the nitrogen at which alkylation or glycosylation has occurred in complex fused heterocyclic systems.

## Experimental Section

Proton magnetic resonance spectra were obtained at 60 MHz on a Hitachi Perkin-Elmer R-20A spectrometer in DMSO-$d_6$ using DSS (sodium 2,2-dimethyl-2-silapentane-5-sulfonate) as an internal reference. A Bruker HX-90 nmr spectrometer operating at 22.62 MHz in the Fourier transform mode was used to obtain the carbon-13 nmr spectra. A Fabri-Tek 1074 signal averager with 4096 word memory was used for data accumulation and a PDP-8/e computer (Digital Equipment Corp.) for data processing. Saturated solutions were prepared in DMSO-$d_6$ and were studied in 10-mm tubes. Chemical shifts were reported in parts per million relative to TMS using the relationship $\delta_{TMS} = \delta_{DMSO\text{-}d_6} + 39.5$ ppm.

Ultraviolet spectra were recorded on a Cary Model 15 spectrophotometer and infrared spectra on a Perkin-Elmer 257 spectrophotometer (KBr pellets). Specific rotations were measured in a 1-dm tube with a Perkin-Elmer Model 141 automatic digital readout polarimeter. Elemental analyses were performed by MHW Laboratories, Garden City, Mich.

Evaporations were carried out under reduced pressure with bath temperature below 30°. Detection of components on silica gel F-254 (EM Reagents) was by ultraviolet light and by a 10% sulfuric acid in methanol spray followed by heating. Chromatography solvent mixtures were by volume.

The anions of various heterocycles were formed by neutralization with LiOH in DMSO-$d_6$. Trimethylsilyl derivatives of heterocycles were prepared using the general procedure of Wittenburg.[15] The heterocycle of interest was heated under reflux in an excess of freshly distilled hexamethyldisilazane with a catalytic amount of ammonium sulfate under anhydrous conditions until complete solution was achieved and evolution of ammonia ceased (~15 hr). The excess hexamethyldisilazane was removed by distillation under reduced pressure and the residue (syrup or crystalline solid) was used directly without further purification. 7-Amino-*v*-triazolo[4,5-*d*]pyrimidine, 7-amino-3-β-D-ribofuranosyl-*v*-triazolo[4,5-*d*]pyrimidine, and 7-amino-2-β-D-ribofuranosyl-*v*-triazolo[4,5-*d*]pyrimidine used in this study were prepared as previously reported.[8] The synthesis of 3- and 4-(β-D-ribofuranosyl)-*s*-triazolo[1,5-*a*]pyrimidin-7-one had been reported by Winkley, *et al.*,[11] and Revankar, *et al.*[16]

**4-β-D-Ribofuranosylpyrazolo[1,5-*a*]pyrimidin-7-one (V).** To tetra-*O*-acetyl-β-D-ribofuranose (10.5 g, 0.033 mol) in dry dichloromethane (50 ml) at −20° was added a solution of dry dichloromethane (originally 50 ml) which had been saturated at −20° with dry hydrogen bromide gas. The mixture was protected from moisture with a drying tube and allowed to warm to 0°. The solvent was evaporated and the resulting syrup was coevaporated twice with dry toluene (50 ml). The residual syrup was dissolved in "Nanograde" acetonitrile (100 ml) and was added to the syrupy trimethylsilyl derivative of 7-hydroxyryrazolo[1,5-*a*]pyridine [prepared from 4.05 g (0.030 mol) of base[10]] in dry acetonitrile (50 ml). The reaction vessel was sealed and the mixture was stirred at room temperature. After 3 days the reaction mixture was filtered to remove some heterocyclic starting material (0.7 g) and the dark filtrate was evaporated to a syrup. Sodium bicarbonate (5.0 g), water (15 ml), and ethanol (50 ml) were added. The mixture was evaporated to dryness. Coevaporation with absolute ethanol several times afforded a dry residue which was extracted with chloroform (3 × 100 ml). The combined extracts were washed with cold saturated aqueous sodium bicarbonate solution (2 × 10 ml) followed by water (3 × 10 ml) and dried over anhydrous sodium sulfate. The chloroform was evaporated to dryness and the residual syrup was dissolved in a minimum volume of chloroform and applied to a silica gel column (4.5 × 35 cm) prepacked in chloroform. The column was eluted with chloroform–acetone (8:2) and each of the 25-ml fractions was collected. The fractionation was monitored by tlc and appropriate fractions were pooled and solvent evaporated to yield colorless foam, 7.40 g (75.8%).

The above blocked nucleoside (7.0 g) was dissolved in methanolic ammonia (200 ml, methanol presaturated with ammonia at 0°) and the solution was allowed to stand at room temperature overnight. The crystalline solid that separated was collected and washed with a little methanol. The combined filtrate and washings were evaporated to dryness. The resulting foam was triturated with cold methanol, and the solid that separated was collected and crystallized from aqueous ethanol to provide pure V, 4.4 g (92.5%) (70% for two steps): mp 265°; $[\alpha]^{25}D$ −23.0° (c 1.0, DMSO); uv $\lambda_{max}$ (pH 1) 255 nm (ε 7200), 303 (8300); $\lambda_{max}$ (pH 7) 255 nm (ε 7500), 303 (8800); $\lambda_{max}$ (pH 11) 255 nm (ε 7200), 303 (8550); ir $\lambda_{max}$ (KBr) 1690 $cm^{-1}$ (C=O of heterocycle); pmr (DMSO-$d_6$) δ 8.30 and 5.95 (doublets, for C-5 H and C-6 H, respectively, $J_{5,6}$ = 7.5 Hz) and 8.00 and 6.60 (doublets, for C-2 H and C-3 H, respectively, $J_{2,3}$ = 2 Hz).

*Anal.* Calcd for $C_{11}H_{13}N_3O_5$: C, 49.44; H, 4.90; N, 15.72. Found: C, 49.49; H, 4.89; N, 15.71.

**5-Methyl-4-β-D-ribofuranosylpyrazolo[1,5-*a*]pyrimidin-7-one.** A solution of 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide from 5.25 g (0.0165 mol) of tetra-*O*-acetyl-β-D-ribofuranose in dry acetonitrile (80 ml) was added to the trimethylsilyl derivative of 5-methylpyrazolo[1,5-*a*]pyrimidin-7-one [prepared from 2.24 g (0.015 mol) of base[17]] and the resulting solution was stirred at room temperature for 4 days in a sealed reaction vessel. The dark reaction mixture was filtered to remove some heterocyclic starting material (0.9 g) and the filtrate was evaporated to dryness. The residue was extracted with chloroform (150 ml), and the chloroform phase was washed with saturated aqueous sodium bicarbonate solution followed by water (3 × 75 ml) and dried over anhydrous sodium sulfate. The chloroform was evaporated to dryness and the residual syrup was dissolved in a minimum volume of ethyl acetate and applied to a silica gel column (4.5 × 35 cm) prepacked in ethyl acetate–water–1-propanol (4:2:1, upper phase). The column was eluted with the same solvent system and 15-ml fractions were collected. The fractionation was monitored by tlc on silica gel using the eluting solvent as the developer. Fractions 31–80 were pooled and the solvent was evaporated to yield cream-colored foam, 2.25 g (61.5%): uv $\lambda_{max}$ (pH 1) 253 nm (sh) (ε 6500), 298 (10,600); $\lambda_{max}$ (pH 7) 253 nm (sh) (ε 6500), 300 (10,200); $\lambda_{max}$ (pH 11) 253 nm (sh) (ε 6500), 300 (10,200).

The above blocked nucleoside (2.0 g) was dissolved in methanolic ammonia (80 ml, methanol presaturated with ammonia at 0°) and the solution was allowed to stand at room temperature overnight. The solution was evaporated to dryness and the residue was triturated with anhydrous ether (5 × 30 ml). The ether-insoluble material was dissolved in ethyl acetate containing a few drops of water and chromatographed on a silica gel column (2.5 × 35 cm) eluting with ethyl acetate–water–1-propanol (4:2:1, upper phase). The appropriate fractions were pooled and the solvent was evaporated. The residue was dissolved in water (50 ml), frozen, and lyophilized to obtain hygroscopic solid, 0.9 g (65.2%), no definite melting point: uv $\lambda_{max}$ (pH 1) 250 nm (ε 5900), 298 (8150); $\lambda_{max}$ (pH 7) 250 nm (ε 5050), 298 (8150); $\lambda_{max}$ (pH 11) 250 nm (ε 5600), 298 (8400); ir $\lambda_{max}$ (KBr) 1680 $cm^{-1}$ (C=O of heterocycle); pmr (DMSO-$d_6$) δ 7.90 and 6.87 (doublets, for C-2 H and C-3 H, respectively, $J_{2,3}$ = 2 Hz), 5.85 (singlet, C-6 H).

*Anal.* Calcd for $C_{12}H_{15}N_3O_5 \cdot H_2O$: C, 48.16; H, 5.72; N. 14.04. Found: C, 48.50; H, 5.51; N, 13.81.

**2-Methylthio-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazolo[1,5-*a*]-*s*-triazin-4-one (X).** A solution of 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide from 7.0 g (0.022 mol) of tetra-*O*-acetyl-β-D-ribofuranose in dry acetonitrile (100 ml) was added to the trimethylsilyl derivative of 2-methylthiopyrazolo[1,5-*a*]-*s*-triazin-4-one [prepared from 3.64 g (0.020 mol) of base[18]] and the resulting solution was stirred at room temperature for 2 days in a sealed reaction vessel. The brown reaction mixture was filtered to remove 0.6 g of heterocyclic starting material. The filtrate was evaporated to dryness and dissolved in chloroform (150 ml). The chloroform solution was washed successively with saturated aqueous sodium bicarbonate solution (3 × 75 ml) and water (3 × 100 ml) and dried over anhydrous sodium sulfate. The residual foam, after removal of chloroform, was dissolved in a minimum volume of chloroform and chromatographed on a silica gel column (3.5 × 50 cm); the eluting solvent was chloroform–acetone (8:2). The appropriate fractions were pooled and the solvent was evaporated, which afforded orange-colored foam, 6.10 g (83.0%): $[\alpha]^{25}D$ +13.7° (c 1.0, DMSO); uv $\lambda_{max}$ (pH 1) 226 nm (ε 8600), 287 (9900); $\lambda_{max}$ (pH 7) 226 nm (ε 9050), 286 (10,300); $\lambda_{max}$ (pH 11) 230 nm (ε 5500), 286 (9900); ir $\lambda_{max}$ (KBr) 1340 ($SCH_3$), 1750 $cm^{-1}$ (OAc); pmr (DMSO-$d_6$) δ 8.08 and 6.45 (doublets, for C-2 H and C-3 H, respectively, $J_{2,3}$ = 2 Hz), 2.65 (singlet, for $CH_3$).

*Anal.* Calcd for $C_{17}H_{20}N_4O_8S$: C, 46.36; H, 4.58; N, 12.72. Found: C, 46.56; H, 4.43; N, 12.94.

**3-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)pyrazolo[1,5-*a*]-*s*-triazin-4-one (XI).** Freshly prepared Raney nickel (30 g) was added to a solution of 2-methythio-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazolo[1,5-*a*]-*s*-triazin-4-one (X, 3.0 g, 0.0068 mol) in

50 ml of absolute ethanol. The suspension was heated at reflux on a steam bath for 1 hr. The catalyst was removed by filtration on a Celite pad and washed with hot ethanol (3 × 15 ml). The combined filtrate and washings were evaporated to dryness, dissolved in the minimum volume of chloroform, and chromatographed on a silica gel column (3.5 × 50 cm) eluting with chloroform–acetone (8.5:1.5). The appropriate fractions were pooled and the solvent was evaporated to yield a colorless foam, 1.80 g (67.0%): $[\alpha]^{25}D$ +2.7° (c 1.0, DMSO); uv $\lambda_{max}$ (pH 1) 262 nm (ε 10,300); $\lambda_{max}$ (pH 7) 262 nm (ε 9900); $\lambda_{max}$ (pH 11) 262 nm (ε 9900); ir $\lambda_{max}$ (KBr) 1750 $cm^{-1}$ (OAc); pmr (DMSO-$d_6$) δ 8.05 and 6.50 (doublets for C-7 H and C-8 H, respectively, $J_{7,8}$ = 2 Hz), 8.20 (singlet for C-2 H).

*Anal.* Calcd for $C_{16}H_{18}N_4O_8 \cdot H_2O$: C, 46.60; H, 4.89; N, 13.59. Found: C, 46.80; H, 4.80; N, 13.49.

**Acknowledgment.** The authors wish to thank Drs. Mason G. Stout and Rich B. Meyer, Jr., for helpful discussions of this work.

**Registry No.**—I, 52259-78-6; II, 10299-44-2; III, 28279-62-1; IV, 52259-79-7; V, 52217-05-7; V 5-methyl derivative, 52217-08-0; VI, 52259-80-0; VII, 32817-07-5; VIII, 33037-54-6; IX, 52259-81-1; X, 52217-06-8; XI, 52217-07-9; tetra-O-acetyl-β-D-ribofuranose, 13035-61-5; 2,3,5-tri-O-acetyl-D-ribofuranosyl bromide, 39110-68-4.

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# "Octakis-O-(3-aminopropyl)sucrose" as a Bifunctional Catalyst for the Dedeuteration of Isobutyraldehyde-2-*d*[1]

Jack Hine* and Stephen S. Ulrey

*Department of Chemistry, The Ohio State University, Columbus, Ohio 43210*

*Received January 15, 1974*

"Octakis-O-(3-aminopropyl)sucrose" (OAPS) containing about seven aminopropyl side chains per sucrose moiety has been prepared by reduction of octakis-O-(2-cyanoethyl)sucrose. Measurements of its basicity and equilibrium constant for forming imines with isobutyraldehyde have been made. OAPS is an effective catalyst for the dedeuteration of isobutyraldehyde-2-*d* in aqueous solution; a pH–rate plot shows a maximum around pH 8.4 at 35°. Under these conditions the catalytic activity is about 14 times that which would be expected if the catalyst were acting only monofunctionally. Hence it is concluded that one amino group on the catalyst transforms the aldehyde to an iminium ion, and then the activated α-deuteron in this isobutyraldiminium ion is removed by another amino group from the same molecule of catalyst. Reasons why this bifunctional catalytic activity is more efficient than that due to polyethylenimines, but less efficient than that due to 8-amino-1-dimethylamino-2-octyne, are discussed.

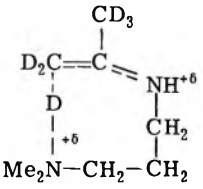
Primary amine salts catalyze α-hydrogen exchange reactions of isobutyraldehyde-2-*d*, acetone-$d_6$, and other aldehydes and ketones by transforming them to iminium ions, whose α-hydrogen atoms are much more rapidly removed by bases than are the α-hydrogen atoms of the original carbonyl compounds.[2,3] The monoprotonated forms of

$$Me_2CDCHO + RNH_3^+ \rightleftharpoons Me_2CDCH{=}NHR^+ + H_2O$$

$$Me_2CDCH{=}NHR^+ + B \rightleftharpoons Me_2C{=}CHNHR + BD$$

$$Me_2C{=}CHNHR \xrightarrow{BH} \xrightarrow{H_2O} Me_2CHCHO + RNH_3^+$$

amines of the type $Me_2N(CH_2)_nNH_2$, where $n$ is 2, 3, 4, and 5, show a catalytic activity toward isobutyraldehyde-2-*d* that increases monotonically with increasing basicity (increasing $n$),[4,5] but the monoprotonated form of 3-dimethylaminopropylamine is by far the best catalyst toward acetone-$d_6$.[4,6] These results indicate bifunctional



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catalysis of the dedeuteration of acetone-$d_6$ *via* a transition state like 1. The absence of such catalysis in the case of isobutyraldehyde-2-*d* was explained in terms of the destabilizing steric interactions between a methyl group from the aldehyde and the NH-bound methylene group from the catalyst that would be present in the analogous transition state for isobutyraldehyde. Such strain may be avoided if the basic group that removes the α-deuteron and the primary amino group that forms the iminium ion are separated by a long enough chain for internal deuteron removal

to be feasible in the trans form of the intermediate iminium ion. This requirement is met in polyethylenimines[1b,7,8] and 8-amino-1-dimethylamino-2-octyne,[5] which are bifunctional catalysts for the dedeuteration of isobutyraldehyde-2-*d*. The catalytic activity of polyethylenimines is considerably reduced by their tendency to tie up the aldehyde as imidazolidine derivatives, and the understanding of their catalysis is made difficult by the varied and incompletely known structures of these rather random polymers. To avoid these disadvantages but maintain the advantage of having a large number of amino groups in a small space, we decided to prepare octakis-*O*-(3-aminopropyl)sucrose and to study its catalytic activity.

**Preparation and Properties of "Octakis-*O*-(3-aminopropyl)sucrose."** The material labeled cyanoethyl sucrose used as the starting material fell short of being pure octakis-*O*-(2-cyanoethyl)sucrose in that it contained about 0.8 wt % water, 3.75 wt % bis(2-cyanoethyl) ether, and an average of only about 7.5 cyanoethyl groups per sucrose moiety. Furthermore, about 23% of the disaccharide derivatives had been hydrolyzed to monosaccharide derivatives. Hydrogenation of this material at low pressure using Raney nickel in ammoniacal methanol[9] followed by chromatographic purification gave an off-white, amorphous, hygroscopic solid, which will be called OAPS. This material fell short of being pure octakis-*O*-(3-aminopropyl)sucrose in that it contained about 1.55 molecules of water and 1.35 molecules of carbon dioxide (probably present as carbonate or bicarbonate) per molecule of sucrose moiety. Also there were only about seven 3-aminopropyl groups per sucrose moiety, and there were probably about 0.14 secondary amino groups[10] per sucrose moiety.

Interpretation of the titration curve of OAPS was complicated by the presence of the carbonate impurity. The eight breaks that might be expected if the eight p$K$ values were widely enough separated were not observed. This fact, the impure nature of the material, and the difficulties of estimating activity coefficients for species with as many as eight positive charges discouraged us from trying to calculate the true p$K_a$ values. Instead, p$K_{app}$ values, where $K_{app}$ is defined in eq 1, were calculated at various points

$$K_{app} = \frac{[H^+][Am]}{[AmH^+]} \quad (1)$$

throughout the titration. [Am] and [AmH$^+$] are the concentrations (normalities) of unprotonated and protonated amino groups in the solution. Corrections for the effect of the carbonate impurity on the titration were made by use of the ionization constants of carbonic[11] acid and by using the Davies equation[12] to calculate activity coefficients, with ionic strengths being calculated as if each protonated amino group were an independent unicharged cation. A plot of p$K_{app}$ *vs.* the fraction of amino groups protonated in a titration of 0.0865 $N$ (in amino groups) OAPS with 1.000 $M$ hydrochloric acid is shown in Figure 1. Because of the carbonate impurity 30% of the amino groups were already protonated at the start of the titration; p$K_{app}$ values obtained within 10% of the end point were regarded as too unreliable to plot. The monotonic decrease in p$K_{app}$ that accompanies addition of acid reflects the fact that the amino groups protonated early in the titration have few protonated amino groups in the same molecule whereas those protonated near the end of the titration have many.

The equilibrium "constant" for isobutyraldimine formation, defined as shown in eq 2, in which the concentrations of imine and amine will be expressed as normalities and the

$$K_{Im} = \frac{[Im]}{[i\text{-}PrCHO][Am]} \quad (2)$$

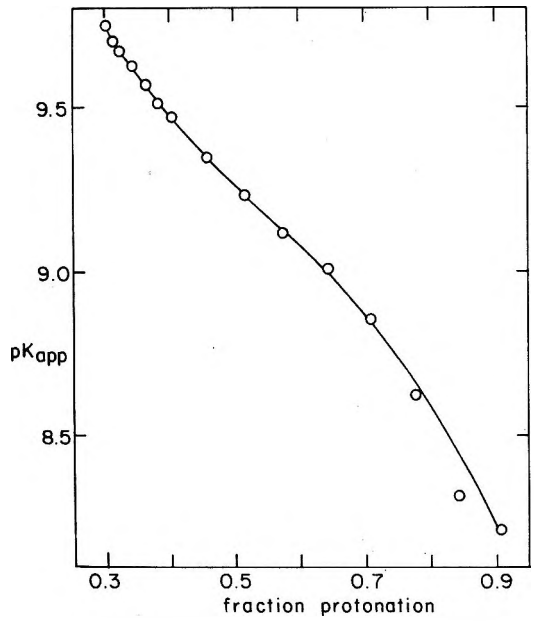


**Figure 1.** Plot of p$K_{app}$ of OAPS *vs.* fraction protonation in water at 35°.

concentration of aldehyde will include that of the aldehyde hydrate in equilibrium with it, should have a value that depends on the extent of protonation of the OAPS and, to a lesser degree, on the extent of imine formation, since electron-withdrawing substituents are known to decrease equilibrium constants for the formation of imines from isobutyraldehyde.[13] Two independent methods, both used previously,[13] were used to obtain values of $K_{Im}$. In one method the effect of OAPS on the absorption at the 285-nm maximum of isobutyraldehyde was determined and the imine (and any other products formed) was assumed to have the same absorbance as the amine from which it was formed. In calculating $K_{Im}$, 1 equiv of amine was assumed to be used up per mole of aldehyde that disappeared. Small corrections also had to be made for the shift in the carbonate–bicarbonate equilibrium brought about by the drop in pH that accompanied addition of aldehyde to the OAPS solution. A $K_{Im}$ value of 46 $M^{-1}$ was obtained using a solution whose equilibrium pH was 10.1 and a value of 21 $M^{-1}$ at a pH of 8.39, where the average amino group has a larger number of electron-withdrawing ammonio substituents in the same molecule with it. Values were also calculated from the magnitude of the drop in pH that accompanied addition of isobutyraldehyde to an OAPS solution. As in the case of monoamines,[13] imine formation causes the pH to drop because the concentration of free amine decreases. In the case of OAPS, however, the introduction of electron-withdrawing aldimino substituents reduces the basicity of free amino groups in the same molecule, thus making the decrease in pH larger than it would otherwise be. Our inability to assess the substituent effect of aldimino groups on the basicity of OAPS decreases the reliability of $K_{Im}$ values determined by the pH method. However, uv measurements support the assumption that an amount of isobutyraldehyde that lowers the pH of an OAPS solution to the same extent that a given amount of strong acid does also lowers its p$K_{app}$ value by about the same amount. This assumption led to $K_{Im}$ values of 24, 25, 36, 35, and 36 $M^{-1}$ at pH's of 7.98, 8.39, 8.68, 8.71, and 9.04, respectively. If small amounts of large-ring aminals are also formed in the reaction of isobutyraldehyde with OAPS, the assumption of 1:1 stoichiometry used in calculating $K_{Im}$ will be in error. Small amounts of this side reaction will have little ef-

**Table I**
**Kinetics of the Dedeuteration of Isobutyraldehyde-2-*d* in Water at 35° [a]**

| [Catalyst], [b] N [c] | pH | $10^5 k$, $sec^{-1}$ |
|---|---|---|
| 0.0865[d] | 9.82 | 8.55 |
| 0.0863[d] | 9.33 | 14.20 |
| 0.0862[d] | 9.04 | 16.22 |
| 0.0861[d] | 8.71 | 17.60 |
| 0.0858 | 8.39 | 20.02 |
| 0.0856 | 7.98 | 17.50 |
| 0.0855 | 7.64 | 13.01 |
| 0.0854 | 7.25 | 7.11 |
| 0.0859 | 8.68 | 19.22 |
| 0.0959 | 8.53 | 21.5 |
| 0.0482 | 8.62 | 15.8 |
| 0.0241 | 8.42 | 7.38 |
| 0.189 | 8.54 | 35 |
| 0.086[e] | 9.09 | 1.60 |

[a] $[Me_2CDCHO]_0$ = 0.046. [b] OAPS, unless otherwise noted. [c] Normalities in total amine (protonated, unprotonated, or in the form of imine). [d] Using 3-week-old catalyst solutions. [e] 2-Methoxyethylamine.

fect on the $K_{Im}$ values calculated from uv data; they will make the $K_{Im}$ values calculated from pH measurements somewhat larger than they should be. When the logarithms of the $K_{Im}$ values reported here are placed in the plot of log $K_{Im}$ for monoamines *vs.* $pK$[13] the average deviation (0.06) is not much larger than that observed with the monoamines of the type $RCH_2NH_2$, where R contains an $sp^3$-hybridized carbon atom at its point of attachment (0.05). This suggests that our values refer very largely to imine formation.

**Catalysis by OAPS.** Catalysis of the dedeuteration of isobutyraldehyde-2-*d* in aqueous solution at 35° was studied in the presence of 0.0860 ± 0.0006 *N* (in total amine) OAPS at a number of pH's and at pH 8.52 ± 0.10 in the presence of several different concentrations of OAPS, with the results shown in Table I. All the runs were carried out with fresh catalyst solutions except the first four, in which solutions that were about 3 weeks old were used. The fact that the rate constant obtained in the fourth run is 8% smaller than that obtained in the ninth run, which is almost a duplicate of it, suggests a small amount of deterioration of the catalyst solution on standing. However, correction for such deterioration would not significantly change any conclusions drawn from the plot of *k vs.* pH shown in Figure 2.

The plot, in Figure 3, of *k vs.* the concentration of catalyst at pH 8.5, including a point for 0.086 *N* catalyst interpolated from Figure 2 and one for no catalyst calculated from the catalysis constants for water and hydroxide ions, suggests that the rate may level off at higher concentrations, but the amount of catalyst available was not sufficient to test this suggestion. This tendency for the rate to level off as the catalyst concentration increases resembles that observed with polyethylenimines[1b,7,8] and is explained in the same way. Most of the reaction proceeds *via* the rapid reversible transformation of isobutyraldehyde-2-*d* to a complex, which is mainly imine, with much smaller amounts of iminium ion. The rate-controlling step is a first-order reaction of the complex, in which the iminium form is attacked by an amino group present in the same ion. The rate of reaction by this mechanism would have to

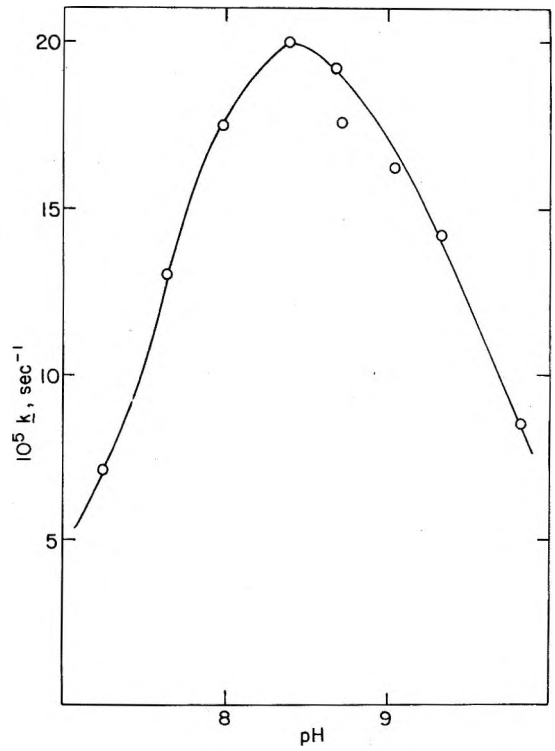


**Figure 2.** Rate constants for dedeuteration of 0.0546 *M* isobutyraldehyde-2-*d* by 0.086 *N* OAPS at various pH's in water at 35°.

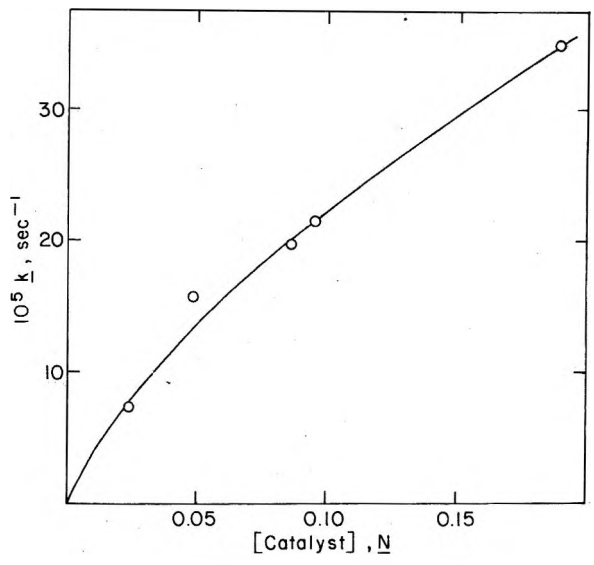


**Figure 3.** Rate constants for dedeuteration of 0.0546 *M* isobutyraldehyde-2-*d* at pH 8.5 in the presence of various concentrations of OAPS in water at 35°.

level off when there is enough catalyst to transform all the aldehyde to complex. Since ultraviolet measurements show that 0.086 *N* catalyst complexes about 30% of the aldehyde at pH 8.5, the first-order rate constant for reaction of complexed aldehyde must be about $(20 \times 10^{-5}/0.3)$, or $7 \times 10^{-4}$ $sec^{-1}$.

The pH–rate profile shows a clear maximum around pH 8.4. The principal reason for this maximum is that at lower pH there are not enough unprotonated amino groups to provide the required internal basic catalysis, and at higher pH not enough of the complexed aldehyde is in the protonated active iminium form. The location of the maximum may be rationalized as follows. Take the rate-controlling step as being a reaction between the isobutyraldiminium

$$v = k[\mathrm{Am}][\mathrm{ImH^+}] \quad (3)$$

ion ($ImH^+$) and amine (Am) with rate as shown in eq 3. Let the equilibrium constant for the formation of the iminium ion from aldehyde and primary ammonium ion be $K_I$. This gives eq 4, which may be compared with eq 5 for the observed first-order rate constant $k_1$ to give eq 6. The species

$$v = kK_I[\mathrm{Am}][\mathrm{AmH^+}][\mathrm{RCHO}] \quad (4)$$

$$v = k_1[\mathrm{RCHO}]_{total} \quad (5)$$

$$k_1 = kK_I[\mathrm{Am}][\mathrm{AmH^+}][\mathrm{RCHO}]/[\mathrm{RCHO}]_{total} \quad (6)$$

Am and $AmH^+$ are not constant species; the average Am in an acidic solution, for example, is in a molecule with more positively charged ammonio substituents and so it is more weakly basic than the average Am in a more basic solution. Hence $k$ and $K_I$ are pH dependent. However, it is known from studies of catalysis of the dedeuteration of isobutyraldehyde-2-*d* by various primary ammonium salts in the presence of pyridine buffers that when Am is held constant and $AmH^+$ is varied a plot of log ($kK_I$) *vs.* $pK_{AmH}$ has a slope of about −0.40.[14] Similarly, a study of catalysis by methylammonium ions in the presence of various tertiary amines shows that a plot of log ($kK_I$) *vs.* $pK_{AmH}$ has a slope of about 0.42.[15] Hence, when both Am and $AmH^+$ are varied, with the decrease in the basicity of the former being equal to the increase in acidity of the latter, the product $kK_I$ should not change very much. The product $[Am][AmH^+]$ would have a maximum value at the pH at which the amine and ammonium concentrations are equal if the sum of these two concentrations were kept constant. However, this sum increases somewhat with decreasing pH because of the concomitant decrease in the equilibrium constant for imine formation ($K_{Im}$), which also causes the ratio $[RCHO]/[RCHO]_{total}$ to increase with decreasing pH. Therefore the rate maximum is expected to occur at a pH somewhat lower than the pH at which OAPS is half protonated. This pH is 9.27 in the absence of isobutyraldehyde but it would be somewhat lower in the presence of the aldehyde, which lowers the basicity of the OAPS. Hence the occurrence of the rate maximum at pH 8.4 is consistent with the proposed mechanism.

Like any amine, OAPS must have the ability to act as a monofunctional catalyst in the dedeuteration of isobutyraldehyde-2-*d*. Bifunctional catalysis will be observable only if it is as important as monofunctional catalysis or more so. (Monofunctional catalysis can lead to rate eq 4 if the amine and ammonium groups are in different catalyst molecules.) We have estimated the efficiency to be expected of monofunctional catalysis in two ways. We have studied the catalytic activity of 2-methoxyethylamine, a compound whose steric requirements near the reaction center resemble those of OAPS and whose basicity ($pK_a$ = 9.09) is about the same as that of half-neutralized OAPS ($pK_{app}$ = 9.27). At pH 9.09, where its catalytic activity *via* the iminium-ion mechanism should be nearly maximal, 2-methoxyethylamine is seen (from the last entry in Table I) to be only about one-tenth as good a catalyst as is OAPS under the same conditions. We also used the extensive previous work on amine catalysis of the dedeuteration of isobutyraldehyde-2-*d* to estimate the monofunctional catalytic activity, employing linear free energy relationships as described in more detail in several other cases.[5,6,16] Application of this method to the run with 2-methoxyethylamine gave a $k$ of $1.7 \times 10^{-5}$ $sec^{-1}$, in good agreement with the value shown in Table I. Application to the run on OAPS at pH 8.39 gave the value $1.4 \times 10^{-5}$ $sec^{-1}$. According to this estimate 92.7% of the reaction at pH 8.39 arises from bifunctional catalysis, 5.5% from the attack of an amino group from one OAPS molecule on an isobutyraldiminium ion derived from another OAPS molecule, 1.7% from attack of an amino group on free isobutyraldehyde-2-*d*, and 0.1% from all other mechanisms combined. From these figures it follows that the average effective concentration of the amino groups in the same molecule with an isobutyraldiminium ion is 0.28 *N*.

On a normality basis the catalytic activity of OAPS is about three times that of PEI-50,000[1b] (polyethylenimine with an average molecular weight of 50,000, the most active of the PEI catalysts studied) at concentrations around 0.1 *N*; furthermore, aldehyde complexed to OAPS is about three times as reactive as that complexed to PEI-50,000, at the optimum pH's of about 8.5 and 7.5, respectively. One advantage of OAPS over PEI is that it gives less nonproductive binding; much of the aldehyde bound by PEI is held as imidazolidine derivatives. Also, nearly all the amino groups of OAPS are primary and hence suitable for imine formation as well as basic catalysis, whereas about three-fourths of the amino groups in PEI are rather hindered secondary and tertiary amino groups, which probably give negligible amounts of iminium ion formation and considerably less basic catalysis than they would if they were less hindered. On the other hand, PEI has a lower equivalent weight than OAPS and is almost as good a catalyst on a weight basis. The activity of OAPS is only about one-third that of the monoprotonated form of 1-dimethylamino-8-amino-2-octyne,[5] which has an unhindered tertiary amino group, the most effective type of basic catalyst.[15,17] In general, it seems that the "shotgun" approach of using catalysts such as OAPS and PEI's can give bifunctional catalysis, but that carefully designed bifunctional species offer more promise for highly effective bifunctional catalysis.

## Experimental Section

**"Octakis-*O*-(2-cyanoethyl)sucrose."** Eastman cyanoethylsucrose [ir (neat) 3480 (OH), 2950 and 2900 (CH), 2260 (C≡N), and 1100 $cm^{-1}$ (C–O); nmr ($CDCl_3$) $\tau$ 7.35 (t, 16.1, $J$ = 6 Hz, $CH_2CN$), 6.27 (m, 29.1, $OCH_2C$ and $OCHC_2$), 4.68 (d, 0.16, $J$ = 3 Hz, $O_2CHC$), and 4.40 ppm (d, 0.9, $J$ = 3 Hz, $O_2CHC$)] was ordinarily used without further treatment.

*Anal.* Calcd for $C_{36}H_{46}N_8O_{11}$: C, 56.39; H, 6.05; N, 14.61. Found (average of four analyses with standard deviations): C, 55.34 ± 0.09; H, 6.18 ± 0.04; N, 14.06 ± 0.10.

The doublets at $\tau$ 4.40, 4.68, and 5.42 ppm were attributed to C-1 hydrogen atoms of the glucose moiety of cyanoethylsucrose, cyanoethylated $\alpha$-glucose, and cyanoethylated $\beta$-glucose, respectively. This attribution was supported by the increasing size of the $\tau$ 4.68 and 5.42 ppm peaks (the latter being a doublet with a coupling constant of 6.4 Hz) and the decreasing size of the $\tau$ 4.40 ppm peak in samples that had been hydrolyzed with acidic aqueous methanol for increasing lengths of time. It is also supported by observing that the corresponding doublets of sucrose, $\alpha$-glucose, and $\beta$-glucose fall at $\tau$ 4.53 ($J$ = 3 Hz), 4.70 ($J$ = 3 Hz), and 5.30 ppm ($J$ = 7 Hz), respectively.[18] From the relative peak areas and the assumption that cyanoethylated fructose (whose pmr spectrum would be obscured by that of cyanoethylsucrose) was present in the same amount as cyanoethylated glucose, it was calculated that 77% of the sucrose moieties were intact and 23% had been hydrolyzed to monosaccharide derivatives. By a method analogous to that described in more detail in connection with octa(aminopropyl)sucrose, the average number of cyanoethyl groups per sucrose moiety (whether the sucrose moiety exists in the unhydrolyzed form or not) was calculated so as to give the best possible agreement with the elemental analysis of the material. The value 7.36 [plus the amounts of water and bis(2-cyanoethyl) ether known to be present] gave calculated carbon, hydrogen, and nitrogen contents within 0.14 of the average experimental values. This value is within the experimental uncertainty of the value 7.6, which was calculated from the integrated nmr spectrum.

The water content of this material was found to be 0.8 wt % by Karl Fischer titration. Attempts at molecular distillation were unsuccessful but small foreruns of bis(2-cyanoethyl) ether were obtained. High-pressure liquid chromatography using a Porosil C

(silica gel) column showed that a solution of 2.69 g of the cyanoethylsucrose in enough ethyl acetate to give a volume of 10 ml was 0.0814 *M* in bis(2-cyanoethyl) ether. This corresponds to a bis(2-cyanoethyl) ether content of 3.75% by weight.

**"Octakis-O-(3-aminopropyl)sucrose."** Reduction of octacyanoethylsucrose with hydrogen over Raney nickel[19] in acetic anhydride gave material that may well have been the acetyl derivative of the desired product. However, attempts at basic hydrolysis gave either too little reaction or dark brown syrups. Attempted reduction using a rhodium catalyst gave no reaction in twice the time reported for complete reduction of several 3-alkoxypropionitriles.[20] Reduction with diborane[21] gave material whose nmr spectrum showed the presence of little, if any, of the desired product. The method finally adopted used activated Raney nickel (W. R. Grace Co.) at about 60 psi of hydrogen pressure.[9] In a typical run 10.0 g of cyanoethylsucrose and about 40 g of Raney nickel in 250 ml of methanol saturated with ammonia at 10° gave complete reduction in 4 hr at 54°. Three filtrations, the last through 2.0-$\mu$ Millipore Polyvic, and solvent removal *in vacuo* gave a viscous green syrup that was dissolved in water, centrifuged, filtered again through Polyvic, and freeze dried, leaving 8.8 g (85%) of pale green semisolid material.

Chromatography of material prepared as described on basic alumina, Florisil, and activated charcoal using water–methanol mixtures gave various combinations of little or no material eluted from the column and products of decomposition. Gel permeation chromatography using 0.0100 *M* aqueous sodium chloride as the eluent, monitored by optical rotation measurements, gave only one peak with an elution volume only slightly greater than the void volume when Sephadex G-10 was used. Sephadex G-25 gave slower elution but shoulders on the single peak as the only evidence of separation. With Sephadex G-15 on a 2.75 × 53 cm column, two peaks were obtained, the larger with the same relative elution volume as a mol wt 400 ethylene glycol telomer and the smaller (more rapidly eluted) with the same relative elution volume as a mol wt 800 ethylene glycol telomer. Preparative scale chromatography was carried out with 4–5-g samples of material using a 5 × 92 cm column and in some runs a third fraction, with apparent molecular weight about 1100, was observed. The mol wt 800 fraction comprised about 15% of the material put on the column and its nmr spectrum indicated the presence of about 65% sucrose derivative. Rechromatography gave in 4% overall yield a mol wt 800 fraction that appeared to be chromatographically homogeneous: nmr ($D_2O$) $\tau$ 8.10 (quintet, 15.9, $J$ = 6.5 Hz, $CH_2CH_2CH_2$), 7.10 (t, 15.5, $J$ = 7 Hz, $CH_2N$), 6.15 (m, 29.7, $OCH_2C$ and $OCHC_2$), 5.25 (s, DOH), and 4.35 ppm (0.9, $O_2CHC$). A number of batches of doubly chromatographed OAPS were combined to give the one homogeneous sample that was used for the analyses and kinetic studies.

*Anal.* Calcd for $C_{36}H_{78}N_8O_{11}$: C, 54.11; H, 9.84; N, 14.02. Found: C, 48.12, 48.29; H, 8.54, 8.55; N, 11.46, 11.30.

When this material stood in deuterium oxide containing hydrochloric acid, the $\tau$ 4.31 ppm peak, which was attributed to a sucrose derivative, gradually disappeared, and peaks at $\tau$ 4.50 and 5.20 ppm, which were attributed to the $\alpha$ and $\beta$ forms of a glucose derivative, appeared and grew. The $\tau$ 5.20 peak was about 20% larger than the 4.50 ppm peak. The maximum possible area of a $\tau$ 4.50 ppm peak in the purified OAPS corresponded to the presence of no more than 15% fructose and glucose derivatives, assuming a 1:1 ratio of fructose to glucose and a 1:1.2 ratio of $\alpha$- to $\beta$-glucose derivative.

Titration with standard hydrochloric acid gave a sharp end point, from which an equivalent weight of 119.9 was calculated. The carbonate content was determined by acidification of an aqueous solution to the titration end point and injection on a 6 ft × 0.25 in. Poropak QS column at 70°. Peak areas were calibrated using carbon dioxide solutions prepared by acidifying standard aqueous sodium bicarbonate solutions. Manipulations were carried out so as to prevent premature loss of carbon dioxide from the aqueous solutions, and 0.192 mol of carbon dioxide per equivalent of base was found.

The Van Slyke analysis method used gave 99.9% of the theoretical amount of nitrogen, with a standard deviation of 0.7%, for fractionally distilled 3-methoxypropylamine. For bis(3-aminopropyl) ether that was 99.3% pure by glpc and contained 98.7% of the expected amount of base by titration, 99.5 ± 0.9% of the theoretical amount of nitrogen was obtained. Four determinations on the OAPS used for kinetic studies gave 0.0848 ± 0.0010 *N* for the primary amine concentration of solutions that were 0.0865 *N* in total base. This corresponds to 0.98 equiv of primary amine per equivalent of base.

The absence of a nitrile band from the infrared spectrum and blank experiments on bis(2-cyanoethyl) ether showed that less than 1% of the nitrile groups in the reactant escaped reduction.

The elemental analysis was used to calculate the water content and the average number of hydroxy groups per sucrose moiety that had been transformed to $H_2NCH_2CH_2CH_2O$ or $RNHCH_2CH_2CH_2O$ groups. Let $n$ be the number of aminopropylated hydroxy groups, $w$ the number of water molecules, c the number of carbon dioxide molecules, and $s$ the number of secondary amino groups per sucrose moiety (including those that have been hydrolyzed to glucose and fructose derivatives).[22] The carbon, hydrogen, and nitrogen contents may then be expressed as shown in

$$\%C = 96.38(12.011)(12 + 3n + c)/m \quad (7)$$

$$\%H = 96.38(1.008)(22 + 7n + 2w - 3s)/m \quad (8)$$

$$\%N = 96.38(14.007)(n - s)/m \quad (9)$$

$$m = 342.30 + 57.096n + 18.015w + 44.013c - 17.031s \quad (10)$$

eq 7–9, in which the term 96.38 arises from the presence of 3.62% sodium chloride and $m$ is an apparent molecular weight, which is defined in eq 10. The equivalent weight, Van Slyke determination, and carbon dioxide analysis show that $s$ and $c$ are equal to $0.0196n$ and $0.1882n$, respectively. Substitution of these values into eq 7–10 and determination of the values of $n$ and $w$ that permitted calculation of %C, %H, and %N with the smallest sum of the squares of the deviations gave values of 7.16, 1.55, 0.14, and 1.35 for $n$, $w$, $s$, and c, respectively. This corresponds to 6.88 3-aminopropyl groups per sucrose moiety. Most of the 1.55 molecules of water may be accounted for as carbonate if the carbon dioxide is present in this form (rather than as carbamates) and much of the remainder may be that which has gone into the hydrolysis of ~15% of the sucrose moieties.

**The Carbobenzoxy Derivative of "Octakis-O-(3-aminopropyl)sucrose."** In hope of obtaining a crystallizable product OAPS was carbobenzoxylated.[23] To 1.0 g of crude OAPS and 1.94 g of sodium bicarbonate in 50 ml of 85:15 methanol–water was added 2.22 g of recrystallized benzyl chloroformate with stirring during 1 hr. After stirring overnight the solution and a white syrup were separated from white crystals of sodium salts. Addition of 50 ml of water to the solution precipitated a syrup that was combined with the syrup that had separated during the reaction. Three more precipitations by water from methanol gave 2.20 g (94%) of the carbobenzoxy derivative: ir (neat) 3340 (N–H), 3075 and 3040 (aromatic C–H), 2950 and 2880 (aliphatic C–H), 1700 (C=O), 1135, and 1080 $cm^{-1}$ (C–O); nmr $\tau$ 8.5 (m, 17.2, $CCH_2C$), 7.0 and 6.6 (m, 44.0, $CCH_2N$ and OCH–), 5.1 (s, 15.8, $PhCH_2O$), and 2.9 ppm (s, 39.3, Ph). Theoretical integrals are 16, 45, 16, and 40, respectively. The material gave a negative ninhydrin test. It could not be crystallized, but a methanol solution deposited some white flakes when cooled to −78°. Hydrogenolysis of these flakes and of the material remaining in solution was carried out in methanol using 5% palladium on charcoal. The nmr spectra and gel permeation chromatograms of the OAPS produced showed some differences but not enough to promise a useful method of purification.

**Kinetics.** The rate of dedeuteration of isobutyraldehyde-2-*d* was followed by extracting the acid-quenched reaction mixture with chloroform and making nmr measurements on the extracts.[2,17] The pH of an OAPS solution was adjusted by addition of hydrochloric acid and measured again after the addition of aldehyde. The change in pH caused by addition of aldehyde was the basis of one of the two methods used for calculating $K_{Im}$. On the average, six points were taken per kinetic run.

**Registry No.**—Octakis-O-(2-cyanoethyl)sucrose, 18304-13-7; octakis-O-(3-aminopropyl)sucrose, 52341-49-8; isobutyraldehyde-2-*d*, 4303-51-9.

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(21) *Cf.* H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.*, **82**, 681 (1960).
(22) In this calculation a molecule of tetrakis(aminopropyl)glucose plus a molecule of tetrakis(aminopropyl)fructose will appear as a molecule of octakis(aminopropyl)sucrose plus a molecule of water.
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# Synthesis of α-Ylidene-γ-butyrolactones Using an α-Phosphono-γ-butyrolactone Carbanion

Toru Minami,* Ichiro Niki, and Toshio Agawa

*Department of Petroleum Chemistry, Faculty of Engineering, Osaka University, Yamadakami, Suita, Osaka, 565, Japan*

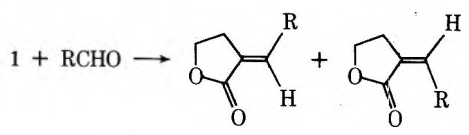
*Received May 22, 1974*

Reactions of an α-phosphono-γ-butyrolactone carbanion with aldehydes, ketones, heterocumulenes, and nitrosobenzene gave α-ylidene-γ-butyrolactones and α-anilino-γ-crotonolactone in good yields.

Phosphono carbanions bearing an electron-withdrawing substituent on the carbon α to the phosphorus function are useful reagents for olefin synthesis.[1] As an extension of this phosphonate olefin synthesis, we have investigated the reactions of an α-(*O,O*-diethylphosphono)-γ-butyrolactone carbanion (**1**)[2] with aldehydes, ketones, heterocumulenes, and nitrosobenzene.

The phosphonate carbanion **1** easily reacted with benzaldehyde to give only α-*trans*-benzylidene-γ-butyrolactone (**2**) in almost quantitative yield, regardless of the reaction temperatures employed. The structure of **2** was determined as follows. The nmr spectrum ($CDCl_3$) of **2** shows β-methylene (d–t, 2 H), γ-methylene (t, 2 H), phenyl (s, 5 H), and olefinic protons (t, 1 H) at δ 3.10, 4.45, 7.30, and 7.40, respectively. Although it is anticipated that the olefinic proton of the trans isomer would be observed downfield from the corresponding proton of the cis isomer, with the above data alone we cannot determine whether **2** is the trans or cis isomer. However, a change of solvent from $CDCl_3$ to benzene-$d_6$ produced a downfield shift of 0.20 ppm for the olefinic proton of **2**, whereas other protons suffered upfield shifts of 0.30–1.10 ppm. This result suggests that the olefinic proton is situated at the cis position to the carbonyl group.[3] Therefore, the structure was determined to be α-*trans*-benzylidene-γ-butyrolactone.

Reactions of **1** with *p*-nitrobenz-, cinnam-, and trichloroacetaldehyde similarly gave α-*trans*-(*p*-nitrobenzylidene)- (**3**), α-cinnamylidene- (**4**), and α-*trans*-(2,2,2-trichloroethylidene)-γ-butyrolactone (**5**) in 71, 55, and 100% yields, respectively.



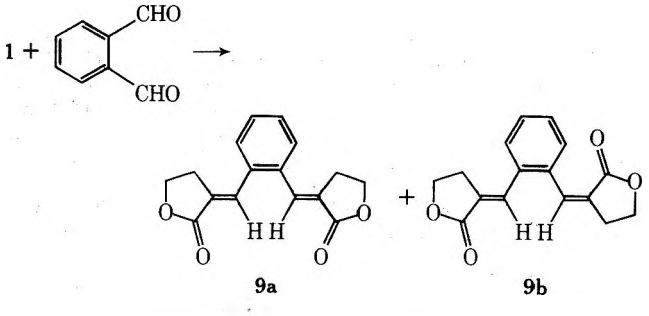

trans cis

**2**, R = Ph **6b**, R = *i*-Pr
**3**, R = *p*-$NO_2C_6H_4$ **7b**, R = Et
**4**, R = $Ph_2CH$=CH
**5**, R = $CCl_3$
**6a**, R = *i*-Pr
**7a**, R = Et

In contrast, the reactions with isobutyr- and propionaldehyde resulted in the formation of the mixtures of the corresponding α-*trans*- (**6a** and **7a**) and α-*cis*-(substituted ylidene)-γ-butyrolactones (**6b** and **7b**), ratios of which were approximately 1:1 and 3:2 by nmr, in good yields. Although separation of individual α-*trans*- (**6a**) and α-*cis*-(isobutylidene)-γ-butyrolactone (**6b**) was unsuccessful, their structural assignments rested upon nmr data and hydrogenation of the mixture over a platinum/carbon catalyst to α-isobutyl-γ-butyrolactone (**8**).

Thus, in the cases using aldehydes containing bulky substituents such as the phenyl, styryl, and trichloromethyl groups, only trans olefins were obtained, but use of aldehydes having rather small substituents such as the isopropyl and ethyl groups yielded mixtures of trans and cis olefins.

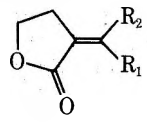
Interestingly, the reaction with *o*-phthalaldehyde gave a mixture of α,α′-bis(*trans,trans-o*-xylidene)- (**9a**, 47%) and α,α′-bis(*cis,trans-o*-xylidene)-γ-butyrolactone (**9b**, 7.3%).

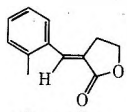
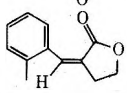
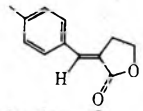
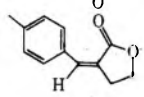



**9a** **9b**

In the reaction with *p*-phthalaldehyde, α,α′-bis(*trans,trans-p*-xylidene)- (**10a**) and α,α′-bis(*cis,trans-p*-xylidene)-γ-butyrolactone (**10b**) were likewise obtained in 67 and 4.4% yields. No corresponding α,α′-bis(*cis,cis*-xylidene)-γ-butyrolactones could be detected in either reaction. Although the formation of the trans,trans isomers, **9a** and **10a**, in both reactions is in accord with the results ob-

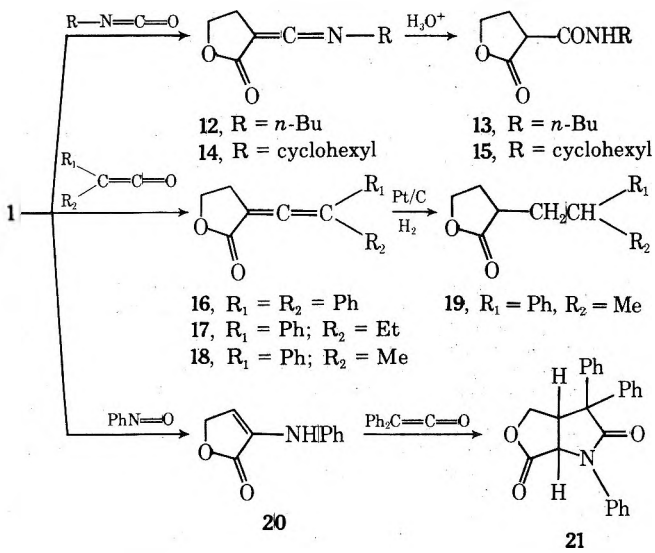
**Table I**
**α-Ylidene-γ-butyrolactones**



| Compd | Substituents $R_1$ | $R_2$ | Yield, % | Mp [bp (mm)], °C | Ir (Nujol), $cm^{-1}$ $\nu_{C=C}$ | $\nu_{C=C=N}$ or $\nu_{C=C=C}$ | Empirical formula[a] |
|---|---|---|---|---|---|---|---|
| **2** | H | Ph | 100 | 118.5 | 1640 | | $C_{11}H_{10}O_2$ |
| **3** | H | $p$-$NO_2C_6H_4$ | 71 | 189–190 | 1640 | | $C_{11}H_9NO_4$ |
| **4** | H | PhCH=CH | 55 | 135–136 | 1630 | | $C_{13}H_{12}O_2$ |
| **5** | H | $CCl_3$ | 100 | 76.0 | 1650 | | $C_6H_5O_2Cl_3$ |
| **6a + 6b** | H or $i$-Pr | $i$-Pr or H | 89 | [55–57 (0.5)] | 1650 | | $C_8H_{12}O_2$ |
| **7a + 7b** | H or Et | Et or H | 100 | [60 (0.5)] | 1670 | | $C_7H_{10}O_2$ |
| **9a** | H |  | 47 | 255–259 | 1640 | | $C_{16}H_{14}O_4$ |
| **9b** | H |  | 7.3 | 152–153 | 1645 | | $C_{16}H_{14}O_4$ |
| **10a** | H |  | 67 | 283–284 | 1640 | | $C_{16}H_{14}O_4$ |
| **10b** | H |  | 4.4 | 208–210 | 1630 | | $C_{16}H_{14}O_4$ |
| **11** | $-(CH_2)_5-$ | | 92 | [106 (0.5)] | 1670 | | $C_{10}H_{14}O_2$ |
| **12** | =N-$n$-Bu | | 91 | [110–115 (0.5)] | | 2050 | $C_9H_{13}NO_2$ |
| **14** | =N-$C_6H_{11}$ | | 95 | | | 2050 | $C_{11}H_{15}NO_2$ |
| **16** | $=CPh_2$ | | 100 | 132–133 | | 1945 | $C_{18}H_{14}O_2$ |
| **17** | =C(Ph)Et | | 100 | 60–61 | | 1940 | $C_{14}H_{14}O_2$ |
| **18** | =C(Ph)Me | | 81 | Viscous liquid | | 1950 | $C_{13}H_{12}O_2$ |

[a] Satisfactory analytical data (±0.4% for C, H, N) were found for all new compounds except for compounds 12, 14, and 18 in the table.

**Scheme I**




tained above with bulky monoaldehydes, the formation of the cis,trans isomers, **9b** and **10b**, is difficult to explain.

The reaction with cyclohexanone similarly gave α-cyclohexylidene-γ-butyrolactone (**11**) in 92% yield but the reaction with benzophenone afforded no olefin.

Reactions with isocyanates and ketenes under mild conditions yielded ketenimines **12** and **14** and allenes **16**, **17**, and **18** in almost quantitative yields (Scheme I). The acid-catalyzed hydrolysis of the ketenimines readily led to α-carbamoyl-γ-butyrolactones **13** and **15**.[6] Hydrogenation of the allene **18** over a platinum/carbon catalyst gave α-(2-phenylpropyl)-γ-butyrolactone (**19**)[6] in quantitative yield.

The reaction with nitrosobenzene gave α-anilino-γ-crotonolactone (**20**, 94%), which was heated together with diphenylketene in a sealed tube to yield 2,3,3a,4,6,6a-hexahydro-2,6-dioxo-1,3,3-triphenyl-1*H*-furo[3,4-*b*]pyrrole (**21**, 35%) as the only isolable product.

These results are summarized in Table I.

## Experimental Section[4]

**General Procedure.** To sodium hydride (50%, 0.50 g, 0.01 mol) in 40 ml of dry benzene was added dropwise α-diethylphosphono-γ-butyrolactone[5] (2.22 g, 0.01 mol) in 10 ml of dry benzene with stirring. After the addition, the solution was stirred at 50–60° for 30 min until gas evolution had ceased. To the resulting yellowish-orange solution were added 0.01 mol of aldehydes (or ketones, heterocumulenes, or nitrosobenzene) in 10 ml of benzene. The reactions were run under dry $N_2$.

***α-trans*-Benzylidene-γ-butyrolactone (2).** To a benzene solution containing the phosphonate carbanion I prepared above was added freshly distilled benzaldehyde (1.06 g, 0.01 mol) in 10 ml of benzene with stirring and then the reaction mixture was refluxed for 2.5 hr. After removal of insoluble sodium diethyl phosphate by

filtration, the filtrate was concentrated *in vacuo* to give 3.90 g (100%) of **2**. The crude product **2** was recrystallized from benzene–hexane to afford the pure sample as white needles: nmr ($CDCl_3$) $\delta$ 3.10 (d–t, $J$ = 7.5, 3 Hz, 2 H, $OCH_2CH_2$–), 4.45 (t, $J$ = 7.5 Hz, 2 H, $OCH_2CH_2$–), 7.30 (s, 5 H, phenyl protons), and 7.40 (t, $J$ = 3 Hz, 1 H, olefinic proton); nmr ($C_6D_6$) $\delta$ 2.00 (d–t, 2 H), 3.80 (t, 2 H), 7.10 (s, 5 H), and 7.60 (t, 1 H); mass spectrum (70 eV) $m/e$ 174 ($M^+$), 146 ($M^+ - CO$), and 129 ($M^+ - CO_2 - H$).

In the reaction at ambient temperature for 2.5 hr, an only trans isomer **2** was similarly obtained in 98% yield.

**Reduction of α-(Isobutylidene)-γ-butyrolactone (6a and 6b).** A solution of 1.00 g (7.14 mmol) of a mixture of **6a** and **6b** dissolved in ethanol was shaken in a hydrogen atmosphere over $PtO_2$. After the theoretical amount of hydrogen was consumed (50 hr), the reaction was stopped. The catalyst was removed and the solution was concentrated. The residue was vacuum distilled to give 1.01 g of **α-isobutyl-γ-butyrolactone (8):** bp 56° (0.4 mm); $n^{20}D$ 1.4446; ir (neat) 1760 $cm^{-1}$ (C=O); mass spectrum (70 eV) $m/e$ 142 ($M^+$); nmr ($CCl_4$) $\delta$ 0.95 (d, $J$ = 6 Hz, 6 H, methyl protons), 1.10–2.50 (m, 6 H, methylene and methine protons), and 4.20 (split t, 2 H, O $CH_2CH_2$–).

*Anal.* Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.93. Found: C, 67.45, H, 10.32.

**α,α′-Bis(*o*-xylidene)-γ-butyrolactone (9a and 9b).** The reaction was carried out using the procedure described above with **1** and *o*-phthalaldehyde. After removal of insoluble sodium diethyl phosphate by filtration while hot, the filtrate was allowed to stand at room temperature overnight. The resulting solid was filtered and recrystallized from a large quantity of ethanol–benzene to give pure **α,α′-bis(*trans,trans*-*o*-xylidene)-γ-butyrolactone (9a,** 47%): nmr (DMSO-$d_6$) $\delta$ 3.20 (d–t, $J$ = 7.5, 3 Hz, 4 H, $OCH_2CH_2$–), 4.40 (t, $J$ = 7.5 Hz, 4 H, $OCH_2CH_2$–), 7.55–7.67 (4 H, phenyl protons) and 7.70 (t, $J$ = 3 Hz, 2 H, olefinic proton); mass spectrum (70 eV) $m/e$ 270 ($M^+$), 241 ($M^+ - CO - H$), 226 ($M^+ - 2CO_2$).

The filtrate was concentrated and the resulting solid was recrystallized from benzene–hexane to afford pure **α,α′-bis(*cis,trans*-*o*-xylidene)-γ-butyrolactone (9b,** 7.3%): nmr ($CDCl_3$) $\delta$ 3.20 (d–t, $J$ = 7.5, 2 Hz, 4 H, $OCH_2CH_2$–), 4.40 (t, $J$ = 7.5 Hz, 4 H, $OCH_2CH_2$–), 7.20 [t, $J$ = 2 Hz, 1 H, trans H of –HC=C(CO)–], 7.30–7.45 (s, 4 H, phenyl protons), and 7.60 [t, $J$ = 3 Hz, 1 H, cis H of –HC=C(CO)–]; nmr ($C_6D_6$) $\delta$ 1.90–2.40 (2 d–t, $J$ = 7.5, 3, 2 Hz, 4 H, $OCH_2CH_2$–), 3.35–3.70 (2 t, $J$ = 7.5 Hz, 4 H, $OCH_2CH_2$–), 6.67 [t, $J$ = 2 Hz, 1 H, trans H of –HC=C(CO)–], 7.12 (d, 4 H, phenyl protons), and 7.80 [t, $J$ = 3 Hz, cis H of –HC=C(CO)–]; mass spectrum (70 eV) $m/e$ 270 ($M^+$), 241 ($M^+ - CO - H$), 226 ($M^+ - CO_2$), and 182 ($M^+ - 2CO_2$).

**2,3,4,5-Tetrahydro-2-oxo-3-[(butylimino)methylene]furan (12).** To 200 ml of a benzene solution of **1** (0.04 mol), butyl isocyanate (3.96 g, 0.04 mol) in 50 ml of benzene was added at 0° with stirring. Then the reaction temperature was generally raised to 60° and held at that temperature for 1 hr. After similar work-up, distillation of the residue gave 6.10 g (91%) of **12:** bp 110–115° (0.5 mm); nmr ($CCl_4$) $\delta$ 0.90–2.00 (m, 7 H, $NCH_2CH_2CH_2CH_3$), 3.00 (t, $J$ = 7.5 Hz, $OCH_2CH_2$–), 3.60 (t, $J$ = 6 Hz, $NCH_2$–), and 4.20 (t, $J$ = 7.5 Hz, $OCH_2CH_2$–); mass spectrum (70 eV) $m/e$ 167 ($M^+$) and 110 ($M^+$ – Bu).

The satisfactory analytical data for **12** were not reported because of its instability.

**α-(*n*-Butylcarbamoyl)-γ-butyrolactone (13).** A solution of **12** (3.0 g, 0.018 mol) in ethanol (50 ml) containing 0.5 *N* hydrochloric acid (2 ml) was refluxed for 48 hr. After removal of solvent *in vacuo*, the residue was extracted with chloroform, followed by washing with water and drying over sodium sulfate. The chloroform layer gave 3.04 g (92%) of **13.** Recrystallization of crude **13** from benzene–hexane (1:1) afforded the pure sample: mp 49°; ir (Nujol) 3210 (NH), 1770 (lactone C=O), and 1630 $cm^{-1}$ (amide C=O); nmr ($CCl_4$) $\delta$ 0.70–1.55 (m, 7 H, $NCH_2CH_2CH_2CH_3$), 2.15–2.80 (m, 2 H, $OCH_2CH_2$–), 3.00–3.75 (m, 3 H, methine and $NCH_2$–protons), 4.15–4.50 (split t, 2 H, $OCH_2CH_2$–) and 7.40 (t, $J$ = 6 Hz, NH); mass spectrum (70 eV) $m/e$ 185 ($M^+$) and 141 ($M^+$ – CO).

*Anal.* Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.05; H, 8.21; N, 7.59.

**α-Anilino-γ-crotonolactone (20).** To 100 ml of a benzene solution of **1** (0.02 mol) was added nitrosobenzene (2.14 g, 0.02 mol) in benzene (20 ml) at 0° with stirring. Then the solution was stirred at ambient temperature for 2 hr. After similar work-up, **20** was obtained (3.28 g, 94% yield). Recrystallization of crude **20** from benzene–hexane gave the pure sample as white needles: mp 152–153°; ir (Nujol) 3300 (NH), 1745 (C=O), and 1654 $cm^{-1}$ (C=C); nmr (DMSO-$d_6$) $\delta$ 4.95 (d, $J$ = 2 Hz, 2 H, $OCH_2CH$=), 6.70 (t, $J$ = 2 Hz, 1 H, olefinic proton), 6.75–7.30 (m, 5 H, phenyl protons), and 8.20 (broad, 1 H, NH); mass spectrum (70 eV) $m/e$ 175 ($M^+$) and 147 ($M^+ - CO$).

*Anal.* Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.21; H, 5.19; N, 8.02.

**Reaction of 20 with Diphenylketene.** A solution of **20** (0.84 g, 4.8 mmol) and diphenylketene (1.86 g, 9.6 mmol) in 20 ml of dry benzene was heated at 160° for 2.5 hr in a sealed tube. Then the reaction mixture was chromatographed on alumina to give 0.60 g (35%) of **2,3,3a,4,6,6a-hexahydro-2,6-dioxo-1,3,3-triphenyl-1*H*-furo[3,4-*b*]pyrrole (21)** and 0.30 g of unidentified brown, polymeric liquid. Recrystallization of crude **21** from benzene–hexane gave the pure sample: mp 142–143.5°; ir (Nujol) 1780 (lactone C=O) and 1745 $cm^{-1}$ (lactam C=O); nmr ($CDCl_3$) $\delta$ 2.00 (t–d, $J$ = 6, 15 Hz, 1 H, methine proton), 2.75 (d–t, $J$ = 15, 10.5 Hz, 1 H, methine proton), 4.30 (d–d, $J$ = 10.5, 6 Hz, 2 H, methylene protons), and 7.30 (broad s, 15 H, phenyl protons); mass spectrum (70 eV) $m/e$ 369 ($M^+$), 250 ($M^+ - PhNCO$), 248 ($M^+ - Ph - CO_2$), and 194 ($Ph_2CCO^+$).

*Anal.* Calcd for $C_{24}H_{19}NO_3$: C, 78.03; H, 5.18; N, 3.79. Found: C, 78.03; H, 5.23; N, 3.96.

**α-Ylidene-γ-butyrolactones[6] 3–7, 10, 11, 14, 16–18.** These derivatives were similarly obtained from **1** and *p*-nitrobenz-, cinnam-, trichloroacet-, isobutyr-, propion- and *p*-phthalaldehydes, cyclohexanone, cyclohexyl isocyanate, and diphenyl-, phenylethyl, and phenylmethylketenes. Yields and some physical data of the products are shown in Table I.

**Registry No.**—**1,** 52217-10-4; **2,** 30959-91-2; **3,** 52216-84-9; **4,** 52216-85-0; **5,** 52216-88-3; **6a,** 52216-86-1; **6b,** 52216-87-2; **7a,** 52216-89-4; **7b,** 52216-90-7; **8,** 13888-02-3; **9a,** 52216-91-8; **9b,** 52216-92-9; **10a,** 52216-93-0; **10b,** 52278-84-9; **11,** 21681-63-0; **12,** 52217-13-7; **13,** 52217-14-8; **14,** 52217-15-9; **15,** 52217-16-0; **16,** 52217-17-1; **17,** 52217-18-2; **18,** 52217-19-3; **19,** 52217-20-6; **20,** 52217-21-7; **21,** 52217-22-8; α-diethylphosphono-γ-butyrolactone, 2907-85-9; benzaldehyde, 100-52-7; *o*-phthalaldehyde, 643-79-8; butyl isocyanate, 111-36-4; nitrosobenzene, 586-96-9; diphenylketene, 525-06-4; *p*-nitrobenzaldehyde, 555-16-8; cinnamaldehyde, 104-55-2; trichloroacetaldehyde, 75-87-6; isobutyraldehyde, 78-84-2; propionaldehyde, 123-38-6; *p*-phthalaldehyde, 623-27-8; cyclohexanone, 108-94-1; cyclohexyl isocyanate, 3173-53-3; phenylethylketene, 20452-67-9; phenylmethylketene, 3156-07-8.

**Supplementary Material Available.** Nmr data of **3–7, 10, 11,** and 14–19 will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-3236.

## References and Notes


(1) (a) W. S. Wadsworth, Jr., and W. D. Emmons, *J. Amer. Chem. Soc.*, **83,** 1733 (1961); (b) L. Horner, H. Hoffmann, and H. G. Wippel, *Chem. Ber.*, **91,** 61 (1958); (c) for a recent review, see J. Boutagy and R. Thomas, *Chem. Rev.*, **74,** 87 (1974).

(2) It has previously been reported that the carbanion **1** reacts with 17α-methyldihydrotestosterone and cholestan-3-one to give olefinic mixtures: R. L. Evans and H. E. Stavely, U. S. Patent 3,248,392 (1966); *Chem. Abstr.*, **65,** 2332 (1966).

(3) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969, p 246.

(4) All melting points of products were determined with a Yanagimoto micromelting apparatus and uncorrected. The nmr spectra were obtained on a JEOL LNM 3H-60 spectrometer with tetramethylsilane as an internal standard. The ir spectra were recorded with a Jasco IR-E spectrometer. The mass spectra were taken with a Hitachi RMU-6E spectrometer.

(5) K. H. Buechel, H. Roechling, and F. Korte, *Justus Liebigs Ann. Chem.*, **685,** 10 (1965).

(6) See paragraph at end of paper regarding supplementary material.

# Synthesis of Fagaronine. An Anticancer Benzophenanthridine Alkaloid

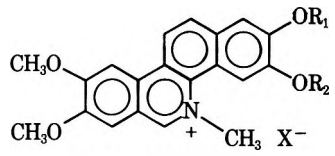
John P. Gillespie, Luis G. Amoros, and Frank R. Stermitz*

*Department of Chemistry, Colorado State University, Fort Collins, Colorado 80521*

*Received May 29, 1974*

A structural proof for fagaronine has been attained by synthesis. The sequence employed represents a new approach to the synthesis of such alkaloids by use of the Kessar benzyne cyclization. Various phenolic protecting groups were explored, of which the isopropoxy group was found to be most compatible with the overall synthetic scheme.

Recently, an extremely active antileukemic alkaloid, fagaronine, was isolated[1] from *Fagara zanthoxyloides* (Rutaceae). The structure of fagaronine was left somewhat in doubt, however, as spectral methods were insufficient to absolutely distinguish between **1a** and **1b**, although **1a** was suggested[1] as the more likely structure.



**1a**, $R_1$ = H; $R_2$ = $CH_3$; X = $Cl^-$
**b**, $R_1$ = $CH_3$; $R_2$ = H; X = $Cl^-$
**c**, $R_1$ = H; $R_2$ = $CH_3$; X = $CH_3OSO_3^-$

We wish to report a short synthesis of fagaronine which chemically establishes its structure unambiguously, supporting Farnsworth's recent[2] spectroscopic structural proof. The basis of the method is the Kessar phenanthridine synthesis,[3] which has been applied for the first time for the preparation of benzophenanthridine alkaloids.

## Results and Discussion

Our synthesis is outlined in Scheme I. The key transformation in this synthetic approach is the cyclization of the anil **6**. Attempts to cyclize **6a** failed completely, presumably because of the presence of a free phenolic group. Possible reasons for such failures have been discussed by Kessar.[3]

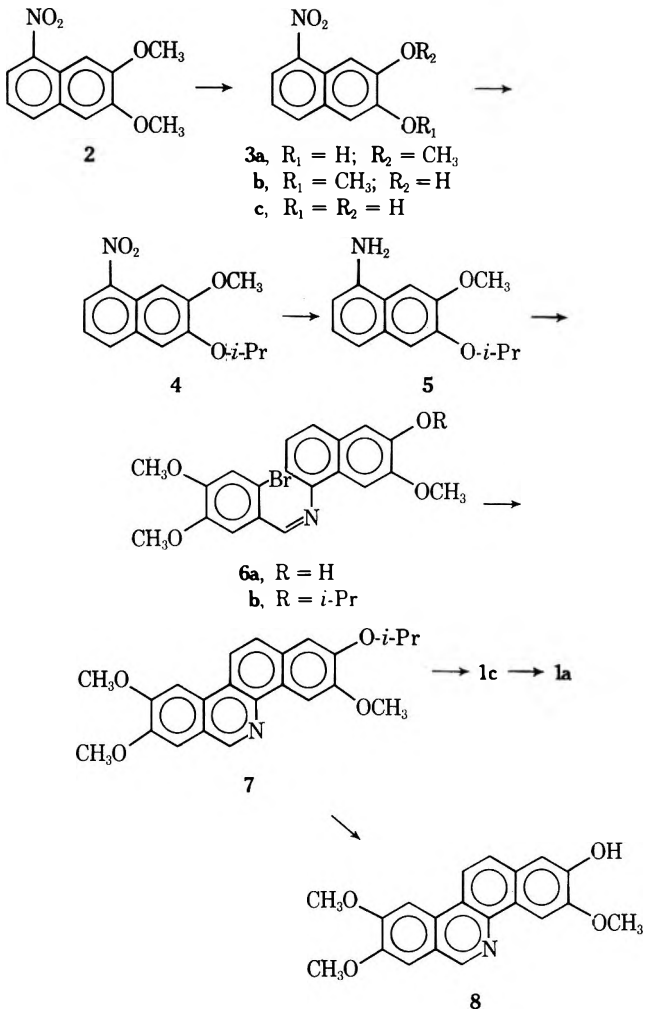
Therefore, a series of protecting groups was examined. The choice of a suitable group unexpectedly proved to be the most imposing problem of the synthesis. With model compounds seven different phenolic protecting groups were investigated. Six were discarded for the reasons shown in Table I. Although some limited success was achieved with the benzyl group in model compounds, only the isopropoxy group[4] possessed none of the undesirable properties listed in Table I.

Nitration of 2,3-dimethoxynaphthalene with fuming nitric acid in acetic acid gave all three possible nitro isomers as reported[5] by Chang, Moore, and Scheuer. However, we have circumvented the laborious chromatographic separation procedure[5] by the use of suitable crystallization solvents, from which all three isomers can be obtained in pure form. The progress of the successive fractional crystallizations was monitored by liquid chromatography.[6a]

Cleavage of **2** carried to 50% completion gave a 1:1 mixture[6b] of **3a** and **3b**, which were readily separated by crystallization. The compound **3a** is known,[7] being the exclusive product of the photolysis of **2** in $CH_3CN$–0.8 *N* NaOH in $H_2O$. The photolysis procedure[7] was found to be inconvenient for larger scale preparative work.

The nitrophenol **3a** was smoothly isopropylated in DMF and isopropyl bromide in the presence of $K_2CO_3$.[8] Reduction of the nitro groups in **4** was achieved by Pd/C and hydrazine in ethanol,[9] giving the naphthylamine **5** in high yield. Condensation of **5** with *o*-bromoveratraldehyde proceeded rapidly to give the anil **6b**. Cyclization of the anil under the Kessar conditions[3] ($NaNH_2$ in liquid $NH_3$) gave the extremely insoluble benzophenanthridine **7**.

**Scheme I**



Originally, we had planned to cleave the isopropoxy group to give **8** and then N-alkylate the phenolic free base. Indeed, the isopropoxy group was easily and selectively removed in the presence of the methoxy functionalities[4] in HBr–HOAc at 100°. Unfortunately, **8** alkylated poorly and inconsistently under the reaction conditions (40–65% conversion was typical). Further, the free base **8** is difficult to separate from **1c**.

However, N-alkylation of **7** directly gave reasonable conversion. Isolation of the mixture and reexposure to the reaction conditions (dimethyl sulfate, xylene, nitrobenzene, 180°) cleaved the isopropoxy group and a careful work-up

**Table I**
**Protecting Groups ArOR**

| R | Reason for rejection |
|---|---|
| H | *b*, *d*, *f* |
| $CH_2OCH_3$ | *b*, *e*, *f* |
| $SO_2C_6H_5$ | *g* |
| $SO_2C_6H_4NO_2$-*p* | *c* |
| $CH_2C_6H_5$ | *a*, *e*, *f* |
| $CO_2Me$ | *c* |
| $CH_2CH_2C_6H_5$ | *b*, *c* |

[a] Renders extreme lability to the intermediate naphthylamine. [b] Interferes with the anil formation reaction. [c] Unstable to liquid $NH_3$–$NaNH_2$. [d] Prevents cyclization (see text). [e] Renders the product free base soluble (insolubility is important for the isolation step). [f] Interferes with N-alkylation. [g] Could not be removed after completion of the N-alkylation step.

(see Experimental Section) gave a fair conversion to **1c**. Exchange of the methosulfate conterion for chloride in aqueous NaCl[10] yielded a sample of **1a** identical in all respects with authentic fagaronine. Work in progress indicates that this synthetic method is adaptable to the synthesis of many benzophenanthridine alkaloids in sufficient amounts for possible preclinical or clinical testing.

## Experimental Section

**5-Nitro-2,3-dimethoxynaphthalene (2).** The procedure of Bell and Buck[11] was followed for the nitration. A solution of 150 g of 2,3-dimethoxynaphthalene in 1800 ml of acetic acid was treated with a mixture of 150 ml of fuming nitric acid in 150 ml of acetic acid. After stirring for 50 min, the mixture was poured into 3 l. of cold water and extracted twice with a total of 1100 ml of $CHCl_3$. The organic layer was extracted with 2 l. of 12.5% KOH. A green solid formed and the emulsion was filtered. The organic extract was combined with an additional washing of 100 ml of $CHCl_3$ and dried. Removal of the solvent gave 157.5 g of a mixture of the 1-, 5-, and 6-nitro isomers. The crude residue was dissolved in 2400 ml of 95% ethanol and allowed to stand overnight. Filtration gave 65 g of the 5 and 6 isomers uncontaminated by the 1 isomer. Further crystallization of this mixture from ethyl acetate or acetic acid gave pure **2**, mp 158–159° (lit.[5] mp 157–158°).

**2-Hydroxy-3-methoxy-5-nitronaphthalene (3a). Method A.** Photolysis according to Havinga[7] of a solution of 700 mg of **2** in 5 l. of a mixture of 65% $CH_3CN$ and 35% 0.8 *N* NaOH through a Pyrex filter with a 450-W Hanovia lamp gave, after 1 hr, a deep red solution. The $CH_3CN$ was removed by rotary evaporation and the basic solution was extracted several times with $CHCl_3$. The aqueous layer was acidified and again extracted with $CHCl_3$. The latter extract was dried, the solvent was removed, and the residue was crystallized from ethanol–water to yield 550 mg (90%) of **3a**: mp 126–127° (no literature melting point given); nmr ($CDCl_3$) $\delta$ 4.12 (s, $OCH_3$), 6.15 (s, OH), 7.33 (s, $H_4$), 7.35 (t, $J$ = 8 Hz, $H_6$), 7.92 (d of d, $J$ = 1.5, 8 Hz, $H_5$), 8.05 (s, $H_1$), 8.17 (d of d, $J$ = 1.5, 8 Hz, $H_7$); uv (EtOH) $\lambda_{max}$ 357 nm (log $\epsilon$ 3.65), 222 (4.85); ir ($CHCl_3$) 3542 (OH), 1515 and 1345 $cm^{-1}$ ($NO_2$).

*Anal.* Calcd for $C_{11}H_9NO_4$: C, 60.27; H, 4.13; N, 6.39. Found: C, 60.43; H, 4.07; N, 6.33.

**Method B.** A solution of 20 g of **2** in 500 ml of HOAc and 100 ml of 48% HBr was heated at 100° for 3 hr, which brought the reaction to approximately 50% completion. The solution was poured into 2.0 l. of $H_2O$ and extracted several times with $CHCl_3$. The organic extract was washed several times with water to remove small amounts of **3c** formed as a by-product of the reaction. Shaking with 10% NaOH formed a deep red aqueous layer which was washed several times with $CHCl_3$. The combined organic layers yielded the neutral fraction of 2, mp 155–157°. Acidification of the aqueous layer and extraction with $CHCl_3$, drying, and solvent removal gave the phenolic products as an approximate 1:1 mixture of **3a** and **3b**. Fractional crystallization alternately from benzene and $CH_3CN$ gave pure samples of the two isomers: **3a**, 1.5 g, mp 124.5–126° ($CH_3CN$); **3b**, 3.7 g, mp 159–160° (benzene), nmr ($CDCl_3$) $\delta$ 4.10 (s, $-OCH_3$), 6.22 (s, OH), 7.25 (s, $H_4$), 7.38 (t, $J$ = 8 Hz, $H_6$), 8.0 (d of d, $J$ = 2, 8 Hz), $H_5$), 8.18 (s, $H_1$), 8.20 (d of d, $J$ = 2, 8 Hz, $H_7$).

*Anal.* Calcd for $C_{11}H_9NO_4$: C, 60.27; H, 4.13; N, 6.39. Found: C, 60.32; H, 4.29; N, 6.40.

**2-Isopropoxy-3-methoxy-5-nitronaphthalene (4).** To 5 g of **3a** in 10 ml of DMF was added 10 g of anhydrous $K_2CO_3$.[8] Isopropyl bromide (10 ml) was added and the mixture was heated at 100°. After 2.5 hr the red color faded and was replaced by a yellow precipitate. The mass was poured into water and extracted with $CHCl_3$. The organic layer was extracted several times with water to remove the DMF, then dried and evaporated. Recrystallization of the residue from ethanol yielded 5.5 g (92%) of **4**: mp 109–110°; nmr ($CDCl_3$) $\delta$ 1.48 [d, $J$ = 6 Hz, $-CH(CH_3)_2$], 4.05 (s, $-OCH_3$), 4.78 [septet, $J$ = 6 Hz, $-CH(CH_3)_2$], 7.23 (s, $H_1$), 7.43 (t, $J$ = 8 Hz, $H_6$), 7.95 (d of d, $J$ = 2, 8 Hz, $H_5$), 8.08 (s, $H_4$), 8.18 (d of d, $J$ = 2, Hz, $H_7$); uv (EtOH) $\lambda_{max}$ 357 nm(log $\epsilon$ 3.75), 260 (sh) (4.04), 223 (4.79); ir ($CHCl_3$) 1510 and 1339 $cm^{-1}$ ($NO_2$).

*Anal.* Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.78; N, 5.36. Found: C, 64.68; H, 5.58; N, 5.31.

**2-Isopropoxy-3-methoxy-5-aminonaphthalene (5).** The general procedure[9] of Dewar and Mole was used. Ethanol (100 ml), hydrazine (5 ml), 4 (5.0 g), and 10% Pd/C (0.5 g) were heated on a steam bath for 1 hr. Filtration through a filter cell removed the Pd/C and evaporation of the ethanol and hydrazine with the aid of benzene gave 4.4 g (99%) of a viscous oil which, after standing overnight, contained a few tiny crystals. Addition of ether induced complete crystallization. Sublimination gave an analytical sample: mp 88–89°; nmr ($CDCl_3$) $\delta$ 1.37 [d, $J$ = 6 Hz, $-CH(CH_3)_2$], 3.81 (s, $-OCH_3$), 3.91 (broad s, $-NH_2$), 4.63 [septet, $J$ = 6 Hz, $-CH(CH_3)_2$], 6.55 (d of d, $J$ = 4, 5 Hz, 1 H), 6.95–7.18 (m, 4 H); uv (EtOH) $\lambda_{max}$ 308 nm (log $\epsilon$ 3.48), 254 (4.57), 241 (4.36), 222 (4.52); ir ($CHCl_3$) 3470 and 3395 $cm^{-1}$ ($NH_2$).

*Anal.* Calcd for $C_{14}H_{17}NO_2$: C, 72.72; H, 7.36; N, 6.06. Found: C, 72.45; H, 7.51; N, 5.89.

**2-Bromo-4,5-dimethoxybenzal-2′-isopropoxy-3′-methoxy-5-naphthylamine (6b).** A 100-ml benzene solution of **5** (4.0 g) and o-bromoveratraldehyde (4.24 g) was refluxed with a Dean-Stark trap until water evolution ceased. Removal of the benzene gave a yellow solid. Trituration with ether and filtration yielded 7.45 g (91%) of **5**, mp 150–152°. An analytical sample crystallized from ethyl acetate had mp 153–154°; nmr ($CDCl_3$) $\delta$ 1.46 [d, $J$ = 6 Hz, $-CH(CH_3)_2$], 3.96 (s, $OCH_3$), 4.06 (s, 2-$OCH_3$), 4.76 [septet, $J$ = 6 Hz, $-CH(CH_3)_2$], 6.90–7.60 (m, 5 H), 7.70 (s, 1 H), 8.0 (s, 1 H), 9.25 (s, –CH=N–); uv (EtOH) $\lambda_{max}$ 358 nm (log $\epsilon$ 3.86), 332 (3.91), 280 (4.20), 246 (sh) (4.73), 217 (4.79); ir ($CHCl_3$) 1621 $cm^{-1}$ (C=N).

*Anal.* Calcd for $C_{23}H_{24}BrNO_4$: C, 60.26; H, 5.27; N, 3.05. Found: C, 60.09; H, 5.17; N, 2.75.

**2-Isopropoxy-3,8,9-trimethoxybenzo[*c*]phenanthridine (7).** Cyclization of 6 was by the method of Kessar.[3] To a suspension of sodium amide (from 2.10 g of Na) in liquid ammonia was added 7.0 g of **6b** as a finely pulverized powder. After 0.5 hr, ammonium chloride was added until the red-brown color of the ammonia changed to yellow. Work-up of the residue after evaporation of the $NH_3$ with $CHCl_3$ and water gave, after drying and evaporation of the organic layer, a dark yellowish-brown oil. Addition of 200 ml of ethanol and boiling on a steam bath caused precipitation of a yellow solid. Filtration yielded 1.38 g (24%) of **7**, mp 264–266°. An analytical sample crystallized from $CH_3NO_2$ had mp 270–272°; nmr ($CD_3CO_2D$) $\delta$ 1.49 [d, $J$ = 6 Hz, $CH(CH_3)_2$], 4.09 (s, $OCH_3$), 4.13 (s, $OCH_3$), 4.24 (s, $OCH_3$), 4.90 [septet, $J$ = 6 Hz, $-CH(CH_3)_2$], 7.41 (s, 1 H), 7.67 (s, 1 H), 7.87 (s, 1 H), 7.98 (d, $J$ = 9 Hz, 1 H), 8.22 (s, 1 H), 8.29 (d, $J$ = 9 Hz, 1 H), 9.47 (s, 1 H); uv (EtOH) $\lambda_{max}$ 328 nm (log $\epsilon$ 4.04), 310 (sh) (4.36), 285 (4.80), 275 (4.80); ir ($CHCl_3$) 1623 $cm^{-1}$ (–C=N–).

*Anal.* Calcd for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71. Found: C, 73.05; H, 6.24; N, 3.74.

**2-Hydroxy-3,8,9-trimethoxybenzo[*c*]phenanthridine (8).** To a solution of **7** (200 mg) in 15 ml of HOAc was added 1 ml of 48% HBr. After heating for 3 hr, tlc indicated the absence of **7**. The mixture was poured into water, neutralized to pH 8, and extracted with $CHCl_3$. Evaporation of the dried solvent gave 160 mg (90%) of a tan solid. Crystallization from EtOAc gave a sample: mp 274–276°; nmr[2] (DMSO-$d_6$) $\delta$ 4.05 (s, $OCH_3$), 4.12 (s, $OCH_3$), 4.17 (s, $OCH_3$), 7.38 (s, $H_1$), 7.70 (s, $H_7$ or $H_{10}$), 7.86 (d, $J$ = 9 Hz, $H_{12}$), 8.15 (s, $H_7$ or $H_{10}$), 8.55 (d, $J$ = 9 Hz, $H_{11}$), 8.68 (s, $H_4$), 9.35 (s, $H_6$); uv (EtOH) $\lambda_{max}$ 228 nm (log $\epsilon$ 4.21), 27 (5.02), 283 (5.03), 315 (4.45); ir ($CHCl_3$) 3510 (OH), 1624 $cm^{-1}$ (C=N).

**Fagaronine Methosulfate (1c).** A 400-mg sample of **7** was heated at 180° in 8 ml of nitrobenzene and 4 ml of xylene. Dimethyl sulfate (1 ml) was added down the condenser. The mixture darkened immediately and heating was continued for 7 min. After cooling, ether was added and the precipitate (380 mg) was collected by

filtration. An nmr spectrum in DMSO-$d_6$ indicated approximately 70% alkylation and that the isopropoxy group was still present. The entire sample was reexposed to the above reaction conditions. After heating for 10 min, the mixture was allowed to cool. The precipitate of about 200 mg was collected by filtration and shown by nmr to be a 1:1 mixture of **8** and **1c**. The filtrate was added to 25 ml of ether and the brownish precipitate was collected (150 mg). Tlc analysis indicated the absence of any of the free base **8**. Recrystallization of this material from methanol gave 95 mg of pure **1c**: mp >350° dec, softens at 220°; nmr[12] (DMSO-$d_6$) $\delta$ 3.77 (s, $-OSO_3CH_3$), 4.08 (s, $OCH_3$), 4.15 (s, $OCH_3$), 4.26 (s, $OCH_3$), 5.03 (s, $NCH_3$), 7.63 (s, $H_1$), 7.97 (s, $H_7$), 8.23 (s, $H_4$), 8.25 (d, $J$ = 9 Hz, $H_{12}$), 8.35 (s, $H_{10}$), 8.85 (d, $J$ = 9 Hz, $H_{11}$), 9.99 (s, $H_6$).

*Anal.* Calcd for $C_{22}H_{23}NO_8S \cdot H_2O$: C, 55.11; H, 5.22; N, 2.92. Found: C, 54.97; H, 5.04; N, 2.97.

**Fagaronine Chloride (1a).** The exchange of counterions was by the method of Zee Cheng and Cheng.[10] In an 8% aqueous NaCl solution (12 ml) was suspended 50 mg of **1c**. After stirring for 0.5 hr at room temperature, filtration gave 36 mg (88%) of **1a**, mp 198–200°, with resolidification and remelting at 260–261° (lit.[1] 202°, 255°). The nmr, ir, uv, and base-shifted uv were identical with those of an authentic sample.[2]

**Acknowledgment.** This work was supported in part by Grants CA 13648 from the National Cancer Institute and GM 15425 from the National Institute of General Medical Sciences, National Institutes of Health.

**Registry No.**—**1a**, 52259-64-0; **1c**, 52259-66-2; **2**, 7311-22-0; **3a**, 24309-45-3; **3b**, 52259-67-3; **4**, 52259-68-4; **5**, 52259-69-5; **6b**, 52259-70-8; **7**, 52259-71-9; **8**, 52259-72-0; *o*-bromoveratraldehyde, 5392-10-9.

## References and Notes

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(2) During the course of this work, we were informed (M. Tin-Wa, C.L. Bell, C. Bevelle, H.H.S. Fong, and N.R. Farnsworth, *J. Pharm. Sci.*, in press) that fagaronine had been converted to the *N*-demethyl base (identical with **8**) whose spectral properties clearly established the fagaronine as **1a**. We thank Dr. Farnsworth for a preprint of his work and for a standard sample of fagaronine.
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# 7-Hydroxymyoporone, a New Toxic Furanosesquiterpene from Mold-Damaged Sweet Potatoes

Leo T. Burka,* Robert M. Bowen, and Benjamin J. Wilson

*Center in Environmental Toxicology, Vanderbilt University School of Medicine, Nashville, Tennessee 37232*

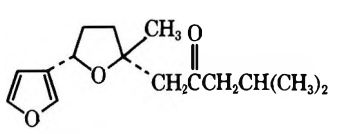
Thomas M. Harris

*Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37235*

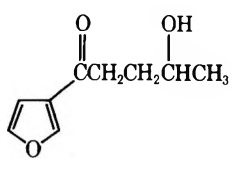
*Received May 21, 1974*

A new stress metabolite of the sweet potato has been isolated and identified as 1-(3-furoyl)-4,8-dimethyl-7-hydroxy-1,6-nonanedione (7-hydroxymyoporone). The structure assignment was based on spectral data and transformation to 3-methyl-5-(3-furoyl)pentanoic acid. The degradation product was synthesized by a reaction sequence involving the acylation of methyl 3-methyl-5-oxocyclopentanecarboxylate with 3-furoyl chloride and cleavage of the resulting diketo ester with aqueous base. The toxicity of 7-hydroxymyoporone is similar to that of the well-known sweet potato phytoalexin, ipomeamarone.

Sweet potatoes, when infected by fungus or when subjected to certain other stress conditions, elaborate numerous furanoid metabolites, all of apparent terpenoid origin.[1] Ipomeamarone was the first of these to be isolated



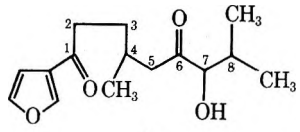
ipomeamarone



4-ipomeanol

and identified.[2] The compound is hepatotoxic and is usually the most abundant of the furan metabolites. We have been particularly interested in a group of 1,4-dioxygenated 1-(3-furyl)pentanes, also isolated from mold-damaged sweet potatoes.[3] These compounds, especially 1-(3-furyl)-4-hydroxy-1-pentanone (4-ipomeanol), show a marked specific pulmonary toxicity in laboratory animals.

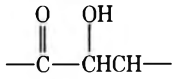
As part of our continuing investigation of the phytoalexins of the sweet potato, we have isolated a new furanosesquiterpene which has been identified as 1-(3-furyl)-7-hydroxy-4,8-dimethyl-1,6-nonanedione (7-hydroxymyoporone, **1**).[4] The compound was obtained from sweet potato slices that had been incubated with cultures of *Ceratocystis fimbriata*.[5] The isolation involved extraction into ethyl acetate and chromatography on silica gel followed by preparative glpc of the partially purified material, after treatment with a trimethylsilylating reagent. The trimethylsilyl ether was cleaved with tetra-*n*-butylammonium fluoride[6] to give the pure metabolite in a yield of 20 mg/kg of sweet potatoes (wet weight).



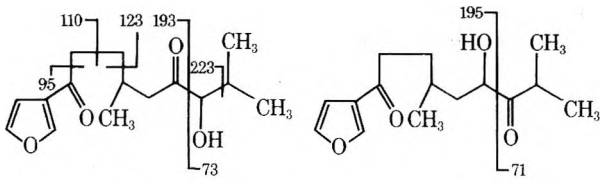
**1**

The empirical formula, $C_{15}H_{22}O_4$, of **1** was established from the elemental analysis and from the parent ion at *m/e* 266 in the mass spectrum. The 1-(3-furyl)-1-alkanone moiety was indicated by the characteristic pmr signals ($\delta$ 6.72, 7.41, and 8.00) for the furyl protons[7] and by the conjugated carbonyl stretching frequency (1670 $cm^{-1}$) and the furyl absorptions (3130, 1560, 1500, and 870 $cm^{-1}$) in the infrared spectrum and further substantiated by the ion at *m/e* 95 (3-furyl–C≡$O^+$) in the mass spectrum. The presence of a nonconjugated ketone and a hydroxyl group was also inferred from the infrared spectrum.

Compound **1** gave a positive test with Tollen's reagent which suggested the presence of an acyloin structure, since the spectra provided no evidence for the presence of any other easily oxidized group. Pmr spectra limited the possible locations for the acyloin group. In the spectrum of the trimethylsilyl ether of **1**, the methinyl proton appeared as a doublet at $\delta$ 3.55; after cleavage of the silyl ether this signal was transformed into a less clearly defined multiplet at $\delta$ 4.01. The partial structure

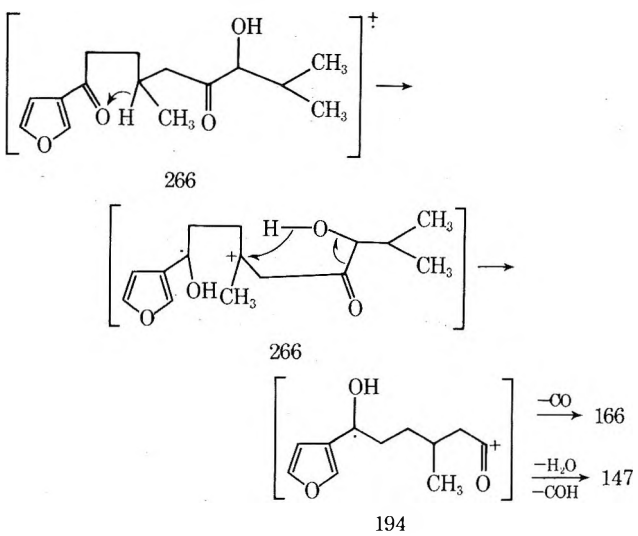


is indicated for **1**. If a normal sesquiterpene skeleton, such as that in ipomeamarone, can be assumed, then the keto and hydroxyl groups of the acyloin must respectively be at positions 2 and 3, 6 and 5, or 6 and 7. The first of these possibilities can be immediately eliminated by the presence of an intense ion at *m/e* 110 (3-furyl–C(OH)=$CH_2$·$^+$) in the mass spectrum. The third possibility, but not the second, was in accord with the mass spectrum. Interpretation was complicated by an apparent isomerization of **1** into acyloin **2** in the mass spectrometer. Such a rearrangement of $\alpha$-ketols in the mass spectrometer has previously been observed.[8] Assignments for major fragment ions from **1** and **2** are shown below.

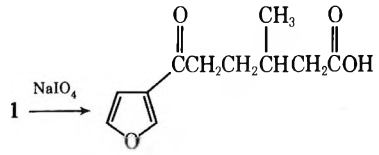


**1** **2**

Ions at *m/e* 194, 166, and 147 are thought to result from a cleavage between carbons 6 and 7 concurrent with a hydrogen shift and followed by further fragmentation.

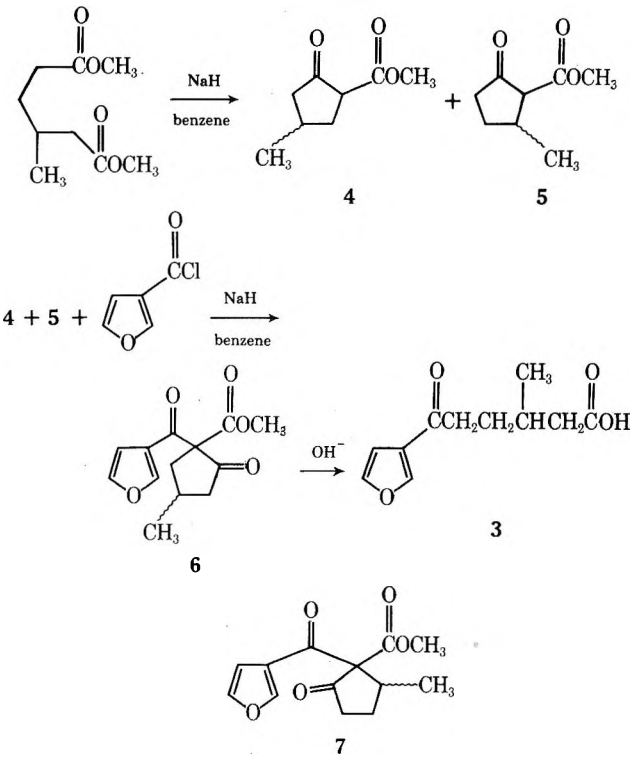


Further evidence for the proposed structure **1** was obtained by cleavage of the acyloin with sodium periodate. Carboxylic acid **3** obtained from the oxidation gave a parent ion at *m/e* 210 in the mass spectrum, suggesting the empirical formula $C_{11}H_{14}O_4$, as would be expected with oxidative cleavage between positions 6 and 7. The presence in **3** of the 1-(3-furyl)-1-alkanone moiety and the carboxylic acid group was substantiated by pmr and infrared spectra.



**3**

Unequivocal proof of the structure of **3** was obtained by independent synthesis. A Dieckmann cyclization of the dimethyl ester of 3-methyladipic acid gave a 2.5:1 mixture of keto esters **4** and **5**. Useful quantities of pure **4** could not be



obtained by distillation or chromatography, but acylation of the mixture with 3-furoyl chloride gave **6** which is the acylation product of **4**. A small quantity of isomer **7** may have been formed, but it was not detected. The difference in rate of acylation of **4** and **5** is ascribed to steric hindrance caused by the *C*-methyl group in **5**. The fact that the mixture of unreacted **4** and **5** recovered from the reaction was significantly enriched in **5** is consistent with this difference in reactivity. In a similar reaction sequence beginning with a Dieckmann condensation of the diethyl ester of 3-methyladipate followed by alkylation with ethyl bromoacetate, Sorm reported finding only products resulting from alkylation of the ethyl ester homolog of **4**.[9]

The pmr spectrum of **6** suggested that it was a mixture of diastereoisomers, but supported its gross structure. The mass spectrum provided further support; a strong ion at *m/e* 69 is assigned as $CH_3CH{=}CHC{\equiv}O^+$, derived from a fragmentation of the cyclopentanone ring.[10] Loss of this fragment is consistent with structure **6** but not **7**.

Reaction of **6** with aqueous base at room temperature gave a 20% yield of racemic **3** as a crystalline product. The material could not be compared by mixture melting point

with the optically active material obtained by oxidation of **1**, but their identity was otherwise established by spectroscopic (ir, pmr, mass spectral) comparison.

In preliminary studies 7-hydroxymyoporone was found to be hepatotoxic to mice upon intraperitoneal administration of 200–250 mg/kg doses.

## Experimental Section

The infrared spectra were obtained using a Perkin-Elmer Model 621 spectrophotometer. Pmr spectra were obtained using a JEOL JMN-MH-100 spectrophotometer with tetramethylsilane (TMS) as internal standard. Cmr spectra were obtained using a Varian XL-100 equipped with a Transform Technology, Inc., TT-100 Fourier transform accessory; TMS was used as the internal standard. Mass spectra were obtained using an LKB gas chromatograph–mass spectrometer, Type 9000. Ultraviolet spectra were obtained using a Cary Model 14 recording spectrophotometer. Gas–liquid phase chromatography (glpc) was carried out using a Aerograph Model A-700 gas chromatograph. Optical rotatory dispersion was measured using a Cary Model 60 spectropolarimeter. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are corrected.

**Bioproduction of 7-Hydroxymyoporone (1).** Sweet potatoes (11 kg), washed with sodium hypochlorite solution, cut into 1-cm thick slices, and coated with a 15% mannitol solution, were inoculated with *Ceratocystis fimbriata* grown in a potato starch–sucrose medium. Six days after inoculation, the slices were frozen with Dry Ice and ground in a grain mill. The ground material was extracted with ethyl acetate and the ethyl acetate solution was dried and concentrated to yield 23.8 g of brown oil. The oil was placed on a 5-cm diameter column containing 125 g of silica gel (Matheson Coleman and Bell, Grade 62, 60–200 mesh) and eluted first with hexane, then with ether–hexane (1:19). The ether–hexane eluent contained 2.0 g of a yellow oil which, according to glpc, contained three major components in approximately 1:3:10 ratio. Silylation of 700 mg of the mixture with Tri-Sil/BSA (Pierce Chemical Co.) and preparative glpc using a 2.5 m × 1 cm glass column containing 10% UC-W98 on 80/100 Chromosorb Q operated at 205° and 125 ml/min helium flow produced 140 mg of the trimethylsilyl derivative of the major component: pmr ($CCl_4$) $\delta$ 0.10 (s, 9 H), 0.92 (m, 9 H), 1.58 (m, 2 H), 1.95 (m, 2 H), 2.37 (m, 2 H), 2.62 (t, $J$ = 7 Hz, 2 H), 3.55 (d, $J$ = 7 Hz, 1 H), 6.59 (m, 1 H), 7.27 (m, 1 H), and 7.82 (m, 1 H); *m/e* 338 ($M^+$).

The purified silyl ether (107 mg) was dissolved in tetrahydrofuran (THF) and treated with 1 ml of 1 *N* tetra-*n*-butylammonium fluoride in THF at 0° for 10 min. The THF was removed by evaporation in a stream of nitrogen and the residue was placed on a small column of deactivated silica gel and eluted with ether–hexane (1:1). Evaporation of the solvent gave 75 mg of 1 as a colorless oil: $[\alpha]^{26}D$ +12.3° (*c* 0.64, $CH_3OH$); ir ($CHCl_3$) 3480, 3130, 2955, 2865, 1705, 1670, 1560, 1500, 1460, 1150, and 870 $cm^{-1}$; pmr ($CDCl_3$) $\delta$ 0.72 (d, $J$ = 7 Hz, 3 H, $CH_3$), 0.96 (d, $J$ = 7 Hz, 3 H, $CH_3$), 1.12 (d, $J$ = 7 Hz, 3 H, $CH_3$), 1.50–1.85 (m, 2 H, 4- and 8-CH), 1.95–2.30 (m, 2 H, 3-$CH_2$), 2.41 (m, 2 H, 5-$CH_2$), 2.78 (t, $J$ = 7 Hz, 2 H, 2-$CH_2$), 3.37 (broad singlet, 1 H, OH), 4.01 (m, 1 H, 7-CH),[11] 6.72 (m, 1 H, 4-furyl), 7.41 (m, 1 H, 5-furyl), and 8.00 (m, 1 H, 2-furyl); uv ($CH_3OH$) 213 nm ($\epsilon$ 6600) and 253 (3000); major mass spectral peaks at *m/e* (rel intensity) 266 (2), 233 (2), 195 (60), 194 (71), 193 (27), 166 (83), 147 (85), 137 (38), 123 (77), 110 (69), 95 (100), 73 (38), 71 (19), and 55 (58); cmr ($CCl_4$) 15.1 (methyl at C-4), 19.8 (methyls at C-8), 28.6 (C-8), 30.8 (C-3 or C-4), 30.9 (C-4 or C-3), 37.8 (C-2), 45.1 (C-5), 81.0 (C-7), 108.8 (4-furyl), 127.7 (3-furyl), 143.9 (5-furyl), 147.0 (2-furyl), 193.4 (C-1), and 211.3 ppm (C-6).

*Anal.* Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.88; H, 8.42.

**Periodate Oxidation of 1.** Sodium periodate (75 mg, 0.35 mmol) dissolved in 4 ml of 1 *N* sulfuric acid was added to 90 mg (0.33 mmol) of 1 in 5 ml of methanol. After heating at 40° for 15 min, the solution was cooled and extracted with ether. Extraction of the ether with sodium bicarbonate, followed by acidification and ether extraction of the aqueous phase, then drying and concentrating the ether solution gave 3-methyl-5-(3-furoyl)pentanoic acid (**3**). Recrystallization from hexane gave colorless needles: mp 47–48°; ir ($CCl_4$) 3360–2790, 3145, 2965, 1710, 1680, 1560, 1510, 1455, 1410, 1390, 1380, 1295, 1160, and 875 $cm^{-1}$; pmr ($CDCl_3$) $\delta$ 1.01 (d, $J$ = 7 Hz, 3 H, $CH_3$), 1.54–2.20 (m, 3 H), 2.31 (three-line multiplet with 6 Hz separation between lines, 2 H, 2-$CH_2$), 2.78 (t, $J$ = 7 Hz, 2 H, 5-$CH_2$), 6.76 (m, 1 H, 4-furyl), 7.40 (m, 1 H, 5-furyl), 8.02 (m, 1 H, 2-furyl), and 9.60 (broad singlet, 1 H, $CO_2H$); major mass spectral peaks at *m/e* (rel intensity) 210 (2), 164 (2), 151 (1), 150 (1), 123 (3), 111 (1), 110 (28), 96 (6), 95 (100), and 67 (9). The optical rotatory dispersion was obtained in the 275–400-nm region: $[\alpha]_{325}$ −70° (c 0.039, $CH_3OH$).

**Synthesis of 3.** Dimethyl 3-methyladipate (5 g, 27 mmol), sodium hydride (50% oil dispersion, 5 g, 104 mmol), benzene (75 ml), and 5 drops of methanol were heated at reflux for 1 hr. After this time the mixture was cooled and poured into 100 g of ice and 15 ml of acetic acid. The layers were separated and the aqueous layer was extracted with ether. The combined organic layers were washed with water, saturated sodium bicarbonate, and saturated sodium chloride, then dried and concentrated. The residue was distilled to give 2.9 g (70% yield) of a colorless liquid: bp 110–111° (14 Torr) [lit.[12] bp 110° (15 Torr)]; pmr ($CCl_4$) $\delta$ 1.1–1.3 (m, apparently a pair of doublets superimposed on a doublet, 3 H), 1.6–2.8 (m, 5 H), 3.0–3.4 (m, 1 H), and 3.70–3.85 (m, 3 H). On the basis of integration of the signals at $\delta$ 1.1–1.3 the material was estimated to be a 2.5:1 mixture of methyl 3-methyl-5-oxocyclopentanecarboxylate (**4**) and methyl 2-methyl-5-oxocyclopentanecarboxylate (**5**).

The mixture of keto esters **4** and **5** (2.5 g, 16 mmol) was added slowly to 0.5 g (21 mmol) of sodium hydride suspended in benzene and then stirred at room temperature for 30 min. After this time 3-furoyl chloride, prepared from 2.0 g (18 mmol) of 3-furoic acid and 5 ml of oxalyl chloride, was added and the reaction mixture was refluxed for 1 hr. The mixture was allowed to cool and then filtered. Chromatography (silica gel, ether–hexane, 1:49) of the residue obtained from concentration of the filtrate produced 1.0 g of unreacted **4** and 5 and 1.4 g of 2-(3-furoyl)-2-carbomethoxy-4-methylcyclopentanone (**6**): ir (neat) 3150, 2960, 1765, 1730, 1670, 1560, 1510, 1455, 1435, 1305, 1285, 1265, 1240, 1160, 1145, 1035, 875, 865, and 735 $cm^{-1}$; pmr ($CDCl_3$) $\delta$ 0.96 (d, $J$ = 6 Hz, 3 H, 4-$CH_3$), 1.85–3.10 (m, H), 3.71 (s, 3 H, $OCH_3$), 6.71 (m, 1 H, 4-furyl), 7.39 (m, 1 H, 5-furyl), and 8.08 (m, 1 H, 2-furyl); major mass spectral peaks at *m/e* (rel intensity) 250 (5), 181 (20), 149 (17), 95 (100), 69 (9), and 39 (18).

*Anal.* Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.63. Found: C, 62.30; H, 5.43.

Diketo ester **6** (1.1 g, 4.4 mmol) was suspended in 10 ml of water containing 0.6 g (10 mmol) of sodium hydroxide and stirred at 40°. After 3 hr the mixture was extracted with ether, then acidified and again extracted with ether. The second ether extract was dried and concentrated to give 0.92 g of acidic material. Two recrystallizations from hexane produced 0.19 g (20% yield) of **3** as white needles: mp 58–59°; ir ($CHCl_3$) 3370–2850, 3150, 2965, 2935, 1710, 1680, 1560, 1510, 1460, 1410, 1390, 1380, 1295, 1160, and 875 $cm^{-1}$; pmr ($CDCl_3$) $\delta$ 1.02 (d, $J$ = 7 Hz, 3 H, $CH_3$), 1.40–2.20 (m, 3 H), 2.31 (three-line multiplet with 6 Hz separation between lines, 2 H, 2-$CH_2$), 2.82 (t, $J$ = 7 Hz, 2 H, 5-$CH_2$), 6.75 (m, 1 H, 4-furyl), 7.41 (m, 1 H, 5-furyl), 8.03 (m, 1 H, 2-furyl), and 10.9 (broad singlet, 1 H, $CO_2H$); major mass spectral peaks at *m/e* (rel intensity) 210 (3), 164 (2), 151 (1), 150 (2), 123 (4), 111 (4), 110 (53), 96 (6), 95 (100), and 67 (5).

*Anal.* Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 63.02; H, 6.58.

About 20 mg of 3-furoic acid (mp 118–121°) was obtained from the hexane-insoluble material by recrystallization from benzene.

**Acknowledgment.** This work was supported by Training Grant 5 T01 ES00112-7 and Center in Toxicology Grant ES00267 to Vanderbilt University from the U. S. Public Health Service. We are indebted to Dr. J. D. Puett for the ORD determination.

**Registry No.**—**1**, 52259-61-7; **3**, 52259-62-8; **6**, 52259-63-9.

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# The Structure of Catechinic Acid. A Base Rearrangement Product of Catechin

Karl D. Sears,* R. L. Casebier, and H. L. Hergert

*Contribution No. 135 from the Research Divisons of ITT Rayonier Inc., Shelton, Washington 98584*

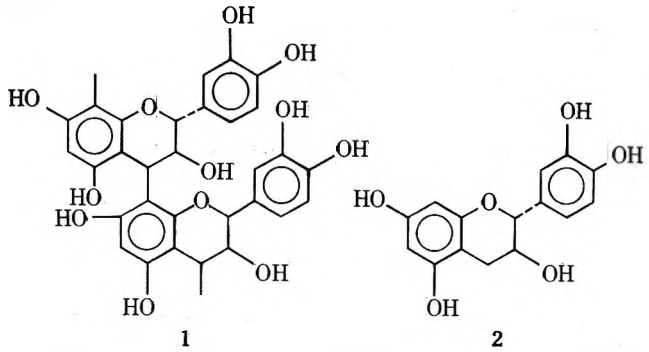
George H. Stout and Larry E. McCandlish

*Department of Chemistry, University of Washington, Seattle, Washington 98105*

*Received June 17, 1974*

Catechinic acid, a base rearrangement product of the flavanol catechin, has been shown by both chemical and X-ray evidence to be the enol of 6-(3,4-dihydroxyphenyl)-7-hydroxy-2,4,9-bicyclo[3.3.1]nonatrione (**5**). The structure of this product is relevant to the transformation which occurs to polyflavanoids in wood and bark when similarly treated with base to give "bark phenolic acids."

Polyphenolic polymers derived from substituted flavan-3-ols or flavan-3,4-diols occur in all species of coniferous bark investigated thus far and in the heartwood and bark of a significant number of deciduous trees.[1] Part of this polymeric material cannot be extracted from wood or bark by inert solvents such as ethanol or hot water but can only be isolated by extraction with hot, dilute aqueous base or alkaline bisulfite solution.[2] Since the base-isolated product[3] shows the analytical properties of a carboxylic acid with a mass of ~800 Daltons/–COOH,[4] the question arose as to whether carboxyl groups are present in the polymer *in situ*[4,5] or generated through alkaline rearrangement and/or oxidation of a flavanol unit during the extraction procedure.[6] Catechin (**2**) is an excellent model for the principal structural unit **1** in conifer bark polyphenolic polymers.[7]



**1** **2**

Treatment of **2** with base could be expected to provide insight into any corresponding reactions taking place in the polymer.

Treatment of (+)-catechin (**2**) with refluxing 0.5% NaOH for 45 min gave a >90% yield of an optically active amorphous acidic material which we have named catechinic acid (CA). Combustion analyses suggested the formula $C_{15}H_{16}O_7$, *i.e.*, a hydrated catechin, but analyses of derivatives favored $C_{15}H_{14}O_6$, with a mole of water of hydration. Similarly, crystalline material obtained from acetone contained acetone of crystallization. Titration showed behavior consistent with a monocarboxylic acid ($pK_a \sim 4.3$).

Methylation of CA with $Me_2SO_4$ in acetone yielded two neutral derivatives, $C_{18}H_{20}O_6$. Both displayed nmr signals indicating three methoxyl groups, and the names trimethylcatechinic acid (TMC) and trimethylisocatechinic acid (TMIC) were assigned.

The nmr spectrum of TMC showed three aromatic proton signals as a multiplet $\tau$ 3.1–3.4. In a 220-MHz spectrum these appeared as two doublets ($J \sim 10$ Hz) and a singlet. This observation, together with the appearance of two of the methoxyl signals at a normal aromatic ether value of $\tau$ 6.14, indicated that the 3,4-dihydroxyphenyl ring of catechin had survived intact. The remainder of the spectrum, however, was inconsistent with the presence of a phloroglucinol system or indeed with any additional aromatic protons. The analysis of KOH fusion products from CA showed the absence of phloroglucinol and the presence of pyrocatechol and protocatechuic acid. Thus, an extensive modification of the parent structure was indicated.

Of the six oxygen atoms, two can be assigned as above to phenolic groups. One was found to be a reactive carbonyl (discussed below) with an ir absorption at 1740 $cm^{-1}$ in TMC, and a fourth is a secondary hydroxyl as shown by an –OH stretch in the ir (3580 $cm^{-1}$) and by an $\alpha$-proton signal at $\tau$ 5.55 which shifts to 4.28 on acetylation. The remaining oxygens were presumably associated with the acid function and in TMC led to a methoxyl signal at $\tau$ 6.41 and a carbonyl band at 1650 $cm^{-1}$.

Although it has been generally assumed that the acidity of bark phenolic acids reflects the presence of carboxyl groups, the carbonyl absorption at 1650 $cm^{-1}$ is inconsistent with a simple methyl ester. The value agrees, however, with those reported for enol ethers derived from $\beta$ diketones. Comparison with literature values for model systems showed excellent agreement in the ir[8] (1650 *and* 1600 $cm^{-1}$), uv[9] [CA enolate anion at 285 nm ($\epsilon$ 19,300), methyl ether at 232 (12,300) and 260 (14,000)], and nmr[10] ($\alpha$ H of

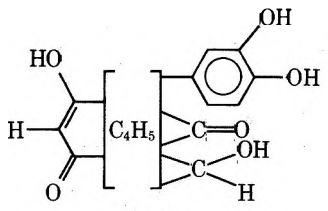
methyl ether $\tau$ 4.25, 1 H singlet). This view allowed the formulation of a partial structure of CA as **3** and additionally accounted for the formation of two very similar trimethylation products in terms of methylation at either end of an unsymmetrical anion.

The reactivity of the isolated carbonyl function was shown by the failure of diazomethane methylation of CA to give either of the trimethyl ethers described above. Instead, a permethylated product, $C_{19}H_{22}O_6$, was obtained which contained an epoxide ring resulting from methylene addition to the carbonyl. The same product was prepared upon diazomethane treatment of trimethylcatechinic acid. Similarly, mild hydrogenation of catechinic acid over palladium yielded a diol which could be trimethylated and then diacetylated.

The relationships among the six unassigned protons were deduced by examination of the nmr spectra of these derivatives. The single proton ($H_D$) $\alpha$ to the hydroxyl group appeared routinely as a six-line signal derived from a triplet ($J$ = 11–12 Hz) and a doublet ($J$ = 5 Hz). The spin constants correspond to the presence of one adjacent equatorial ($H_C$) and two axial ($H_B$, $H_E$) protons. Three 1 H signals at higher field also showed large coupling constants: $H_E$ $\tau$ 6.90 (dd, $J$ = 11, 4 Hz), $H_C$ at 7.36 (ddd, $J$ = 12, 5, 4 Hz), and $H_B$ at 8.02 (td, $J$ = 12, 4 Hz). The shifts and coupling constants are consistent with assignment of $H_E$ and $H_B$ as the axial protons adjacent to $H_D$, while $H_C$ is the equatorial one, also geminally coupled to $H_B$. The downfield position of $H_E$ required it to be benzylic and thus located the dimethoxyphenyl substituent.

The additional couplings of $H_B$, $H_C$, and $H_E$ indicated the presence of other proton(s) coupled with $J \sim 4$ Hz. These could be equated with an ill-resolved two proton signal at $\tau$ ~6.6, and, since this shifts upfield to ~7.2 following addition to the reactive carbonyl, it was ascribed to equatorial $\alpha,\alpha'$ substituents ($H_A$, $H_F$) on the ketone. Thus the remainder of the structure could be formulated as **4**.

Consideration of the partial structures **3** and **4** leads to a final structure **5** (or its enol tautomer) for CA. This formulation accounts for all of the spectral properties of the material and is reasonably derived from **2** by any of a number of base-catalyzed routes, of which that shown is only one possibility. The fact that the relative stereochemistry of CA corresponds to that of catechin might appear to favor a concerted anionic rearrangement, but, since the product is in the most stable conformation, no firm judgement can be made. Further studies on this point are being undertaken.

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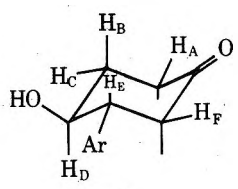


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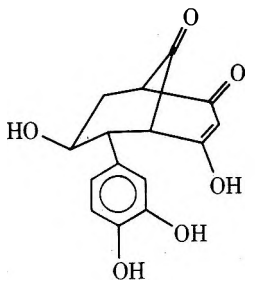


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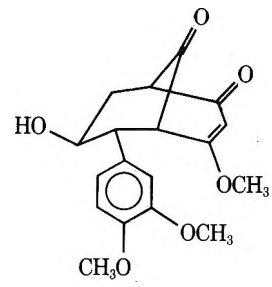
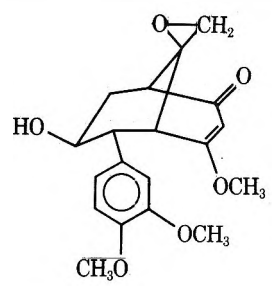
Methylation of the enolizable $\beta$ diketone system may potentially occur on either oxygen, as is shown by the concurrent formation of two trimethyl derivatives. An assignment of the structures may be made by noting that the nmr shifts of the enol ether protons are strikingly different in the two compounds. Examination of models suggests that the higher field signals (trimethylcatechinic acid, $\tau$ 6.41; *cf.* trimethylisocatechinic acid, $\tau$ 6.17) correspond to the structure in which the methoxyl is on the same side of the bridged ring as the aromatic substituent. This is oriented by steric forces so that the methoxyl lies above the aromatic plane and is embedded in the shielding cone produced by the ring current. Thus trimethyl catechinic acid has been assigned the structure **6**. Methylation by diazomethane




6

gives predominantly products with the high-field ether, and these have been assigned the corresponding structure.

The direction of addition to the bridge carbonyl and thus the stereochemistry of the products has not been proved unambiguously. We favor the structure **7** for permethylcatechinic acid, however, on the basis of the nmr spectrum of the diacetate prepared from the diol **8** formed by reduction

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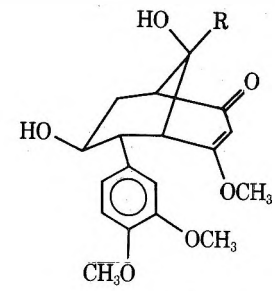



8, R = $CH_3$
9, R = H

of **7**. In this product the secondary acetate, like all the acetates in this series, shows its methyl signal at the high value of $\tau$ 8.2. This, like the corresponding upfield shift of the enol methyl ether, undoubtedly reflects the position of the methyl in the shielding cone of the phenyl group. The tertiary acetate, however, appears at $\tau$ 7.77, *i.e.*, has a significant downfield shift. This may be ascribed both to its axial orientation with respect to the cyclohexane ring[11] and to the fact that the mean position of the methyl is in the plane of the aromatic ring and is thus deshielded. The alternative orientation for the hydroxyl would place the acetate methyl above the plane of the enolic system and so should lead to increased rather than decreased shielding. The diacetate derived from the diol **9** obtained by hydrogenation and methylation of **5** shows the same shifts and presumably has the same stereochemistry.

To confirm the proposed structure a single-crystal X-ray structure determination on trimethyl catechinic acid (**6**) has been carried out. This study, the details of which will be reported elsewhere,[12] confirmed our deductions in all respects and showed the molecule represented in Figure 1. In particular, the phenyl ring is oriented approximately normal to the plane of the cyclohexanone, with the enol ether lying above it, as suggested above.

Although no studies have yet been carried out to com-

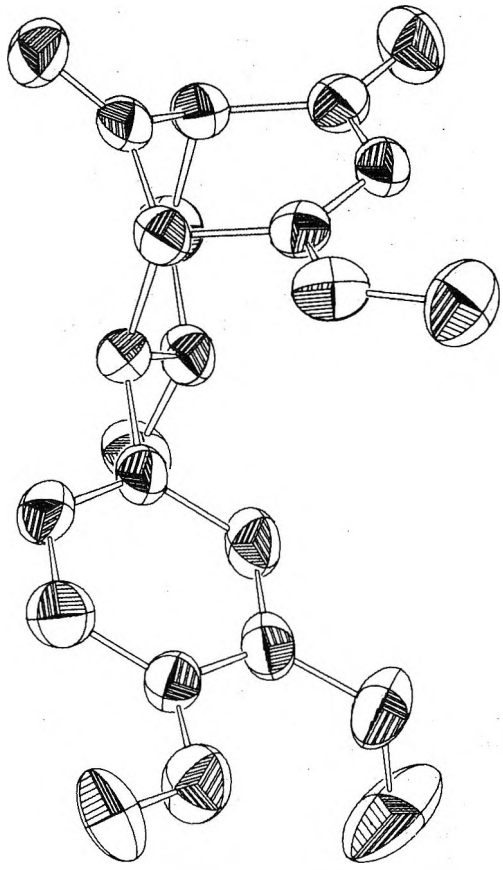
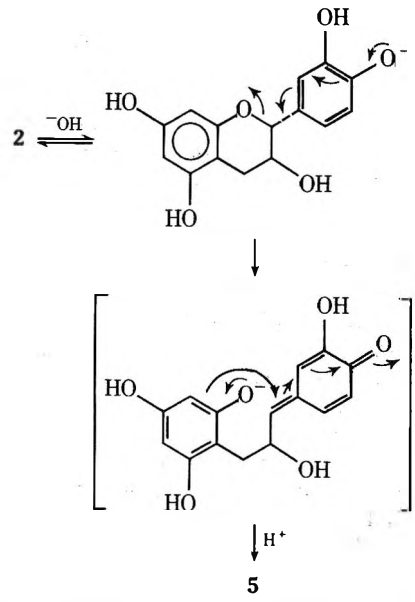


**Figure 1.** X-Ray structure of trimethylcatechinic acid.

pare **5** directly with "bark phenolic acids," the similarities of their physical properties, the known presence of catechin-derived units (**1**) in bark,[7] and the similarity of the conditions used to produce acidic products, all lead us to believe that **2** → **5** is a suitable model for the more complex



reaction. It may thus be suggested that the polymeric bark phenolic acids contain an enolic hydroxyl rather than a carboxyl group as previously postulated.[4]

## Experimental Section

Ir spectra were taken on a Perkin-Elmer Model 21 or on a Beckman Model IR-120 instrument. Nmr data were obtained from Sadtler Research Laboratories, Inc. (Varian A-60A or HA-100D) or were taken on a Varian T-60. The 220-MHz spectra were measured by the Varian Corporation as a courtesy. Uv spectra were measured on a Cary 11 MS. Mass spectral data were obtained by Morgan Schaffer Corp. on a Hitachi Perkin-Elmer RMU-6D. Combustion analyses were performed by A. Bernhardt, Elbach uber Engelskirchen, West Germany.

Column chromatography was carried out on Mallinckrodt silica gel, 200–325 mesh, and tlc on Brinkman silica gel G. Three solvent systems were used: A, 5:4:1 toluene–EtOAc–$HCO_2H$; B, 200:47:15:1 benzene–EtOH–$H_2O$–HOAc—upper phase; C, 9:1 EtOAc–MeOH + 1% HOAc.

**Preparation of Catechinic Acid (5).** (+)-Catechin (2.0 g) was added to a refluxing solution NaOH (1.0 g) in 200 ml of $H_2O$ in a three-necked flask supplied with a continual $N_2$ flush. After 45 min the reaction was cooled in ice, treated with IR-120 resin ($H^+$ form, 35 ml), and stirred for 1 hr. The resin was filtered off and the solution evaporated to dryness to give a light brown resinous product. This was dissolved in acetone (200 ml) and the solution concentrated *in vacuo* until precipitation occurred. The precipitate was filtered off to give 1.37 g of catechinic acid–acetone complex as a white crystalline solid: mp 168–170°; ir (KBr) 1745 (s), 1695 (s), 1610 (s), 1535 (m) $cm^{-1}$; uv ($H_2O$) 285 nm ($\epsilon$ 19,300). Evaporation of the acetone mother liquor gave 0.44 g of unsolvated catechinic acid, essentially the same on tlc comparison (solvent C).

A sample of catechinic acid purified by repeated precipitation from acetone with ether and dried at 75° (0.02 Torr) was a white amorphous powder, charring at 200–220°.

*Anal.* Calcd for $C_{15}H_{14}O_6 \cdot H_2O$: C, 58.44; H, 5.23; mol wt, 308. Found: C, 58.82, 58.87; H, 5.16, 5.28; mol wt, 311 (neut equiv).

**Trimethylation of Catechinic Acid.** Catechinic acid (500 mg), acetone (60 ml), $Me_2SO_4$ (1.4 ml), and $K_2CO_3$ (8.0 g) were refluxed overnight. Tlc (solvent B) showed predominantly two products. These were separated by multiple elution tlc to give 211 mg of trimethylcatechinic acid (more mobile) and 88 mg of the isomer.

**Trimethylcatechinic Acid (6).** Trimethylcatechinic acid crystallized from hexane–$CH_2Cl_2$ as white crystals: mp 193–194°; ir 3580 (w), 1740 (s), 1660 (s), 1600 (s), 1520 (s) $cm^{-1}$; uv (95% EtOH) 232 nm ($\epsilon$ 12,300), 260 (14,000); $[\alpha]^{25}D$ ($CHCl_3$, *c* 1.18 g/100 ml) +202°; nmr ($CDCl_3$ 220 MHz) $\tau$ 3.14 (d, 1), 3.30 (m, 2), 4.25 (s, 1), 5.55 (td, 1, $J$ = 11.5, 5.5 Hz), 6.11 (s, 3), 6.12 (s, 3), 6.41 (s, 3), 6.63 (m, 2), 6.90 (dd, 1, $J$ = 11, 4 Hz) 7.36 (ddd, 1, $J$ = 12, 5.5, 3.5 Hz), 8.02 (dd, 1, $J$ = 12, 4 Hz); mass spectrum (rel intensity) 332 (96), 288 (6), 260 (5), 257 (6), 191 (10), 181 (20), 165 (18), 151 (100), 137 (25).

*Anal.* Calcd for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07; *m/e* 332 (100), 333 (20.01), 334 (3.09). Found: C, 65.21, 65.19; H, 6.20, 5.95; *m/e* 332 (100), 333 (20.13), 334 (2.95).

Acetylation with $Ac_2O$ and NaOAc overnight in refluxing benzene yielded after preparative tlc (solvent B) the monoacetate: ir ($CHCl_3$) 1730 (s), 1650 (s), 1590 (s) $cm^{-1}$; uv (95% EtOH) 232, 259 nm; nmr ($CDCl_3$) $\tau$ 3.25 (s, 1), 3.34 (q, 2), 4.21 (s, 1), 4.28 (m, 1), 6.14 (s, 3), 6.16 (s, 3), 6.44 (s, 3), 6.65 (m), 7.20–8.15 (m), 8.21 (s, 3).

**Trimethylisocatechinic Acid.** Trimethylisocatechinic acid did not crystallize: ir ($CHCl_3$) 3570 (w), 1735 (s), 1655 (s), 1602 (s), 1515 (s) $cm^{-1}$; uv (95% EtOH) 230, 256 nm; nmr ($CDCl_3$) $\tau$ 3.23 (s, 1), 3.33 (m, 2), 4.28 (s, 1), 5.61 (td, 1, $J$ = 11.5, 5.5 Hz), 6.17 (s, 9), 6.60 (m, 2), 6.95 (dd, 1, $J$ = 11, 4 Hz), 7.35 (m), 8.00 (m); mass spectrum (rel intensity) 332 (100), 288 (29), 266 (29), 260 (16), 245 (11), 217 (15), 191 (27), 181 (9), 162 (11), 151 (86).

*Anal.* Calcd for $C_{18}H_{20}O_6$: *m/e* 332 (100), 333 (20.01), 334 (3.09). Found: *m/e* 332 (100), 333 (19.98), 334 (3.08).

Acetylation overnight with $Ac_2O$–NaOAc in refluxing benzene yielded the amorphous monoacetate: ir ($CHCl_3$) 1736 (s), 1660 (s), 1605 (s) $cm^{-1}$; uv (95% EtOH) 232, 255 mn; nmr ($CDCl_3$) $\tau$ 3.22 (s, 1), 3.35 (dd, 2), 4.16 (s, 1), 4.30 (td, 1) 6.12 (s, 3), 6.16 (s, 6), 6.63 (m, 3), 7.35 (ddd, 1), 8.03 (m, 1), 8.20 (s, 3).

**Dihydrotrimethylisocatechinic Acid.** Trimethylisocatechinic acid (50 mg) was hydrogenated at 50 psi overnight in MeOH (20 ml) with platinum oxide (40 mg). Preparative tlc (solvent B) gave recovered starting material (8.5 mg) and product (14 mg): ir ($CHCl_3$) 3580 (w), 1640 (s), 1598 (s), 1510 (s) $cm^{-1}$; uv (95% EtOH) 232, 252 nm; mass spectrum (rel intensity) 334 (96), 316 (4), 273 (34), 193 (20), 164 (19), 151 (100), 137 (30).

*Anal.* Calcd for $C_{18}H_{22}O_6$: *m/e* 334 (100), 335 (20.04), 336 (3.10). Found: *m/e* 334 (100), 335 (20.13), 336 (10.6).

**Permethylcatechinic Acid (7).** Catechinic acid (500 mg) in MeOH was treated with an excess of diazomethane in ether at 4° for 2 days. Evaporation gave a viscous oil which was purified by preparative tlc (solvent B) to give a white amorphous solid (310 mg): ir 3528 (w), 1652 (s), 1602 (s), 1521 (s) $cm^{-1}$; uv (95% EtOH) 233 (11,400), 254 (12,800) nm; nmr ($CDCl_3$, 220 MHz) $\tau$ 3.16 (d, 1),

3.31 (m, 2), 4.40 (s, 1) 5.75 (td, 1, $J$ = 11, 5 Hz), 6.14 (s, 3), 6.15 (s, 3), 6.46 (s, 3) 6.83 (dd, 1, $J$ = 11, 4 Hz), 7.14 (s, 2), 7.71 (m, 4), 8.00 (td, 1, $J$ = 12, 4 Hz); mass spectrum (rel intensity) 346 (52), 274 (4), 193 (24), 180 (27), 167 (51), 162 (30), 151 (100).

*Anal.* Calcd for $C_{19}H_{22}O_6$: C, 65.88, H, 6.40; *m/e* 346 (100), 347 (21.1), 348 (3.32). Found: C, 65.71; H, 6.36; *m/e* 346 (100), 347 (21.1), 348 (3.88).

Treatment of trimethylcatechinic acid with $CH_2N_2$ gave a product which was identical by tlc and ir.

Acetylation of permethylcatechinic acid with NaOAc and $Ac_2O$ in benzene gave the acetate as a viscous oil: ir ($CHCl_3$) 1735 (s), 1660 (s), 1605 (s), 1522 (s) $cm^{-1}$; uv (95% EtOH) 237, 252 nm; nmr ($CDCl_3$) $\tau$ 3.25 (s, 1), 3.35 (m, 2), 4.35 (s, 1), 4.46 (m, 1), 6.15 (s, 3), 6.17 (s, 3), 6.49 (s, 3), 6.56 (m, 1), 7.14 (s, 2), 7.69 (m), 7.80–8.15 (m), 8.21 (s, 3); mass spectrum (rel intensity) 388 (26), 328 (100), 313 (7), 299 (12), 193 (46), 180 (25), 151 (60), 137 (22).

*Anal.* Calcd for $C_{21}H_{24}O_7$: *m/e* 388 (100), 389 (23.3), 390 (4.00). Found: *m/e* 388 (100), 385 (23.7), 390 (4.09).

**Dihydropermethylcatechinic Acid (8).** Permethylcatechinic acid (50 mg) was hydrogenated for 5 hr at 50 psi with 5% Pd/C (100 mg) in MeOH (30 ml). Preparative tlc (solvent B) gave 30 mg of amorphous product: ir ($CHCl_3$), 3620 (w), 3440 (w), 1647 (s), 1605 (s), 1522 $cm^{-1}$; uv (95% EtOH) 230, 258 nm; nmr ($CDCl_3$) $\tau$ 3.30 (m, 3), 4.55 (s, 1), 5.87 (m, 1), 6.16 (s, 3), 6.17 (s, 3), 6.55 (s, 3), 6.85 (br s), 7.45 (m), 7.9 (m), 8.65 (s, 3); mass spectrum (rel intensity) 348 (34), 193 (7), 181 (12), 179 (26), 164 (13), 151 (100), 138 (17).

*Anal.* Calcd for $C_{19}H_{24}O_6$: *m/e* 348 (100), 349 (21.1), 350 (3.32). Found: *m/e* 348 (100), 349 (21.1), 350 (3.35).

Acetylation with NaOAc and $Ac_2O$ in benzene gave the diacetate as a white solid: ir ($CHCl_3$) 1732 (s), 1655 (s), 1608 (s), 1523 (s) $cm^{-1}$; uv (95% EtOH) 233, 255 nm; nmr ($CDCl_3$) $\tau$ 3.35 (m, 3), 4.48 (s, 1), 4.52 (m, 1), 6.14 (s, 3), 6,16 (s, 3), 6.52 (s, 3), 6.65 (m), 7.6–8.02 (m), 7.78 (s, 3), 8.17 (s, 3), 8.38 (s, 3).

**Trimethyldihydrocatechinic Acid (9).** Catechinic acid (400 mg) in MeOH was hydrogenated for 5 hr at 50 psi over 5% Pd/C (500 mg). The filtered reaction mixture was evaporated to dryness and then treated with excess $CH_2N_2$ at 4° for 3 days. Evaporation *in vacuo* gave a viscous oil which was purified by preparative tlc (solvent B) to give the major product (90 mg): ir ($CHCl_3$), 3620 (w), 3420 (w), 1649 (s), 1602 (s), 1520 (s) $cm^{-1}$; uv (95% EtOH) 232, 254 nm; nmr ($CDCl_3$) $\tau$ 3.42 (m, 3), 4.54 (s, 1), 5.94 (m), 6.17 (s, 3), 6.20 (s, 3), 6.34 (m), 6.54 (s, 3), 6.70 (dd, 1), 7.27 (m, 2), 7.93 (m); mass spectrum (rel intensity) 334 (55), 316 (4), 304 (8), 273 (4), 193 (10), 183 (11), 179 (15), 167 (27), 165 (28), 151 (100), 137 (81).

*Anal.* Calcd for $C_{18}H_{22}O_6$: *m/e* 334 (100), 335 (20.04), 336 (3.11). Found: *m/e* 334 (100), 335 (20.02), 336 (4.35).

Acetylation with $Ac_2O$, NaOAc, and benzene at reflux gave the diacetate as an amorphous white solid: ir ($CHCl_3$) 1738 (s), 1660 (s) 1605 (s), 1523 (s) $cm^{-1}$; uv (95% EtOH) 237, 252 nm; nmr ($CDCl_3$) $\tau$ 3.35 (m, 3), 4.43 (s, 1), 4.50 (m, 1), 4.80 (t, 1), 6.14 (s, 3), 6.16 (s, 3), 6.53 (s, 3), 6.65 (dd, 1), 7.06 (m, 2), 7.77 (s, 3), 8.02 (m), 8.20 (s, 3); mass spectrum (rel intensity) 418 (19), 358 (31), 298 (30), 283 (9), 266 (100), 255 (12), 251 (11), 239 (11), 214 (19), 193 (44), 180 (12), 165 (20), 151 (75), 137 (67).

*Anal.* Calcd for $C_{22}H_{26}O_8$: *m/e* 418 (100), 419 (24.4), 420 (4.5). Found: *m/e* 418 (100), 419 (24.7), 420 (4.6).

**Acknowledgment.** We thank Dr. F. W. Herrick, ITT Rayonier Inc., Shelton, Wash., for helpful discussions.

**Registry No.**—**2,** 154-23-4; **5,** 52484-79-4; **6,** 52358-31-3; **6** monoacetate, 52358-32-4; **7,** 52358-33-5; **7** monoacetate, 52358-34-6; **8,** 52358-35-7; **8** diacetate, 52358-36-8; **9,** 52358-37-9; **9** diacetate, 52358-38-0; trimethylisocatechinic acid, 52358-39-1; trimethylisocatechinic acid monoacetate, 52358-40-4; dihydrotrimethylisocatechinic acid, 52358-41-5; diazomethane, 334-88-3.

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# A Novel Synthesis of 4α- and 4β-Methylcholest-5-en-3β-ol from 6β-Bromo-4-methylcholest-4-en-3-one[1]

Furn F. Knapp, Jr., and George J. Schroepfer, Jr.*

*Departments of Biochemistry and Chemistry, Rice University, Houston, Texas 77001*

*Received April 30, 1974*

The reduction of 6β-bromo-4-methylcholest-4-en-3-one with a large excess of lithium aluminum hydride (19 equiv of $H^-$) in ether results in the formation of 4α-methylcholest-5-en-3β-ol in high yield (~84%). Reduction of the bromide with lithium aluminum deuteride under similar conditions gives [3α,4β-$^2H_2$]-4α-methylcholest-5-en-3β-ol. Unexpectedly, reduction of 6β-bromo-4-methylcholest-4-en-3-one with lithium aluminum hydride at a lower molar ratio (3 equiv of $H^-$) gave good (~31%) yields of 4β-methylcholest-5-en-3β-ol (in addition to 4α-methylcholest-5-en-3β-ol and a third compound which was not identified). The 4β-methylcholest-5-en-3β-ol formed under these conditions by reduction of the bromide with lithium aluminum deuteride was labeled in the 3α and 4α positions.

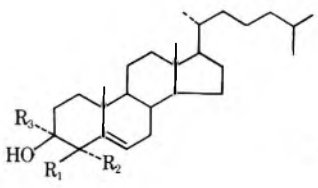
The C-4 demethylation of sterol precursors of cholesterol is an important process which has received considerable attention.[2] The initial demethylation of 4,4-dimethyl precursors has been reported to proceed with initial removal of the equatorial 4α-methyl group with subsequent inversion of the axial 4β-methyl group to the equatorial position.[3–5] We have been interested in the stereochemical fate of the C-4 hydrogen in the demethylation of 4α-monomethyl intermediates. Preliminary studies of the conversion of [2,2,4-$^3H_3$]-4α,14α-dimethylergosta-8,24(28)-dien-3β-ol into [2,2,4-$^3H_3$]-(24*R*)-24-ethylcholesta-5,22-dien-3β-ol by the Chrysophyte *Ochromonas malhamensis* have indicated that during the second demethylation the axial 4β hydrogen appears to be inverted to the equatorial 4α position.[6] We have now directed our efforts at developing a synthetic route to give a 4α-methyl-4β-tritio substrate which can be

used to study the second C-4 demethylation during cholesterol biogenesis. This paper describes our studies involving the hydride reduction of 6β-bromo-4-methylcholest-4-en-3-one.

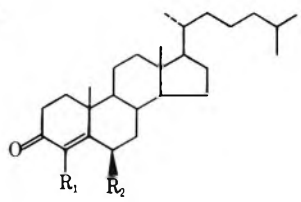
Several years ago Ireland, Wrigley, and Young[7] reported that lithium aluminum hydride reduction of 6β-chlorocholest-4-en-3β-yl benzoate yielded cholest-5-en-3β-ol. It was shown by chemical modification and infrared studies of the product formed by lithium aluminum deuteride reduction of the allylic chloride that the deuterium was stereospecifically introduced into the 4β position. These results were explained by a mechanism involving an intramolecular attack (SNi′) of hydride on the double bond at C-4 followed by double-bond rearrangement resulting in the loss of bromide ion to give [4β-$^2$H]-cholest-5-en-3β-ol. There have been no further studies, however, of the detailed mechanism of this reaction. More recently Knapp, Goad, and Goodwin[6] have found that reduction of 6β-chloro-(24*S*)-24-ethylcholesta-4,22-dien-3β-yl acetate by lithium aluminum deuteride gave [4β-$^2$H]-(24*S*)-24-ethylcholesta-5,22-dien-3β-ol. Degradation of this substance demonstrated that the isotopic hydrogen had been stereospecifically introduced into the 4β position. Collins and Hobbs[8] have reported that sodium borohydride reduction of 6β-bromocholest-4-en-3-one in diglyme gave cholesterol in high yield, although no experimental details were given. The combined results of these studies indicated that hydride reduction of 6β-bromo-4-methylcholest-4-en-3-one might provide an attractive route for the synthesis of 4α-methylcholest-5-en-3β-ol labeled with isotopic hydrogen at carbon atoms 3 and 4.

## Results and Discussion

Methods that have been used successfully to deconjugate cholest-4-en-3-one (VII) proceed in only very low yields



| Compd | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| I | H | H | H |
| II | H | $^2$H | H |
| III | H | $CH_3$ | H |
| IV | $CH_3$ | H | H |
| V | $^2$H | $CH_3$ | $^2$H |
| VI | $CH_3$ | $^2$H | $^2$H |



| Compd | $R_1$ | $R_2$ |
|---|---|---|
| VII | H | H |
| VIII | $CH_3$ | H |
| IX | H | Br |
| X | $CH_3$ | Br |

when applied to the deconjugation of 4-methylcholest-4-en-3-one (VIII). For example, Birch reduction of 4-methylcholesta-3,5-dien-3-acetate, followed by hydride reduction gave the allylic alcohol, 4-methylcholest-4-en-3β-ol, demonstrating rapid reconjugation of the double bond prior to reduction of the C-3 ketone.[9] Similarly, sodium borohydride reduction of 4-methylcholesta-3,5-dien-3-acetate gave a complex mixture of which the major products are the two allylic alcohols, 4-methylcholest-4-en-3β-ol and 4-methylcholest-4-en-3α-ol. 4α-Methylcholest-5-en-3β-ol and 4β-methylcholest-5-en-3β-ol could be isolated in only low yield.[9-11] In addition, kinetically controlled protonation of the enolate anion of VIII gave only starting material.

The first step in our alternative approach to this problem involved bromination of 4-methylcholest-4-en-3-one (VIII) with *N*-bromosuccinimide to give 6β-bromo-4-methylcholest-4-en-3-one (X) in high yield.[12] Initially, we conducted the reductive rearrangement of 6β-bromo-4-methylcholest-4-en-3-one (X) with a large excess of lithium aluminum hydride (19 equiv of $H^-$). From the analogy of the similar hydride reduction of 6β-bromocholest-4-en-3-one (IX), we expected hydride reduction of X to proceed with the formation of 4α-methylcholest-5-en-3β-ol (III). Our results indicate that this is the case. Two minor components (<10%) of the crude reaction mixture, 4-methyl-cholest-4-en-3β-ol and 4-methylcholest-4-en-3α-ol, were inseparable from III on thin layer chromatography but could be removed by crystallization. After purification by crystallization, 4α-methylcholest-5-en-3β-ol (III), chromatographically homogeneous on thin layer and gas liquid chromatographic analysis, was obtained in high yield (~84%). Nuclear magnetic resonance (nmr) studies showed resonance compatible with an olefinic proton, the axial C-3 proton, and the secondary 4α-methyl group (d, $J$ = 6 Hz). The latter was more easily seen in the 60-MHz spectrum by the use of the Eu(dpm)$_3$ shift reagent. Reduction of 6β-bromo-4-methylcholest-4-en-3-one (X) with lithium aluminum deuteride under the same conditions gave [3α,4β-$^2$H$_2$]-4α-methylcholest-5-en-3β-ol (V). The mass spectra of III and V were in accord with the assigned structures (see Experimental Section). The nmr spectrum of V contained a singlet for the C-4 methyl group which was more easily seen in the spectrum expanded with Eu(dpm)$_3$. No absorption due to the C-3 proton was present in the spectrum. The combined results of the nmr and mass spectral studies indicate the location of the isotopic hydrogen at C-3 and C-4. In analogy with examples cited earlier we interpret our results as compatible with an initial reduction of the C-3 ketone followed by intramolecular hydride attack with double-bond participation (SNi′) in the formation of III and V. A mechanism for this type of reaction has been suggested by Ireland, Wrigley, and Young.[7]

Unexpectedly, when the molar ratio of hydride to 6β-bromo-4-methylcholest-4-en-3-one (X) was decreased (3 equiv of $H^-$), it was found that 4β-methylcholest-5-en-3β-ol (IV) was formed in substantial amounts. Analysis of the crude reaction mixture by gas–liquid chromatography (glc) indicated the presence of two minor components with retention times corresponding to those of 4-methylcholest-4-en-3β-ol and 4-methylcholest-4-en-3α-ol and two major components with retention times corresponding to those of 4α-methylcholest-5-en-3β-ol (III) and 4β-methylcholest-5-en-3β-ol (IV). The former compound was partially purified by preparative thin layer chromatography (tlc) but was shown (by nmr and mass spectral (ms) studies; see Experimental Section) to be contaminated by one or more other compounds whose precise chemical nature has not been established. 4β-Methylcholest-5-en-3β-ol (IV) was isolated from the crude reaction mixture in pure form by preparative tlc and crystallization. The isolated compound showed mobilities identical with that of authentic 4β-methylcholest-5-en-3β-ol (IV) (prepared by an alternate route[13]) on tlc and glc analyses. The nmr spectrum showed the presence of an olefinic proton, the axial C-3 proton, the allylic C-4-proton, and the 4β-methyl group. The latter three-proton doublet was easily seen in the spectrum expanded with Eu(dpm)$_3$ (d, $J$ = 8 Hz).

Assignment of the position of the C-4α proton in the spectrum of IV was confirmed by the reduction of X with a limiting amount of lithium aluminum deuteride. Purification of the material chromatographing with IV gave [3α,4α-$^2$H$_2$]-4β-methylcholest-5-en-3β-ol (VI). In the nmr spectrum of this substance the downfield methine proton

and the axial C-3 proton were not present, confirming that these two hydrogens originate from deuteride. In addition, in the spectrum of VI the C-4β methyl resonance was present as a singlet. The downfield position of the allylic C-4 proton and the C-3 proton in IV and the increased coupling of the axial C-4β methyl group must reflect considerable distortion of ring A. This distortion probably results from the large 1,3 interaction between the C-4β methyl group and the C-19 methyl group. In III this interaction is relieved and the C-4 allylic proton is evidently under the methylene envelope in the spectrum of this compound.

The formation of 4β-methylcholest-5-en-3β-ol (IV) by reduction of 6β-bromo-4-methylcholest-4-en-3-one with limiting amounts of hydride represents a unique and unexpected result. Additional detailed chemical and kinetic studies are indicated to define the precise mechanism of the reaction leading to the formation of IV under these conditions. The observed results do provide a new, simple synthetic route for the preparation of 4β-alkyl substituted $\Delta^5$-sterols. Moreover, the results described herein provide an approach to the stereospecific introduction of isotopic hydrogen at carbon atoms 3 and 4 of 4-alkyl substituted $\Delta^5$-3β-hydroxysterols.

## Experimental Section

**General.** The 4-methyl-cholest-4-en-3-one was synthesized by the method of Atwater.[14] Tlc was performed on plates spread with silica gel H using chloroform as the developing solvent. For analytical purposes the plates were spread at a thickness of 0.25 mm and spot colors were detected by spraying the plate after development with molybdic acid spray followed by brief heating to 80°. For preparative experiments the plates were spread 0.50 or 1.0 mm thick and, after two developments in chloroform, the bands were visualized by spraying the plates with an acetone solution of Rhodamine 6G followed by uv irradiation. Glc was performed using a Hewlett-Packard Model 402 instrument equipped with dual flame ionization detectors. The columns were packed (6 ft × 0.25 in., o.d.) with the following phases: 1% SE-30, 1% QF-1, 3% OV-1, and 3% OV-17 on Gas-Chrom Q (100–120 mesh). The carrier gas was helium with a flow rate of 66 ml/min. Ms analyses were determined on a CEC Model 21-110 B double focusing instrument. Nmr spectra were recorded on a Perkin-Elmer HR-12 spectrometer in $CDCl_3$ solution with TMS as the internal standard. The nmr absorptions are reported as parts per million (δ) downfield from the TMS internal standard. The lanthanide shift reagent europium(III) dipivaloylmethanoate [Eu(dpm)$_3$] was purchased from Alpha Inorganics (Beverly, Mass.). Lithium aluminum hydride was purchased from Research Organic/Inorganic Chemicals (Sun Valley, Calif.). Lithium aluminum deuteride was purchased from E. Merck (Darmstadt). Authentic samples of 4-methylcholest-4-en-3α-ol and 4-methylcholest-4-en-3β-ol were prepared by hydride reduction of 4-methylcholest-4-en-3-one. An authentic sample of 4β-methylcholest-5-en-3β-ol was prepared by the method of Julia and Lavaux.[13] Melting points were recorded on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared (ir) spectra were recorded on a Beckman IR-9 spectrometer using KBr pellets.

**4α-Methylcholest-5-en-3β-ol (III).** 4-Methylcholest-4-en-3-one (2.04 g) was refluxed with *N*-bromosuccinimide (960 mg) in $CCl_4$ (40 ml) for 30 min. The solution was cooled in an ice bath and the precipitated succinimide was removed by filtration. The filtrate was evaporated to dryness to give an orange gum which was dissolved in a small amount of ether. Addition of cold methanol resulted in the formation of fine needles. Recrystallization of the first and second crops gave pure 6β-bromo-4-methyl-cholest-4-en-3-one (X): 1.28 g; mp 132–133° dec (lit.[12] mp 135°); uv $\lambda_{max}$ (ETOH) 262 nm (log ε 4.10) [lit.[12] $\lambda_{max}$ (ETOH) 262 nm (log ε 4.11)]; ir $\nu_{max}$ (KBr) 1673 cm$^{-1}$; ms (rel intensity), 478 and 476 (M, 5% and 6%), 398 and 396 (100 and 75%), 397 (M − Br; 38%), 384 (12%), 283 (21%), 275 (16%), 261 (9%), 247 (24%), 243 (11%); nmr 1.48 (s, 3 H, deshielded C-19 $CH_3$), 1.86 (s, 3 H, C-4 $CH_3$), 5.45 (m, 1 H, C-6 H). The bromide (180 mg, 3 mmol) was dissolved in ether (10 ml) and added to a slurry of lithium aluminum hydride (500 mg, 53 mequiv of $H^-$) in ether (100 ml). After the mixture was stirred for 30 min, excess hydride was decomposed by the slow addition of ethyl acetate (50 ml). Hydrochloric acid (2 *N*, 50 ml) was added and the isolated organic layer was washed thoroughly with dilute sodium bicarbonate and water, dried over anhydrous sodium sulfate, and evaporated to dryness. Analysis of the crude product by glc indicated that the major component of the reaction mixture cochromatographed with authentic III. Two minor components (<10%) of the crude reaction mixture, 4-methylcholest-4-en-3β-ol and 4-methylcholest-4-en-3α-ol, were inseparable from III on tlc but could be removed by crystallization. Crystallization from ethanol–water yielded 4α-methylcholest-5-en-3β-ol in the form of fine needles (124 mg): mp 166–167° (lit.[13] mp 162–163°); uv, only end absorption; ir $\nu_{max}$ (KBr) 3440, 1064 cm$^{-1}$; ms (rel intensity) 400 (M, 100%), 385 (M − $CH_3$, 29%), 382 (M − $H_2O$, 38%), 367 (M − $CH_3$ − $H_2O$, 26%), 343 (8%), 331[15] (12%), 301 (7%), 287 (M − side chain, 8%), 275 (20%), 269 (M − $H_2O$ − side chain, 9%), 261 (3%), 247 (7%), 227 (M − $H_2O$ − side chain − 42, 8%); nmr 1.05 (s, 3 H, C-19 $CH_3$), 1.09 (d, 3 H, C-4 $CH_3$, $J$ = 6 Hz), 3.11 (m, 3 H, C-3 H), 5.35 (m, 1 H, C-6 H). The isolated product showed a single component on tlc and on glc (on the four systems described above).

**[3α,4β-$^2H_2$]-4α-Methylcholest-5-en-3β-ol (V).** 6β-Bromo-4-methylcholest-4-en-3-one (X, 130 mg) was reduced with lithium aluminum deuteride (500 mg) as described above. Crystallization of the product from ethanol–water gave V as plates: mp 165–166°; ir $\nu_{max}$ (KBr) 3410, 1080 cm$^{-1}$; ms (rel intensity) 402 (100%), 387 (20%), 384 (43%), 369 (26%), 344 (12%), 331[15] (14%), 301 (9%), 289 (5%), 275 (29%), 271 (10%), 261 (5%), 247 (12%), 229 (10%); nmr 1.09 (s, 3 H, C-4 $CH_3$), 5.42 (m, 1 H, C-5 H), absence of the C-3 H resonance. The isolated product showed a single component on tlc and on glc (on the four systems described above).

**4β-Methylcholest-5-en-3β-ol (IV).** 6β-Bromo-4-methylcholest-4-en-3-one (130 mg) was reduced with lithium aluminum hydride (7 mg, 7.4 mequiv of $H^-$) as described above (except for the lower molar ratio of hydride). Analysis of the crude reaction mixture by glc indicated the presence of two minor components with retention times corresponding to those of 4-methylcholest-4-en-3β-ol and 4-methylcholest-4-en-3α-ol and two major components with retention times corresponding to 4α-methylcholest-5-en-3β-ol (III) and 4β-methylcholest-5-en-3β-ol (IV). Analysis of the crude reaction mixture by tlc indicated two major components with $R_f$ values of 0.19 and 0.23. The mixture was subjected to preparative tlc.

The more polar major component was crystallized from ethanol–water to give 4β-methylcholest-5-en-3β-ol (IV, 30.4 mg) in the form of needles: mp 135–137° (lit.[13] mp 132–134°); ir $\nu_{max}$ (KBr) 3410, 1026, 1062 cm$^{-1}$; ms 400 (M, 100%), 385 (M − $CH_3$, 25%), 382 (M − $H_2O$, 32%), 367 (M − $CH_3$ − $H_2O$, 33%), 343 (9%), 331[15] (36%), 301 (7%), 387 (M − side chain, 9%), 275 (19%), 269 (M − $H_2O$ − side chain, 10%), 261 (3%), 247 (9%), 227 (M − $H_2O$ − side chain − 42, 8%); nmr 1.06 (s, 3 H, C-19 $CH_3$), 1.12 (d, 3 H, C-4 $CH_3$, $J$ = 8 Hz), 2.60 (m, 1 H, C-4 H), 3.71 (m, 1 H, C-3 H), 5.40 (m, 1 H, C-6 H). The compound showed a single component on tlc and on glc (on the four systems described above) with the same mobility as authentic IV.

The less polar major component (52.8 mg) from the preparative tlc showed only one component on glc (on the four systems described above) and on tlc on silica gel H and silica gel H–silver nitrate plates as the free alcohol and in the form of the acetate derivative. The mobilities were the same as that observed with authentic III and its acetate derivative. However, both ms and nmr analyses indicated the presence of one or more other components. For example, the nmr spectrum showed the presence of absorptions, in addition to those of III, at 3.90 (m), 4.97 (m), 5.60 (m), and 8.44 (s). The latter signal is compatible with a methyl group attached to an olefinic carbon. The mass spectrum showed the same ions as seen in III and, in addition, showed ions at 398 (30%), 365 (4%), 332 (17%), 285 (3%), and 279 (6%). The precise nature of the component(s) present in addition to III is not known. However, these data suggest that one of the components has two double bonds. The ir spectrum showed no absorption due to a carbonyl function. Analysis of the uv spectrum of the product showed only end absorption in the 210-nm region, indicating the absence of a conjugated diene system.

**[3α,4α-$^2H_2$]-4β-Methylcholest-5-en-3β-ol (VI).** Reduction of 6β-bromo-4-methylcholest-4-en-3-one (X) with lithium aluminum deuteride (7 mg, 7.4 mequiv of $D^-$) in ether was effected and the crude reaction mixture was subjected to preparative tlc as described in the case of the synthesis of IV. The more polar major component on tlc was crystallized from ethanol–water to yield [3α,4α-$^2H_2$]-4β-methylcholest-5-en-3β-ol (VI, 19.1 mg) in the form of needles: mp 131°; ir $\nu_{max}$ (KBr) 3448, 1064 cm$^{-1}$; ms (rel intensity) 402 (100%), 387 (28%), 284 (41%), 369 (32%), 344 (10%), 331[15] (36%), 301 (7%), 289 (18%), 275 (11%), 271 (9%), 261 (3%), 247

(10%), 229 (7%); nmr 1.12 (s, 3 H, C-4 $CH_3$), no resonance for the C-3 proton. The compound showed a single component on analysis by tlc and glc (on four systems noted above).

The less polar major component (19.0 mg) on tlc showed a mass spectrum which was very similar to that of [3α,4β-$^2H_2$]-4α-methylcholest-5-en-3β-ol (V) with additional ions at 399 (90%) and 366 (3%). The nmr spectrum showed the presence of signals 4.95 (m), 5.62 (m), and 8.43 in addition to the resonances seen in the spectrum of III. The spectrum showed no absorbance at 3.71 (C-3 H) or at 3.90 seen in the spectrum of the less polar component obtained as a by-product in the synthesis of IV.

**Registry No.**—III, 15073-00-4; IV, 1251-98-5; V, 52259-51-5; VI, 52259-52-6; VIII, 2041-92-1; X, 2239-49-8.

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# Studies in Mass Spectrometry. A Comparison of the Electron Impact and Chemical Ionization Fragmentations of 8,9-Dehydro-2-adamantanol and 2-*exo*-Protoadamantenol

Barbara L. Jelus, Burnaby Munson, Kevin A. Babiak, and Roger K. Murray, Jr.*

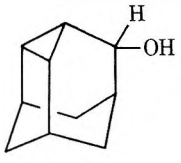
*Department of Chemistry, University of Delaware, Newark, Delaware 19711*

*Received April 11, 1974*

Electron impact (electron energies of 70, 20, and 14.2 eV) and chemical ionization (methane, isobutane, hydrogen, nitrogen, and nitric oxide–nitrogen mixtures as reagent gases) spectra were obtained for 8,9-dehydro-2-adamantanol (1) and 2-*exo*-protoadamantenol (2). Within the limits of experimental reproducibility, the mass spectrometric behavior of the two alcohols was identical when the site of ionization was the alcohol functional group. Only under conditions of electrophilic addition ionization were significant differences observed between 1 and 2.

Significant attention has been devoted to comparisons of the behavior of cyclopropylcarbinyl and homoallyl derivatives in solvolytic reactions.[1] Although it has been contended that "most of the [solvolytic] reactions of allylcarbinyl derivatives may be explained on the basis of the formation of a cyclopropylcarbinyl cation," [2] considerable controversy exists concerning the detailed structures of the intermediate species involved in these reactions.[1,3]

In light of these studies, it is striking that no detailed comparison of the mass spectrometric behavior of any cyclopropylcarbinyl and homoallyl derivatives has appeared. We now wish to report our results concerning the behavior of 8,9-dehydro-2-adamantanol (1) and 2-*exo*-protoadamantenol (2) in the mass spectrometer employing both electron impact and chemical ionization techniques.

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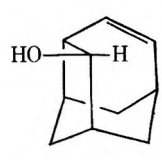


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## Results and Discussion

**Electron Impact Spectra.** The partial electron impact mass spectra of 1 and 2 measured at 70, 20, and 14.2 eV are reported in Table I. The most striking conclusion resulting from a comparison of these data is that there is little difference in the electron impact fragmentations of 1 and 2 over this range of energies. Indeed, any differences in the ionic abundances of 1 and 2 reported in Table I are within the limits of experimental reproducibility. The absence of sig-

**Table I**
**Partial Electron Impact Spectra of 1 and 2**

| | % ionization[a,b] ($100 I_i / \sum_{sample} I_i$) | | | | | | |
|---|---|---|---|---|---|---|---|
| | 70 eV | | 20 eV | | 14.2 eV | | |
| m/e | 1 | 2 | 1 | 2 | 1 | 2 | Comment |
| 43 | 0.9 | 1.0 | 0.9 | 0.8 | 0.8 | 0.6 | |
| 54 | 2.6 | 2.4 | 3.5 | 3.1 | 3.0 | 1.8 | |
| 57 | 1.6 | 1.9 | 1.7 | 1.6 | 1.5 | 1.1 | |
| 72 | 3.2 | 4.4 | 6.8 | 6.3 | 9.4 | 8.9 | |
| 77 | 4.3 | 3.4 | 0.8 | 1.0 | | | |
| 78 | 4.9 | 4.9 | 5.3 | 5.4 | 4.9 | 4.9 | |
| 79 | 12.4 | 14.2 | 12.4 | 14.4 | 6.8 | 6.7 | $C_6H_7$ |
| 80 | 6.9 | 9.7 | 11.4 | 11.2 | 11.9 | 10.8 | |
| 91 | 5.0 | 4.2 | 3.3 | 3.4 | 2.0 | 2.0 | $C_7H_7$ |
| 92 | 1.1 | 1.1 | 1.0 | 1.1 | 0.7 | 0.7 | |
| 93 | 1.6 | 1.7 | 1.8 | 1.9 | 1.3 | 1.4 | |
| 104 | 1.8 | 2.5 | 3.1 | 2.9 | 3.9 | 3.3 | M − ($H_2O$ + $C_2H_4$) |
| 108 | 1.2 | 1.5 | 2.3 | 2.1 | 2.8 | 2.5 | |
| 117 | 4.0 | 5.0 | 6.9 | 6.2 | 6.1 | 5.6 | M − (OH + $CH_4$) |
| 132 | 1.4 | 2.1 | 2.6 | 2.3 | 4.0 | 3.1 | M − ($H_2O$) |
| 133 | 0.3 | 0.7 | 0.9 | 0.7 | 1.3 | 0.8 | M − (OH) and $^{13}C$ of M − ($H_2O$) |
| 150 | 7.6 | 10.0 | 12.3 | 14.2 | 21.2 | 28.4 | M |

[a] The ion intensities reported are uncorrected for $^{13}C$ isotope. [b] The reproducibility of the per cent ionizations reported is ±15% of the reported value.

nificant differences in the electron impact spectra of 1 and 2 is compatible with a common structure for the decomposing molecular ions produced by direct ionization with electrons of these energies.

The electron impact mass spectra of a number of 2-substituted adamantanes have previously been reported,[4-7] and the major fragment ions obtained from the structurally similar alcohol (1) are consistent with these results. However, in contrast to the reported 70-eV electron impact spectrum of 2-adamantanol (3),[5] 1 shows a much more intense molecular ion and a much less abundant $(M - H_2O)^{\cdot+}$ ion. Thus, relative to 3, the presence of the cyclopropyl moiety in 1 stabilizes the molecular ion and inhibits the loss of water from it upon electron impact.

Further examination of Table I shows that as the electron energy is decreased from 70 to 14.2 eV a decrease in the overall amount of fragmentation of the molecular ions of both 1 and 2 occurs. However, even at the lowest energy of 14.2 eV, sufficient differences are not present in the abundances of the fragment ions of 1 and 2 to reveal any significant differences in the structures of the decomposing molecular ions of 1 and 2. Thus, differentiation of 1 and 2 by electron impact mass spectrometry is essentially impossible.

**Chemical Ionization Spectra.** Chemical ionization mass spectrometry[8,9] is a form of mass spectrometry in which the sample is ionized as the result of an ion–molecule reaction between the sample and the ions of some reactant species. The ions of the reactant species are formed by a combination of electron impact ionization and ion–molecule reactions in a high-pressure mass spectrometer source. The reactions in the mass spectrometer source of these reactant ions with the sample, which is present only in trace amounts, produce the chemical ionization mass spectrum of the sample. The chemical ionization mass spectra of substances are usually markedly different from the spectra produced by electron impact ionization and thus the chemical ionization mass spectrum of a compound will often reflect different aspects of its structure than will the electron impact spectrum. Moreover, by varying the nature of the reactant ions, chemical ionization experiments can be carried out which specifically effect proton or hydride transfer, massive particle addition, or charge exchange.

**Proton Transfer Chemical Ionization Spectra.** If the reagent gas employed in chemical ionization produces reactant ions which act as Brønsted acids in the gas phase, then the resulting sample spectrum will be due to $(M + H)^+$ and any of its fragment ions. Of course, as the proton affinity of a species decreases, the strength of its conjugate Brønsted acid increases. Consequently, in chemical ionization the $H_3^+$ reactant ion in hydrogen is a stronger Brønsted acid than the $CH_5^+$ and $C_2H_5^+$ reactant ions formed in methane, which in turn are stronger protonating reagents than the $t\text{-}C_4H_9^+$ reactant ion in isobutane.[10] Thus, by varying the acid strength of the reactant ion, it is possible to vary the exothermicity of the proton transfer reaction and hence the resulting fragmentation.

The chemical ionization spectra of 1 and 2, which were obtained with hydrogen, methane, and isobutane as reagent gases, are summarized in Table II. As expected, the extent of fragmentation of 1 and 2 decreases as the acid strength of the reagent ions decreases; *i.e.*, the greatest fragmentation occurs with hydrogen and the least with isobutane. With hydrogen as the reagent gas, the extent of decomposition of the $(M + H - H_2O)^+$ ions is extensive, but there are essentially no differences present in the relative abundances of the fragment ions of *m/e* less than 133 in the hydrogen spectra of 1 and 2. This suggests that with hydrogen as reagent gas the decomposing ions of *m/e* 133 from 1 and 2 have the same structure. Furthermore, although the methane chemical ionization spectra of 1 and 2 show significantly less decomposition of the ions with *m/e* 133 than is the case with hydrogen, the relative abundances of the low-mass fragment ions in the methane spectra of 1 and 2 are essentially identical. Thus, it also appears with methane as reagent gas that the decomposing ions of *m/e* 133 from 1 and 2 have the same structure. However, speculation on the structures of these fragment ions is unwarranted in the absence of precise mass measurements and studies with labeled compounds.

**Table II**
**Protonation Chemical Ionization Spectra of 1 and 2**

| | % ionization[a,b] $(100I_i/\sum_{\text{sample}} I_i)$ | | | | | | |
|---|---|---|---|---|---|---|---|
| | $H_2$ | | $CH_4$ | | $i\text{-}C_4H_{10}$ | | |
| *m/e* | 1 | 2 | 1 | 2 | 1 | 2 | Comment |
| 67 | 2.4 | 2.5 | 1.0 | 1.0 | 1.4 | | |
| 69 | | | 1.0 | 1.1 | 3.1 | | |
| 71 | 0.9 | 1.1 | 0.8 | 1.0 | 2.1 | | |
| 79 | 4.7 | 4.6 | 1.2 | 1.0 | 1.1 | 1.3 | $C_6H_7$ |
| 81 | 2.2 | 2.5 | 0.6 | 0.6 | 0.9 | | |
| 91 | 12.8 | 15.0 | 9.6 | 13.0 | 5.6 | 7.5 | $C_7H_7$ |
| 92 | 1.1 | 1.2 | 0.8 | 1.2 | | | |
| 93 | 2.2 | 2.1 | 1.1 | 1.0 | 2.1 | | |
| 95 | 1.5 | 1.9 | 0.5 | 0.6 | 2.2 | | |
| 105 | 2.2 | 2.0 | | | | | |
| 107 | 1.8 | 2.5 | | | | | |
| 113 | | | | | 5.1 | 2.4 | |
| 121 | 2.6 | 3.2 | 1.6 | 1.8 | | | |
| 131 | 2.6 | 2.4 | 1.0 | 1.0 | | | |
| 132 | 0.4 | 0.6 | 0.5 | 0.3 | | | |
| 133 | 38.0 | 34.6 | 57.8 | 53.7 | 62.1 | 73.4 | M − OH |
| 134 | 3.6 | 3.8 | 6.7 | 5.6 | 7.2 | 8.9 | |
| 135 | | | 1.2 | 1.7 | | | |
| 149 | 10.7 | 10.3 | 9.2 | 8.2 | 1.1 | 2.4 | M − H |
| 150 | 2.1 | 1.5 | 2.7 | 2.7 | 0.9 | 1.1 | M |
| 151 | 0.8 | 1.1 | 2.5 | 4.0 | 0.9 | 1.6 | M + H |
| 179 | | | | 0.2 | | | M + $C_2H_5$ |
| 191 | | | | 0.04 | | | M + $C_3H_5$ |

[a] The ion intensities reported are uncorrected for $^{13}C$ isotope. [b] The reproducibility of the per cent ionization reported is ±15% of the reported value.

The most intense ion in the isobutane chemical ionization spectra of 1 and 2 is the $(M - OH)^+$ ion. Although this ion is obviously formed by the removal of the hydroxyl group from the alcohols, it is not clear whether the *m/e* 133 ion results from a proton transfer reaction followed by dissociation

$$C_{10}H_{13}OH + t\text{-}C_4H_9^+ \longrightarrow C_{10}H_{13}OH_2^+ + C_4H_8$$

$$C_{10}H_{13}OH_2^+ \longrightarrow C_{10}H_{13}^+ + H_2O$$

or an abstraction reaction.

$$C_{10}H_{13}OH + t\text{-}C_4H_9^+ \longrightarrow C_{10}H_{13}^+ + t\text{-}C_4H_9OH$$

The extent of fragmentation of the $(M - OH)^+$ ions in the isobutane chemical ionization spectra of 1 and 2 is significantly less than that observed with hydrogen or methane as reagents. The small differences in the isobutane spectra of 1 and 2 may be real and may indicate differences in the structures of the decomposing $(M - OH)^+$ ions. However, the differences in the isobutane chemical ionization spectra of 1 and 2 are not sufficiently great to warrant confident interpretation.

**Table III**
**Partial $N_2$ and $N_2$–NO Chemical Ionization Spectra of 1 and 2**

| | % ionization[a,b] ($100 I_i / \sum_{sample} I_i$) | | | | |
|---|---|---|---|---|---|
| | $N_2$ | | $N_2$/7.3% NO | | |
| m/e | 1 | 2 | 1 | 2 | Comment |
| 72 | 1.4 | 1.3 | | | |
| 77 | 1.3 | 1.2 | 0.2 | | |
| 78 | 4.8 | 4.2 | 0.4 | 0.4 | |
| 79 | 21.4 | 24.5 | 3.1 | 2.5 | $C_6H_7$ |
| 80 | 6.5 | 7.0 | 1.0 | 1.0 | |
| 91 | 6.9 | 7.3 | 3.7 | 1.7 | $C_7H_7$ |
| 92 | 1.5 | 1.8 | 0.4 | 0.3 | |
| 93 | 3.0 | 3.0 | 0.9 | 0.8 | |
| 104 | 1.2 | 1.2 | 0.1 | 0.1 | M − ($H_2O$ + $C_2H_4$) |
| 108 | 0.7 | 0.8 | 0.4 | 0.4 | |
| 117 | 3.9 | 3.5 | 0.6 | 0.6 | M − (OH + $CH_4$) |
| 132 | 1.4 | 1.4 | 0.5 | 0.4 | M − $H_2O$ |
| 133 | 14.0 | 13.3 | 26.0 | 8.8 | M − OH |
| 150 | 2.6 | 3.5 | 17.4 | 19.2 | M |
| 162 | | | 1.2 | 1.2 | M + NO − $H_2O$ |
| 180 | | | 22.8 | 42.4 | M + NO |

[a] The ion intensities reported are uncorrected for $^{13}C$ isotope. [b] The reproducibility of the per cent ionizations reported is ±15% of the reported value.

Isobutane chemical ionization spectra of several aliphatic alcohols have been reported.[11] For secondary alcohols there were observed, in addition to $(M - OH)^+$, $(M - H)^+$, and $(M + H)^+$ ions, two ions, $(M + 39)^+$ and $(M + 57)^+$, which have been attributed to the association of the $C_3H_3^+$ and $C_4H_9^+$ ions of the isobutane plasma with the molecule.[11] Although $(M + 39)^+$ and $(M + 57)^+$ ions are present in the isobutane chemical ionization spectrum of an alcohol of similar structure, namely **3**,[12] and the addition of $t$-$C_4H_9^+$ to olefins to form $(M + 57)^+$ ions has been reported,[13] $(M + 39)^+$ and $(M + 57)^+$ ions were not observed in the isobutane chemical ionization spectra of **1** or **2**. This suggests that either the basicities of **1** and **2** are sufficiently increased relative to **3** so that the $t$-$C_4H_9^+$ ion acts only as a Brønsted acid with **1** and **2** to form $(M + H)^+$ ions, some of which then decompose, or the "unsaturation" present in **1** and **2** increases the stability of the $(M - OH)^+$ ions sufficiently so that the decomposition of the $(M + 57)^+$ ions is essentially complete.

Although it is apparent that the chemical ionization spectra of **1** and **2** are different from the electron impact spectra and emphasize different aspects of the two alcohols, it is obvious that the chemical ionization spectra could not be employed to confidently differentiate **1** and **2**.

**Charge Exchange Spectra.** If the reagent gas employed in chemical ionization does not contain hydrogen, then proton transfer reactions cannot occur. When non-hydrogen-containing gases (*e.g.*, the rare gases, nitrogen, oxygen, carbon monoxide, and nitric oxide) are used in chemical ionization experiments, the principal ion–molecule reaction which occurs is charge exchange.[14] Thus, the radical molecular ion of the sample results from an electron transfer reaction (where $G\cdot^+$ is the reactant ion).

$$M + G\cdot^+ \longrightarrow M\cdot^+ + G$$

At pressures of about 1 Torr, the mass spectrum of nitrogen consists of three major ionic species ($N_2^+$, $N_3^+$, and $N_4^+$), all of which are rather high-energy ions that react by charge exchange and produce significant amounts of fragment ions of the sample. The nitrogen charge exchange spectra of **1** and **2** are summarized in Table III. Once again, the striking similarities in the behavior of **1** and **2** are immediately apparent. As is typical,[14] these charge exchange spectra are much more closely related to the electron impact spectra of **1** and **2** than to the chemical ionization spectra of these alcohols. However, it is to be noted that whereas upon electron impact **1** and **2** prefer dehydration to loss of hydroxyl, $(M - H_2O)\cdot^+/(M - OH)^+ \sim 4$–11, this behavior is reversed under charge exchange: $(M - H_2O)\cdot^+/(M - OH)^+ \sim 0.1$.

**Table IV**
**Metastable Transitions Observed in the $N_2$–5% NO Chemical Ionization Spectra of 1 and 2**

| | |
|---|---|
| **1** | |
| $(M + NO)^+$ | $(M + NO - H_2O)^+$ |
| $(M + NO)^+$ | $M\cdot^+$ |
| $(M + NO)^+$ | $(M - OH)^+$ |
| $(M + NO)^+$ | *m/e* 91 |
| $(M + NO - H_2O)^+$ | *m/e* 91 |
| **2** | |
| $(M + NO)^+$ | $(M + NO - H_2O)^+$ |
| $(M + NO)^+$ | $M\cdot^+$ |
| $(M - OH)^+$ | *m/e* 117 |
| $M\cdot^+$ | *m/e* 117 |

Recently, mixtures of 1–10 mol % of nitric oxide in nitrogen have been employed as charge exchange chemical ionization reagents.[15,16] Mixtures of greater than 5 mol % of nitric oxide in nitrogen produce mostly $NO^+$ ions. Previously, it has been shown that chemical ionization with pure nitric oxide also produces $NO^+$ in high abundance which can function as (a) an electron acceptor to provide $M\cdot^+$ radical ions, (b) a hydride abstracting agent to give $(M - H)^+$ ions, or (c) an electrophile to produce $(M + NO)^+$ ions.[17]

The chemical ionization spectra of **1** and **2** produced with a 7.3 mol % mixture of nitric oxide in nitrogen are summarized in Table III. Inspection of Table III shows that there are considerable differences in the nitric oxide–nitrogen chemical ionization spectra of **1** and **2** and that under these conditions **1** and **2** can clearly be distinguished. Thus, $(M + NO)^+$ is the dominant ion in the spectrum of **2** and $(M + NO)^+:M^+:(M - OH)^+ \simeq 5:2:1$, whereas in **1** the ion distributions are quite different and $(M + NO)^+:M^+:(M - OH)^+ \simeq 0.9:0.7:1$. That the amount of fragmentation in **1** and **2** is less in nitric oxide–nitrogen than in nitrogen reflects the fact that the recombination energy of nitric oxide is considerably less than that of nitrogen.[14]

The differences in behavior of **1** and **2** with nitric oxide–nitrogen chemical ionization are graphically illustrated in Figures 1 and 2, in which the contributions of the four major ions [$(M + NO)^+$, $M\cdot^+$, $(M - OH)^+$, and *m/e* 79 (perhaps protonated benzene)] in the spectra of **1** and **2** relative to the total sample ionization are plotted as a function of the mole per cent of nitric oxide in the nitric oxide–nitrogen mixtures. Striking differences for **1** and **2** are evident in the curves for the $(M + NO)^+$ and $(M - OH)^+$ ions. At least some of the $(M - OH)^+$ ions formed from **1** result from the decomposition of the $(M + NO)^+$ adduct, since a metastable transition is observed for this process (see Table IV). However, no metastable transition was observed for this process in **2**. The curves for the variation in concentration of the $M\cdot^+$ ions with increasing nitric oxide concentration are similar for **1** and **2** and metastable transitions for $(M + NO)^+$ ions decomposing to $M\cdot^+$ ions are present for both **1** and **2**. The marked decrease in the nitric oxide–

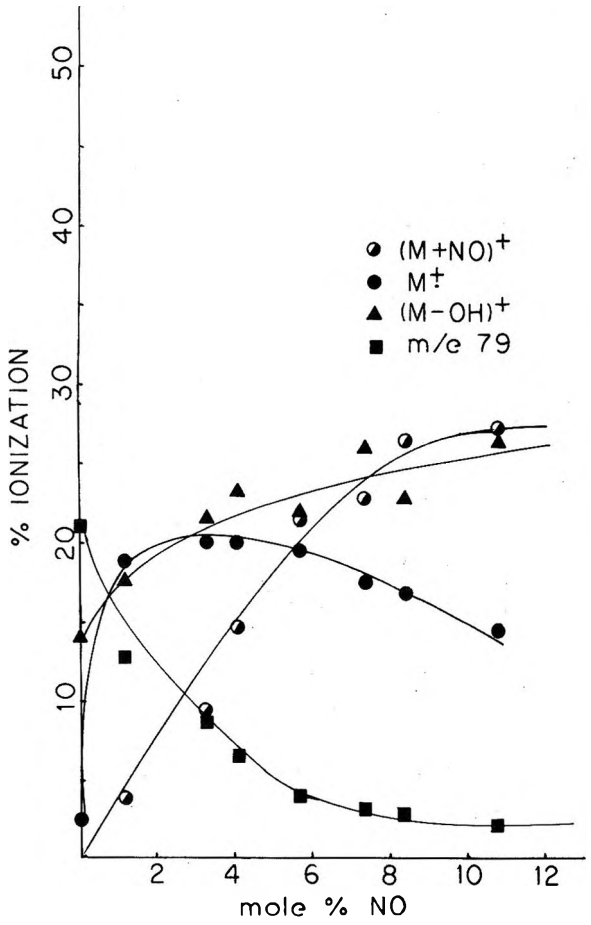


**Figure 1.** Behavior of several ions in the nitric oxide–nitrogen chemical ionization spectra of 1 as a function of the amount of nitric oxide present.

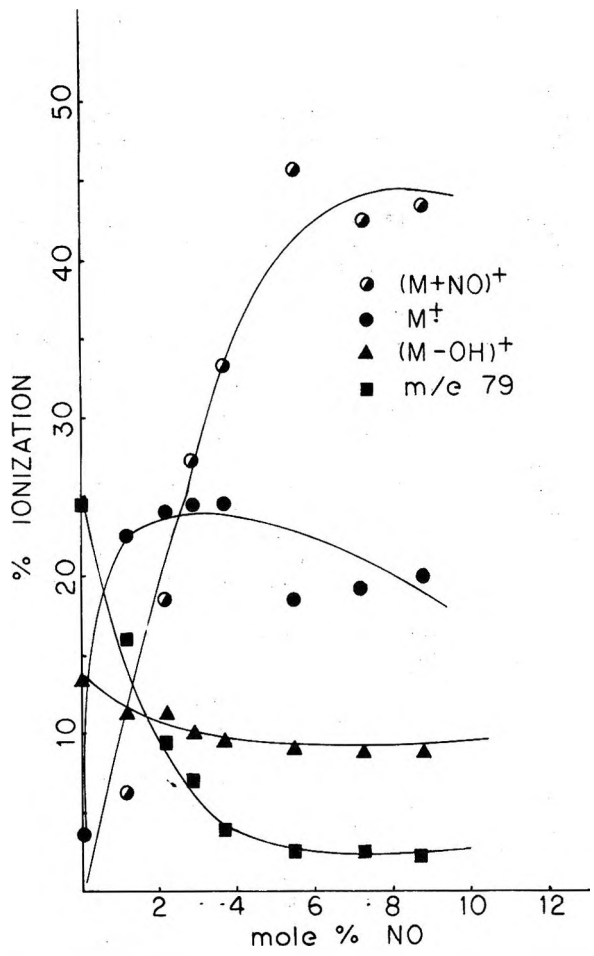


**Figure 2.** Behavior of several ions in the nitric oxide–nitrogen chemical ionization spectra of 2 as a function of the amount of nitric oxide present.

nitrogen spectra in 1 and 2 of the relative abundance of the major fragment ion in the nitrogen charge exchange spectra, *i.e.*, *m/e* 79, suggests that this ion is not produced to a significant extent by reactions of $NO^+$. The small amounts of *m/e* 79 that are still present at high concentrations of nitric oxide may result from a slow reaction of $NO^+$ or they may result from reactions of the small amounts of $N_2^+$, $N_3^+$, or $N_4^+$ ions that are present in the reagent gas.

Hunt and Ryan have reported that the nitric oxide chemical ionization spectra of secondary alcohols show abundant $(M - 1)^+$, $(M - 17)^+$, and $(M - 2 + 30)^+$ ions.[17] It was proposed that the $(M - 2 + 30)^+$ ion is formed by oxidation of the alcohol and subsequent attachment of $NO^+$ to the resulting ketone.[17] However, reaction of $NO^+$ with 1 and 2 yields $(M + 30)^+$ ions and no $(M - 2 + 30)^+$ ions. Thus, it appears that the addition of $NO^+$ to 1 and 2 does not involve exclusive reaction at the alcohol substituent, but rather extensive electrophilic attack occurs at the cyclopropyl or olefinic moieties of 1 and 2. Such behavior is not unprecedented, as the addition of $NO^+$ to olefins and olefinic alcohols to produce $(M + 30)^+$ ions has recently been observed,[18] and the nitric oxide chemical ionization spectrum of cholesterol also shows an abundant $(M + 30)^+$ ion.[14]

The major reactions of $NO^+$ with alcohols 1 and 2 can be summarized as follows:

$$M + NO^+ \longrightarrow$$

$$(M + NO^+)^* \begin{cases} \longrightarrow (M + NO)^+ & \text{(a)} \\ \longrightarrow M^+ + NO & \text{(b)} \\ \longrightarrow (M - OH)^+ + HNO_2 & \text{(c)} \end{cases}$$

Electrophilic attack to produce $(M + NO)^+$ is necessarily an exothermic reaction. The relative amounts of addition and reaction, *i.e.*, a *vs.* b + c, depend upon the stability of the addition ion and the stabilities of the possible reaction ion products. Thus, if reactions b and c are endothermic, then electrophilic addition is expected to predominate. If reactions b and c are strongly exothermic, then the products of these reactions should predominate and relatively little electrophilic addition should be observed. If the reactions are approximately thermoneutral, then small differences in the heats of formation of the reactants and products may produce significant changes in the ionic product distribution. Since the ratio $(M + NO)^+/M^{\cdot+}$ is substantially larger for 2 than for 1, it would appear that charge exchange to 2 is less exothermic than charge exchange to 1, and, consequently, that the ionization potential of 1 is slightly lower than the ionization potential of 2.

## Experimental Section

All electron impact spectra were obtained with a Du Pont CEC 21-110B mass spectrometer. The source block temperature was 100–120°, the repeller voltage 0 V, and the accelerating voltage 8 kV. The low-voltage electron energy was calibrated against the appearance potential of the $CH_3^+$ ion in methane.[19] At ionization energies much below 14.0 eV the total beam current was so small that reproducible spectra could not be obtained with the electron multiplier detector being used.

The chemical ionization experiments were carried out with a Du Pont CEC 21-110B mass spectrometer that had been modified for high-pressure operation.[14,20] The experimental conditions employed were: source block temperature 100–120°, accelerating voltage 6 kV, electron energy 400–600 eV, repeller field strength 0 V/cm, and source pressure 0.7–1.0 Torr. The technique for the mix-

ing of reagent gases for chemical ionization experiments has been described.[15]

All samples were introduced into the source region of the mass spectrometer by direct insertion probe. An all glass probe (manufactured by Mass Spectrometer Accessories, College Station, Tex.), which has a separate heating and control system, was used in all experiments. Probe temperatures necessary for sample vaporization were 35–45°.

**8,9-Dehydro-2-adamantanol (1)** was prepared by the sodium borohydride reduction of 8,9-dehydro-2-adamantanone (**4**) as described by Baldwin and Foglesong.[21] However, an improved procedure for the synthesis of **4** was employed.[22]

**2-*exo*-Protoadamantenol (2).** To 10 ml of an 80% aqueous acetone solution which was 0.05 *M* in perchloric acid was added 100 mg of **1**. The solution was stirred at reflux for 18 hr and then diluted with 20 ml of water, neutralized with saturated sodium bicarbonate solution, and extracted with ether (3 × 30 ml). The combined ether extracts were washed with water and dried over anhydrous magnesium sulfate, and the solvent was evaporated at reduced pressure. Glpc analysis (10 ft × 0.25 in. FFAP column, 190°, 60 ml/min of He) of the residue indicated a single component and pmr analysis (integration of the olefinic proton signals *vs.* chloroform as an internal standard) showed that the olefinic product was obtained in nearly quantitative yield. Pure **2** was isolated by glpc (above conditions) to give a white solid: mp 188–189°; pmr ($CDCl_3$) δ 6.45–5.9 (m, 2 H, olefinic protons), 3.71 [(br s, $W_{1/2}$ = 3.2 Hz, C**H**(OH)], 2.7–1.2 (m, 13 H); ir ($CCl_4$) 3630, 3350, 3035, 2920, 2865, 2850, 1460, 1430, 1365, 1210, 1175, 1150, 1100, 1060, 1050, 1030, 1015, 1000, 975, 945, 920, 900, and 700 $cm^{-1}$.

*Anal.* Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.82; H, 9.27.

The skeletal framework of **2** and the skeletal position and stereochemistry of the hydroxyl substituent in **2** were established by conversion of **2** to the known alcohol,[23] **2-*exo*-protoadamantanol (5).** A solution of 40 mg of **2** in 25 ml of ethanol was stirred with 100 mg of 5% palladium on charcoal under an atmosphere of hydrogen for 24 hr. The reaction mixture was then diluted with 100 ml of pentane and filtered to remove the catalyst. The catalyst was washed with pentane (2 × 20 ml) and the combined organic extracts were washed with several portions of water and then dried over anhydrous magnesium sulfate.

Evaporation of the solvent at reduced pressure provided an oily residue which glpc analysis (5 ft × 0.25 in. FFAP column, 175°, 60 ml/min of He) showed contained a single component. Isolation of this compound by glpc (above conditions) gave pure **5**, which was identified by comparison of its ir spectrum with that of an authentic sample.[23]

**Acknowledgment.** This work was supported by grants from the National Science Foundation (GP 20231), the donors of the Petroleum Research Fund, administered by the American Chemical Society, the University of Delaware Research Foundation, and the Delaware Institute of Medical Education and Research.

**Registry No.**—**1**, 20815-30-9; **2**, 52217-09-1.

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# Reductive Arylation of Aromatic Hydrocarbons. I. Naphthalene and Anthracene[1]

Roberto A. Rossi,* Celso C. Camusso, and Orlando D. Madoery

*Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Córdoba, Argentina*

*Received April 16, 1974*

Reductive phenylation of anthracene and naphthalene *via* treatment of the hydrocarbons with metals (sodium or potassium) in liquid ammonia and then with halobenzenes furnished 9-phenyl-9,10-dihydroanthracene and isomeric 1-phenyldihydronaphthalenes and 2-phenyldihydronaphthalenes in good yields. With lithium metal only the reduction of the hydrocarbon is obtained. A benzyne mechanism is proposed.

Metal–ammonia reduction and reductive alkylation of hydrocarbons have been widely used.[2] The structures of the dihydroaromatic products obtained by metal–ammonia reductions correlate to a remarkable degree with predictions of Hückel molecular orbital theory,[3] and several hydrocarbons such as naphthalene,[4] anthracene,[2b] phenanthrene,[5] chrysene,[6] cycloheptatriene,[7] fluoranthene,[8] biphenyl,[9] and terphenyl[10] have been reduced to the anions and then alkylated. The reductive methylations of anthracene, benz[*a*]anthracene, and dibenz[*a*,*h*]anthracene occur with regiospecificity to furnish the *cis*-dialkyldihydro derivatives.[11]

However, as far as we know, no attempt was made to perform a reductive *arylation* of these hydrocarbons. The recently discovered reaction of phenyl radical with hydrocarbons such as indene, fluorene, 1,3-pentadiene, and anethole[12] by the SRN1 mechanism[13] to furnish the aryl-substituted hydrocarbons prompted us to investigate the possibility of phenylating aromatic hydrocarbons under reductive conditions, and we performed some reactions to try the

reductive arylation of two hydrocarbons, anthracene and naphthalene.

## Results and Discussion

When bromobenzene or chlorobenzene were added to a solution of anthracene dianion prepared from the reaction of anthracene with 2 equiv of potassium metal in liquid ammonia,[2b] they reacted immediately, *before* the addition of potassium metal as electron source to form phenyl radicals,[12,13] giving a mixture of 9,10-dihydroanthracene (40–55%), 9-phenyl-9,10-dihydroanthracene (35–45%), 9,9-diphenyl-9,10-dihydroanthracene (4–10%) and 9,10-diphenyl-9,10-dihydroanthracene (2–6%).

There are three possible mechanisms to explain this reaction. The first is direct nucleophilic displacement of halogen. This possibility has been rejected because aromatic nucleophilic substitution occurs very slowly if at all, with unactivated aromatic substrates.[14]

The second is electron transfer from the dianion to the halobenzene, giving the radical anion of the latter, which then decomposes to phenyl radical, and the reaction with the anion in the usual SRN1 mechanism[12,13] (eq 1).

$$\begin{aligned} An^{2-} + PhX &\longrightarrow An\cdot^{-} + PhX\cdot^{-} \\ PhX\cdot^{-} &\longrightarrow Ph\cdot + X^{-} \end{aligned} \qquad (1)$$

The electron transfer reaction between dianions and neutral molecules is a known process.[15] Iodobenzene and diphenyliodonium bromide gave this reaction with the acetonate anion in liquid ammonia,[16,17] and the rate of decomposition of the former is dramatically increased by irradiation with near-uv lamps,[16] whereas bromobenzene or chlorobenzene do not react without irradiation.[16] Trimethylphenylammonium iodide and diethylphenyl phosphate also give phenyl radicals when treated with potassium metal[17] or irradiated in liquid ammonia.[16]

If the first step in this reaction is an electron transfer, any one of the substrates cited above should give this reaction and also the same product distribution. However, trimethylphenylammonium iodide or diethylphenyl phosphate neither in the dark nor irradiated with 350-nm uv lamps gave phenylated products. This rules out the electron transfer mechanism.[18] However, the addition of potassium metal to a mixture of anthracene dianion and trimethylphenylammonium iodide led to the formation of 9-phenyl-9,10-dihydroanthracene in small yield (run 12, Table I) probably through an SRN1 mechanism.

The third is the benzyne mechanism. Lindow, Cortez, and Harvey demonstrated that the biphenyl dianion and anthracene dianion react with ammonia to give the monoanion and amide ions (eq 2), the proton addition is essentially an irreversible process by experiments with deuterium exchange, and there are doubts whether these dianions can exist in ammonia at all.[9]

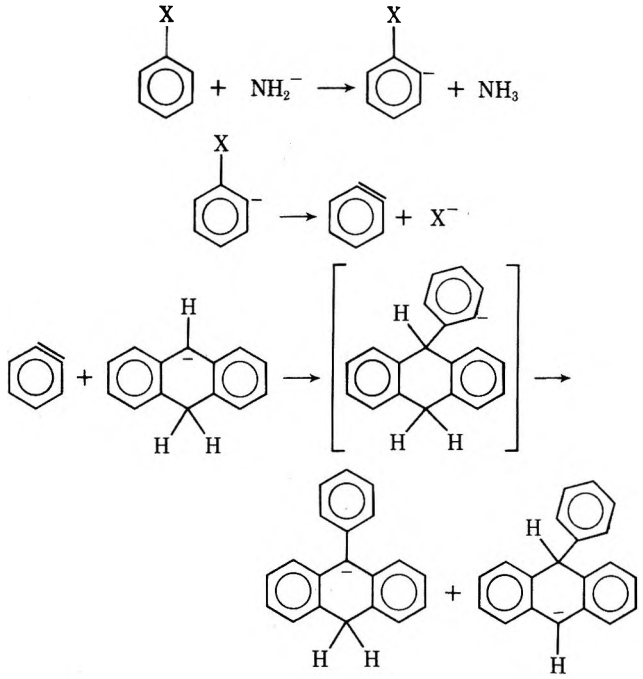
$$An^{2-} + NH_3 \rightleftharpoons AnH^{-} + NH_2^{-} \qquad (2)$$

It is known that amide ion reacts with halobenzenes to give *o*-halophenyl anion, which then decomposes to benzyne,[19a] which in turn could be trapped by anthracene mono- or dianion, giving the observed products (Scheme I). Reactions of benzyne with carbanions are well known.[19b]

9,9-Diphenyl-9,10-dihydroanthracene and 9,10-diphenyl-9,10-dihydroanthracene are products from 9-phenyl-9,10-dihydroanthracene anion and benzyne, and represent a double arylation.

Since the formation of benzyne requires a reaction medium basic enough to form the o-halophenyl anion, addition of lithium metal to form the dianion, instead of potassium metal, will reduce the basicity of the solution owing to the insolubility of the lithium amide in ammonia,[20] which will shift the equilibrium of eq 2 to the right. As expected, when lithium metal was used to form anthracene dianion in ammonia, and chlorobenzene was added, no reaction occurred (run 5, Table I).

**Scheme I**



In the reaction of anthracene dianion with a fivefold excess of chlorobenzene, there is no increase in the yield of phenylation (run 3, Table I), and when anthracene dianion was half neutralized by adding 1 equiv of solid ammonium bromide to form anthracene monoanion, and chlorobenzene was added, no phenylation products were found (run 6, Table I).

From the observations discussed above, we conclude that the anthracene dianion is basic enough to be in equilibrium with amide ion, and form benzyne from halobenzenes, and the latter reacts with anthracene anion to form the products observed.

Further evidence to demonstrate that the reaction occurs *via* a benzyne mechanism is the lack of the reaction of 2,6-dimethylchlorobenzene with naphthalene dianion, owing to the impossibility of this substrate forming benzyne.[21]

All these reactions were carried out after 5 min of the formation of the anion of the reduced species (mono- or dianion), which is recognized by the formation of the red color. When the halobenzene was added 60 min after the red color had been formed, no phenylated products were formed (run 7, Table I). When the halobenzene was added 15 min after the red color had been formed, a decrease in the yield was observed (run 8, Table I). These phenomena are not fully understood and are discussed in the reductive phenylation of naphthalene.

**Reductive Phenylation of Naphthalene.** Metal–ammonia reduction of naphthalene and its derivatives is a well-known reaction, and the reduction proceeds through naphthalene radical anion and dianions.[2] It is generally assumed that the position of protonation by a suitable proton donor is governed by the charge distribution in these intermediates species as provided by esr data[22] or quantum chemical calculations.[3,23]

The reduction of naphthalene with lithium metal in liquid ammonia is very rapid and the initially formed product is 1,4-dihydronaphthalene, undergoing amide-catalyzed

**Table I**
**Reactions of Anthracene Dianion with Monosubstituted Benzenes in Liquid Ammonia**

| Run | Anthracene, mol | K metal, mol | PhX | Mol | Product yield, %[e,f] DHA[a] | 9-PDHA[b] | 9,9-DPDHA[c] | 9,10-DPDHA[d] |
|---|---|---|---|---|---|---|---|---|
| 1 | 0.104 | 0.208 | Cl | 0.112 | 54 | 36 | 4 | 2 |
| 2 | 0.120 | 0.300 | Cl | 0.132 | 38 | 43 | 11 | 6 |
| 3 | 0.128 | 0.260 | Cl | 0.64 | 35 | 40 | 16 | 6 |
| 4 | 0.140 | 0.086[g] | Cl | 0.048 | 40 | 41 | 8 | 4 |
| 5 | 0.040 | 0.280[h] | Cl | 0.152 | 100 | | | |
| 6[i] | 0.072 | 0.144 | Cl | 0.072 | 100 | | | |
| 7 | 0.052 | 0.108 | Cl[j] | 0.052 | 100 | | | |
| 8 | 0.048 | 0.101 | Cl[k] | 0.048 | 78 | 17 | | |
| 9 | 0.192 | 0.404 | Br | 0.212 | 41 | 44 | 9 | 3 |
| 10 | 0.100 | 0.200 | $^{+}NMe_3$ | 0.100 | 100 | | | |
| 11 | 0.048 | 0.104 | $^{+}NMe_3$ | 0.052[l] | 100 | | | |
| 12 | 0.056 | 0.112 | $^{+}NMe_3$ | 0.056[m] | 95 | 5[n] | | |
| 13 | 0.024 | 0.052 | DEPP[o] | 0.024 | 100 | | | |

[a] 9,10-Dihydroanthracene. [b] 9-Phenyl-9,10-dihydroanthracene. [c] 9,9-Diphenyl-9,10-dihydroanthracene. [d] 9,10-Diphenyl-9,10-dihydroanthracene. [e] Yields determined by glpc. [f] Aniline and biphenylamine were detected in small amounts (1–6%). [g] Na metal. [h] Li metal. [i] After the formation of anthracene dianion, 0.072 mol of $NH_4Br$ was added. [j] PhCl was added after 60 min of formation of anthracene dianion. [k] PhCl was added after 15 min of formation of anthracene dianion. [l] Irradiated with 350-nm uv lamps. [m] 0.080 mol of K metal was added to produce phenyl radicals. Other products detected but not quantified: benzene, aniline, and biphenylamine. [o] Diethylphenyl phosphate ester.

**Table II**
**Reactions of Naphthalene Dianion with Monosubstituted Benzenes in Liquid Ammonia**

| Run | Naphthalene, mol | K metal, mol | PhX | Mol | Product yield, %[e,f] DHN[a] | 1-PDHN[b] | 2-PDHN[c] | DPDHN[d] |
|---|---|---|---|---|---|---|---|---|
| 1[g] | 0.044 | 0.092 | Cl | 0.044 | 33 ∓ 7 | 32 ∓ 6 | 25 ∓ 3 | 3 ∓ 1 |
| 2[h] | 0.048 | 0.100 | Br | 0.048 | 35 | 30 | 28 | 2 |
| 3[i] | 0.040 | 0.080 | Cl | 0.040 | 100 | | | |
| 4 | 0.040 | 0.100[j] | Cl | 0.040 | 100 | | | |
| 5 | 0.028 | 0.056 | $^{+}NMe_3$ | 0.028 | 100 | | | |
| 6 | 0.042 | 0.084 | 2,6-DMCB[k] | 0.042 | 100 | | | |

[a] Dihydronaphthalenes. [b] Isomeric 1-phenyldihydronaphthalenes; no attempt was made to identify them. [c] Isomeric 2-phenyldihydronaphthalenes; no attempt was made to identify them. [d] Diphenyldihydronaphthalenes. [e] Yields determined by glpc. [f] Aniline and biphenylamine were detected in small amounts. [g] Average of four runs. [h] Average of two runs. [i] Two runs, at 15 and 60 min after the formation of the naphthalene dianion. [j] Li metal. [k] 2,6-Dimethylchlorobenzene, recovered almost quantitatively.

isomerization to 1,2-dihydronaphthalene in about 1 hr at −33°.[24]

When naphthalene dianion was formed by the reaction of potassium metal and naphthalene in liquid ammonia, and chlorobenzene or bromobenzene were added, a complex mixture of products was found, mainly 1,2-dihydronaphthalene and 1,4-dihydronaphthalene (33–35%), 1-phenyldihydronaphthalenes (30–32%), and 2-phenyldihydronaphthalenes (25–28%). By gas–liquid partition chromatography technique, there were several peaks with similar retention times, probably due to isomeric 1-phenyldihydronaphthalenes and 2-phenyldihydronaphthalenes. No attempt to isolate them was made, and the crude products of phenylation were dehydrogenated to 1-phenylnaphthalene and 2-phenylnaphthalene and characterized as such.

When lithium metal was used instead of potassium metal to form naphthalene dianion, no reaction occurred (run 4, Table II), and when trimethylphenylammonium iodide was used instead of chlorobenzene or bromobenzene, no reaction occurred either (run 5, Table II).

All these facts suggest, as in the reductive phenylation of anthracene, that a benzyne mechanism occurs. As a means to demonstrate absolutely the formation of benzyne as a route to phenylated products, we turned our attention to arylation with 2,6-dimethylchlorobenzene, which cannot form an aryne with a strong base.[21]

As anticipated, it was unreactive with the naphthalene dianion under the same experimental conditions as chloro- or bromobenzene, and it was recovered unchanged (run 6, Table II).

From these observations, we conclude that the reaction of alkali metals with naphthalene in liquid ammonia gives naphthalene dianion, which is protonated by the ammonia in the sense of eq 2, and the amide ion precipitates (lithium amide) or gives benzyne (potassium amide) with halobenzenes, which reacts with naphthalene anion, giving 1-phenyldihydronaphthalenes and 2-phenyldihydronaphthalenes in almost the same ratio, independently of the halobenzene used, probably owing the presence of two isomeric anions.

It is known that 1,4-dihydronaphthalene is formed first and then by an amide-catalyzed reaction gives 1,2-dihydronaphthalene.[24] In an attempt to try to obtain selective phenylation of naphthalene, once it was formed, 1 hr was allowed to pass at −33° before the addition of the halobenzene, but no phenylated products were found. In the previ-

ous reactions, only 5 min was allowed to pass before the addition of the halobenzene. The reaction was repeated after 15 min had passed and again no phenylated products were found.

This rapid decay of the reactivity of the naphthalene anion is not fully understood, but it could be due to the slow protonation of the naphthalene monoanion by ammonia to give the reduced and neutral dihydronaphthalene and amide anions (eq 3).

$$Naph^{2-} + NH_3 \rightleftharpoons NaphH^- + NH_2^- \quad \text{(fast)} \qquad (2)$$

$$NaphH^- + NH_3 \rightleftharpoons NaphH_2 + NH_2^- \quad \text{(slow)} \qquad (3)$$

Kinetic and equilibrium studies of the protonation of the dihydronaphthalene anion and dihydroanthracene anion are being developed in our laboratories to test this idea.

## Experimental Section

**General.** Boiling and melting points have not been corrected. Nmr spectra were recorded on a Varian T-60 nuclear magnetic resonance spectrometer with $CCl_4$ as solvent and all spectra are reported in parts per million relative to TMS ($\delta$). All ir spectra are recorded on a Beckman IR-8 spectrophotometer. Ultraviolet spectra were recorded on a Beckman DB-6 spectrophotometer. Thin layer chromatography was performed on silica gel plates. Gas chromatographic analyses were performed on a F & M biomedical gas chromatograph, Model 400, with flame ionization detector and yields were determined by peak area with a 6 ft × 3/16 in. column packed with 4% silicon rubber SE-30 on 60–80 Chromosorb P.

**Reagents.** Naphthalene (Eastman), anthracene (Fluka), chlorobenzene (Fluka), and bromobenzene (Fluka) were commercially available and were used as received. Trimethylphenylammonium iodide and diethylphenyl phosphate ester were available from previous work.[17] 2,6-Dimethylchlorobenzene was obtained by a Sandmeyer reaction of 2,6-dimethylaniline (K & K Laboratories): bp 181–184° (720 mm) (lit.[25] bp 185–187°); nmr $\delta$ 2.32 (s, 6 H) and 7.12 (s, 3 H). Alkali metals were cut in small pieces and washed free of oil with dried ether or pentane immediately before addition to reaction mixtures. Liquid ammonia was dried with sodium metal and distilled under nitrogen into the reaction flask.

**Reductive Phenylation of Anthracene.** A procedure for reductive phenylation of anthracene is representative. The reaction was performed in a three-neck round-bottom flask fitted with a Dry Ice–isopropyl alcohol condenser, stirred by a magnetic stirrer and constantly swept by a slow stream of dry nitrogen. To distilled liquid ammonia (350 ml) potassium metal (0.101 mol) was added and solid anthracene (0.048 mol) was added to the blue solution. After the blue color of the alkali metal had changed to a dark orange-red color (about 4–8 min), bromobenzene (0.053 mol) was added drop by drop from a separatory funnel. At the end the color changed to a dark violet. After 10 min of reaction, solid ammonium chloride was then added to quench the reaction, followed by 150 ml of diethyl ether, and the ammonia was allowed to evaporate. The ether extract was washed with water and dried over anhydrous $Na_2SO_4$. A small portion of the ether extract was analyzed by glpc. The ether was evaporated from the rest of the ether layer, and the residue was fractionately sublimed. The products isolated were 9,10-dihydroanthracene (60–70°, 1 Torr), mp 106–108° (lit.[26] mp 89–90°), nmr spectrum $\delta$ 3.86 and 3.94 (2 H), 5.14 (1 H), and an authentic sample,[27] and 9-phenyl-9,10-dihydroanthracene (110–115°, 1 Torr), recrystallized from ethanol, mp 88–90° (lit.[28] mp 89–90°), nmr spectrum $\delta$ 3.86 and 3.94 (2 H), 5.14 (1 H), and *ca.* 7.2 (13 H) [lit.[28] ($CS_2$ as solvent) $\delta$ 3.70 and 3.88 (2 H) and 5.04 (1 H)]. A sample was dehydrogenated to 9-phenylanthracene by heating with sulfur at 190–200° during 30 min, and the residue was crystallized from ethyl alcohol, mp 150–152° (lit.[29] mp 154–155°).

A mixture of 9,9-diphenyl-9,10-dihydroanthracene and 9,10-diphenyl-9,10-dihydroanthracene sublimed at 150–160° (1 Torr), determined by nmr and glpc analysis. 9,10-Diphenyl-9,10-dihydroanthracene was isolated pure by fractional recrystallization from diethyl ether, mp 188–193° (lit.[30] mp 194–195°), and by nmr analysis there were two isomers, cis and trans, $\delta$ 5.25 and 5.33 (2 H) and 7.13 and 7.22 (18 H). After the ether was distilled off, 9,9-diphenyl-9,10-dihydroanthracene was obtained, nmr $\delta$ 3.86 (2 H) and *ca.* 7.1 (18 H).

**Attempt to Phenylate Anthracene Dianion with Trimethylphenylammonium Iodide.** The procedure was similar to the phenylation using halobenzenes, except that solid trimethylphenylammonium iodide was added. The reactions were carried out in the dark, or irradiated with two 350-nm 250-W high-pressure mercury lamps (Philips, Model HPT) during 1 hr. The reactions were quenched and the work-up was similar to the previous one, but no phenylated products were found.

**Potassium Metal as Catalyst.** The procedure was similar to the method described previously.[12] Once trimethylphenylammonium iodide was added to the anthracene dianion in ammonia, potassium metal was added in small pieces. After all the K metal was added, the reaction was quenched by adding ammonium chloride and the work-up was similar to those of the other reactions. 9-Phenyl-9,10-dihydroanthracene was obtained in 5% yield by glpc.

**Reductive Phenylation of Naphthalene.** The procedure was similar to the reductive phenylation of anthracene. To 250 ml of dry ammonia, K metal (23 mmol) was added and solid naphthalene (11 mmol) was added to the blue solution. When the blue color of the alkali metal had changed to a dark red color (about 3–7 min) and after 5 min with this color, chlorobenzene (11 mmol) was added and the reaction mixture was quenched by adding ammonium chloride after 10 min of reaction. The ammonia was allowed to evaporate and the residue was treated with water and twice extracted with diethyl ether. The ether extract was washed with water and dried over anhydrous $Na_2SO_4$. A small portion of the ether was analyzed by glpc. The ether was evaporated and the residue was treated with powdered sulfur (11 mmol) and heated to 230–240° for 0.5 hr.[31] The black residue was extracted with ether, and a small portion was analyzed by glpc. The ether was evaporated and vacuum distilled, giving naphthalene, 1-phenylnaphthalene (210–230°, 67 Torr), and 2-phenylnaphthalene (230–250°, 67 Torr). Pure 1-phenylnaphthalene was obtained by column chromatography on silica gel, using light petroleum as solvent, giving a waxy, white solid, uv (cyclohexane) $\lambda_{max}$ 228 and 285 nm [lit.[32] uv (cyclohexane) $\lambda_{max}$ 228 and 285 nm]. 2-Phenylnaphthalene was purified by recrystallization in ethanol, giving a white solid, mp 102–103° (lit.[33] mp 101–102°), uv (cyclohexane) $\lambda_{max}$ 250 and 285 nm [lit.[34] uv (cyclohexane) $\lambda_{max}$ 250 and 285 nm].

**Acknowledgment.** The gas chromatograph made available to us by Dr. R. Caputto is greatly appreciated.

**Registry No.**—Naphthalene, 91-20-3; anthracene, 120-12-7; chlorobenzene, 108-90-7; bromobenzene, 108-86-1; trimethylphenylammonium iodide, 98-04-4; diethyphenylphosphate ester, 2510-86-3; 2,6-dimethylchlorobenzene, 6781-98-2; 9-phenyl-9,10-dihydroanthracene, 13577-28-1; *cis*-9,10-diphenyl-9,10-dihydroanthracene, 52196-17-5; *trans*-9,10-diphenyl-9,10-dihydroanthracene, 52196-18-6; 9,9-diphenyl-9,10-dihydroanthracene, 7477-39-6; 1-phenylnaphthalene, 605-02-7; 2-phenylnaphthalene, 612-94-2.

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# Stereoselective Organometallic Alkylation Reactions. III. "Ate" Complex Addition to Cyclic and Bicyclic Ketones[1]

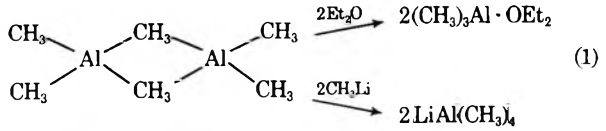
Eugene C. Ashby,* Li-Chung Chao, and Joseph Laemmle

*School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332*

*April 8, 1974*

The stereochemistry of addition of a variety of "ate" complexes with such ketones as 4-*tert*-butylcyclohexanone, 3,3,5-trimethylcyclohexanone, norcamphor, and camphor has been studied. The reaction of $LiAl(CH_3)_4$ and $LiAl(i\text{-}C_4H_9)_3CH_3$ with 4-*tert*-butylcyclohexanone in benzene, diethyl ether, tetrahydrofuran, and dimethoxyethane results in predominant axial attack to form equatorial alcohol (*via* methylation), regardless of reactant ratio or reaction time. However, the reaction of other "ate" complexes such as $LiB(CH_3)_4$ and $Li_nM(CH_3)_{2+n}$ compounds (where M = Mg and Zn and $n$ = 1, 2, or 3) with 4-*tert*-butylcyclohexanone yields predominantly equatorial attack in diethyl ether. Reaction of all ate complexes studied with 3,3,5-trimethylcyclohexanone yields 100% axial alcohol. Reaction of norcamphor and camphor with all ate complexes studied yields 95% endo alcohol and 99% exo alcohol, respectively, regardless of reactant ratio.

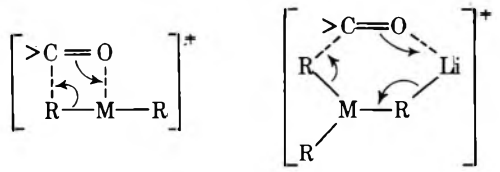
Ate complexes are the result of interaction between an electron-deficient metal alkyl and a Lewis base.[2] Trimethylaluminum, for example, exists as a dimer with two methyl groups bridge bonded in such a way that the coordination about the aluminum atom is tetrahedral.[3] In ether solution the weak methyl bridge bonds are broken in favor of ether solvation of the trimethylaluminum. If methylithium is added to the solution, the ether molecule is replaced by a methyl carbanion to form the ate complex $LiAl(CH_3)_4$. Basically these are simply acid–base reactions where the Lewis acid $[Al(CH_3)_3]$ reacts with a base (*e.g.*, ether or $CH_3Li$) to form a salt. In general, the tendency toward




(1)

ate complex formation and the stability of the complex depend to a large degree on the particular metals involved and to a lesser degree on the ligand size and charge. For example, the tendency of the adducts $LiM(C_6H_5)_3$ to dissociate into phenyllithium and $M(C_6H_5)_2$ increases in the order $LiBe(C_6H_5)_3 < LiZn(C_6H_5)_3 < LiMg(C_6H_5)_3 < LiCd(C_6H_5)_3 < LiHg(C_6H_5)_3$. In general, the smaller the central metal atom and the more electropositive the group I metal the more stable is the adduct. Indeed, in the above series the largest metal, mercury, shows no tendency to form an adduct.

No reports concerning either the mechanism or stereochemistry of ate complex addition to ketones has appeared in the literature. Since the central metal atom of ate complexes such as $LiAl(CH_3)_4$ or $Li_2Mg(CH_3)_4$ do not have available orbitals for complexation with a carbonyl group as do $(CH_3)_3Al$ and $(CH_3)_2Mg$, there is reason to believe that the mechanism and hence stereochemistry of reaction should be different. In addition it was felt that since lithium is capable of complexing with carbonyl compounds, possibly ate complexes of the type $Li_nM(CH_3)_{2+n}$ might react by complexation of the lithium atom with the carbonyl oxygen atom. Such possibilities, in addition to recent re-




ports concerning the composition of ate complexes in solution,[4] have prompted us to investigate these compounds as stereoselective alkylating agents.

## Experimental Section

**Materials.** Methyllithium was obtained from Foote Mineral Co. and was used without further purification. Analysis of $CH_3Li$ gave $CH_3$:Li ratios ranging from 0.95:1 to 1:1 and essentially no halide was detected. Solutions of $CH_3Li$ were refrigerated in serum capped bottles and their concentrations were checked prior to use. Dimethylmagnesium was prepared from dimethylmercury by reaction with Dow Chemical Co. doubly sublimed magnesium turnings.[5] Trimethylborane was prepared by reaction of $BF_3 \cdot O(C_2H_5)_2$ with methylmagnesium bromide. The trimethylborane was distilled from the reaction vessel and collected at Dry Ice–acetone temperature. Dimethylzinc was prepared by reaction of methylmagnesium bromide with anhydrous zinc chloride followed by distillation of the dimethylzinc under reduced pressure. Potassium *tert*-butoxide was prepared by reaction of potassium metal with excess *tert*-butyl alcohol. Excess *tert*-butyl alcohol was removed

under vacuum at 80°.[6] Trimethyl- and triisobutylaluminum, obtained from Texas Alkyls, were purified by vacuum distillation.

4-*tert*-Butylcyclohexanone (Frinton) was distilled under vacuum and found by glpc to be 99.9% pure. Tetradecane (99.9% pure, Chemical Sample Co.) was used as an internal standard. 3,3,5-Trimethylcyclohexanone (99% pure, Chemical Sample Co.) was distilled over 4A molecular sieves at 1 mm at 80°. Norcamphor (97% pure, Aldrich Chemical Co., Milwaukee, Wis.) was sublimed at 1.8 mm at 53° and found by glpc to be 99% pure. Camphor (Fisher Scientific Co.) was sublimed at 2 mm at 75° twice and found by glpc to be 99% pure.

**Preparations.** $LiB(CH_3)_4$ and $LiAl(CH_3)_4$ were prepared by addition of $CH_3Li$ to an excess of trimethylborane and trimethylaluminum, respectively, in diethyl ether.[7] The products were purified by removal of all solvent and excess boron or aluminum alkyl by gentle heating (70°) under vacuum followed by redissolution in the appropriate solvent. Ether solutions of $LiAl(i\text{-}C_4H_9)_3CH_3$ were prepared by adding a benzene solution of $(i\text{-}C_4H_9)_3Al$ to ether Analysis after removal of ether indicated the product to be $LiAl(i\text{-}C_4H_9)_3CH_3 \cdot O(C_2H_5)_2$. Even mild heating results in the elimination of isobutylene. Benzene solutions of $LiAl(i\text{-}C_4H_9)_3CH_3$ were prepared by adding a benzene solution of $(i\text{-}C_4H_9)_3Al$ to ether desolvated (90°, 100 $\mu$, 24 hr) $CH_3Li$.

Tri-*n*-octylpropylammonium bromotrimethylaluminate was prepared by addition of an appropriate amount of $(CH_3)_3Al$ in ether or benzene to dry tri-*n*-octylpropylammonium bromide. In the ether case, ate complex formation was indicated by the fact that the ammonium salt, which shows little solubility in diethyl ether, immediately dissolved on addition of trimethylaluminum. Preparation of ate complexes such as $KMg(CH_3)_2O\text{-}t\text{-}C_4H_9$, $KAl(CH_3)_3O\text{-}t\text{-}C_4H_9$, $LiMg(CH_3)_3$, $Li_2Mg(CH_3)_4$, $Li_2Zn(CH_3)_4$, etc., were prepared by mixing the appropriate alkali metal alkyl or alkoxide to the appropriate alkaline earth metal alkyl in the appropriate ratios. No attempt was made to characterize these ate complexes since information concerning their formation and stability exists in the literature.[2,4]

**Reactions.** All reactions were carried out on a vacuum manifold equipped with three-way glass stopcocks attached to ₹ 24/40 inner joints. Round-bottom flasks equipped with ₹ 24/40 outer joints were attached to the manifold and the system was evacuated, flamed, and refilled with nitrogen three times prior to use. Standard solutions of reagents were introduced into the reaction vessel *via* syringes equipped with stainless steel needles. Mixing was accomplished *via* rapid stirring with a Teflon stirring bar. After a desired amount of time had elapsed, the reaction mixtures were hydrolyzed with distilled water or saturated ammonium chloride and prepared for analysis.

**Analysis.** Product analysis for the isomeric alcohols resulting from methylation of 4-*tert*-butylcyclohexanone,3,3,5-trimethylcyclohexanone, and norcamphor have been previously described.[8] Products resulting from methylation of camphor were analyzed by glpc. The identity of the peaks was determined by comparison of the hydrolyzed products formed on reaction of camphor with methyllithium and methylmagnesium bromide.[9]

Aluminum analysis was carried out by EDTA–zinc acetate titration at pH 4 using dithizone as an indicator. Magnesium and zinc analysis were carried out by EDTA titration at pH 10 using Eriochrome Black T as an indicator. Potassium and lithium analysis were carried out employing flame photometry. Gas analysis was carried out on a high vacuum line.

## Results and Discussion

The stereochemistry of reaction of ate complexes of magnesium, boron, and zinc with several ketones is illustrated in Table I. The stereochemistry of addition of $CH_3Li$, $(CH_3)_2Mg$, and $(CH_3)_2Zn$ is also shown for comparison. The data in Table I represents only a fraction of the total data collected, but demonstrates all factors discussed. The principle feature of all these reactions is that attack by the ate complex occurs predominantly at the less hindered side of the carbonyl group in every case. In addition, the ratio of isomeric alcohols obtained by alkylation with ate complexes is essentially the same as that found for alkylation by the separate reagents which compose the ate complex. Thus, the following general reaction scheme, employing $Li_2Mg(CH_3)_4$ as a specific example, can be written for ate complex addition to ketones. The fact that the separate

$$\begin{array}{ccccc} Li_2Mg(CH_3)_4 & \rightleftharpoons & 2CH_3Li & + & Mg(CH_3)_2 \\ \downarrow \text{ketone, path I} & & \downarrow \text{ketone, path II} & & \downarrow \text{ketone, path III} \\ \text{products} & & \text{products} & & \text{products} \end{array} \quad (2)$$

reactants in each case [$CH_3Li$, $(CH_3)_2Mg$, and $(CH_3)_2Zn$] give the same stereochemistry as the ate complex appears to indicate that ate complex alkylation may occur *via* paths II and III rather than path I. To investigate this more fully, the ate complex $LiMg(C_6H_5)_2CH_3$ was prepared. The separate reactants $CH_3Li$ which attacks 4-*tert*-butylcyclohexanone predominantly from the equatorial side and $(C_6H_5)_2Mg$ which attacks 4-*tert*-butylcyclohexanone to a slightly greater extent from the axial side might form an ate complex from which the stereochemistry of methyl transfer would be considerably different from that observed with $CH_3Li$. If the latter proved to be the case, it would strongly indicate that path I is the correct description of ate complex alkylation. Unfortunately, $LiMg(C_6H_5)_2CH_3$ methylates 4-*tert*-butylcyclohexanone with essentially the same stereochemistry as $CH_3Li$. Thus, a clear choice between path I and paths II and III cannot be made, although it appears that these reactions are proceeding by path I.

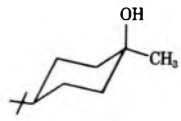
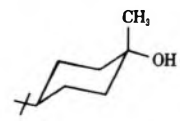
The presence of a salt, tri-*n*-octylpropylammonium bromide, in the reaction of $CH_3MgBr$ with 4-*tert*-butylcyclohexanone had negligible effect on the stereochemistry. Ate complex formation was definitely indicated in this case since the ammonium salt itself is insoluble in diethyl ether but dissolves on addition of an equivalent amount of $CH_3MgBr$ [or $(CH_3)_3Al$]. The addition of a strong base, potassium *tert*-butoxide, in the reaction of $(CH_3)_2Mg$, $(CH_3)_3Al$, and $CH_3MgBr$ with the same ketone has no effect on the stereochemical results.

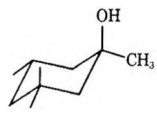
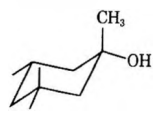
Special mention must be made of alkylation involving $LiB(CH_3)_4$ with 4-*tert*-butylcyclohexanone.This ate complex, as previous reports indicate,[7] is stable in a variety of polar solvents, *e.g.*, water, isopropyl alcohol, diethyl ether, and benzene.[10] Attempted alkylation of 4-*tert*-butylcyclohexanone using $LiB(CH_3)_4$ in diethyl ether, isopropyl alcohol, or benzene at room temperature failed to yield any evidence of the expected alcohols even after prolonged reaction times. Although no reaction was observed in isopropyl alcohol at reflux temperature, reaction did occur slowly in benzene at reflux temperature to yield 48% total alcohol products after 3 days at a 5:1 reagent:ketone reactant ratio. Although it is not clear whether reaction occurred *via* path I or path II in this case, it is noteworthy that to our knowledge this is the first reported alkylation of a ketone by a saturated alkylborane.

The isomer ratios in all reactions reported in this paper are independent of reaction time. Consequently, isomer equilibrium is not a factor under the conditions of these reactions.

The ate complexes of aluminum are considered separately due to the unusual stereochemistry observed in their reaction with 4-*tert*-butylcyclohexanone (Tables II and III). Lithium tetramethylaluminate alkylates 4-*tert*-butylcyclohexanone predominantly from the most hindered axial side in diethyl ether, tetrahydrofuran, and dimethoxyethane. This is an unusual result because all reagents except excess $(CH_3)_3Al$ in benzene[7] and $(CH_3)_2Zn$ and $(CH_3)_2Cd$ in the presence of magnesium halide[11] attack this ketone from the less hindered equatorial side. The per cent equatorial alcohol formed (~58%) is essentially the same in all solvents and is independent of reactant concentrations and ratios. In the more basic solvents, a greater amount of ketone is recovered indicating a larger percent-

**Table I**
**Reaction of Ate Complexes of Boron, Magnesium, and Zinc with Ketones in Diethyl Ether**

| Reagent | Initial concentration, *M* | Ratio of reagent:ketone | Ketone[a] | % axial alcohol[b]  | % equatorial alcohol[b]  |
|---|---|---|---|---|---|
| $CH_3Li$ | 0.76 | 4.0 | A | 65 | 35 |
| $(CH_3)_2Mg$ | 0.44 | 4.0 | A | 70 | 30 |
| $(CH_3)_2Zn$ | 0.20 | 4.0 | A | No reaction | |
| $LiB(CH_3)_4$ | 0.20 | 1.0 | A | No reaction after 4 days | |
| $LiB(CH_3)_4$ | 0.20 | 3.0 | A | No reaction after 4 days | |
| $LiB(CH_3)_4$ | 0.20 | 5.0 | A | 67[c] | 33[c] |
| $LiMg(CH_3)_3$ | 0.22 | 1.0 | A | 69 | 31 |
| $LiMg(CH_3)_3$ | 0.36 | 4.0 | A | 70 | 30 |
| $Li_2Mg(CH_3)_4$ | 0.14 | 2.0 | A | 69 | 31 |
| $Li_3Mg(CH_3)_5$ | 0.14 | 2.0 | A | 71 | 29 |
| $LiMg(C_6H_5)_2CH_3$ | 0.10 | 1.0 | A | 65[d] | 35[d] |
| $LiZn(CH_3)_3$ | 0.23 | 1.0 | A | 64 | 36 |
| $LiZn(CH_3)_3$ | 0.37 | 4.0 | A | 70 | 30 |
| $Li_2Zn(CH_3)_4$ | 0.14 | 2.0 | A | 68 | 32 |
| $Li_3Zn(CH_3)_5$ | 0.14 | 2.0 | A | 69 | 31 |
| $KMg(CH_3)_2O\text{-}t\text{-}C_4H_9$ | 0.027 | 4.0 | A | 71 | 29 |
| $[(n\text{-}C_8H_{17})_3C_3H_7N]Mg(CH_3)_2Br$ | 0.132 | 3.0 | A | 75 | 25 |

| Reagent | Initial concentration, *M* | Ratio of reagent:ketone | Ketone | % axial alcohol[b]  | % equatorial alcohol  |
|---|---|---|---|---|---|
| $CH_3Li$ | 0.19 | 1.0 | B | 100 | 0 |
| $(CH_3)_2Mg$ | 0.21 | 1.0 | B | 100 | 0 |
| $(CH_3)_2Zn$ | 0.16 | 1.0 | B | No reaction | |
| $LiMg(CH_3)_3$ | 0.36 | 4.0 | B | 100 | 0 |
| $Li_2Mg(CH_3)_4$ | 0.21 | 1.0 | B | 100 | 0 |
| $Li_3Mg(CH_3)_5$ | 0.27 | 4.0 | B | 100 | 0 |
| $LiZn(CH_3)_3$ | 0.25 | 1.0 | B | 100 | 0 |
| $Li_2Zn(CH_3)_4$ | 0.30 | 4.0 | B | 100 | 0 |
| $Li_3Zn(CH_3)_5$ | 0.25 | 4.0 | B | 100 | 0 |

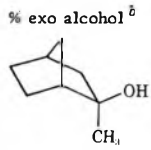
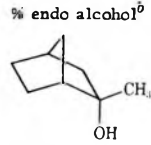
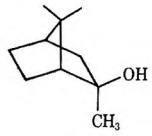
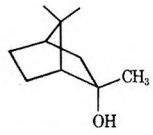
| Reagent | Initial concentration, *M* | Ratio of reagent:ketone | Ketone | % exo alcohol[b]  | % endo alcohol[b]  |
|---|---|---|---|---|---|
| $CH_3Li$ | 0.80 | 4.0 | C | 5 | 95 |
| $(CH_3)_2Mg$ | 0.46 | 3.0 | C | 5 | 95 |
| $(CH_3)_2Zn$ | 0.28 | 3.0 | C | No reaction | |
| $LiMg(CH_3)_3$ | 0.33 | 3.0 | C | 5 | 95 |
| $Li_2Mg(CH_3)_4$ | 0.28 | 1.0 | C | 5 | 95 |
| $Li_3Mg(CH_3)_5$ | 0.27 | 3.0 | C | 5 | 95 |
| $LiZn(CH_3)_3$ | 0.32 | 1.0 | C | 5 | 95 |
| $Li_2Zn(CH_3)_4$ | 0.32 | 3.0 | C | 5 | 95 |
| $Li_3Zn(CH_3)_5$ | 0.27 | 3.0 | C | 5 | 95 |

**Table I**
*(Continued)*

| Reagent | Initial concentration, *M* | Ratio of reagent:ketone | Ketone | % exo alcohol  | % endo alcohol  |
|---|---|---|---|---|---|
| $CH_3Li$ | 0.23 | 1.0 | D | 99 | 1 |
| $(CH_3)_2Mg$ | 0.51 | 4.0 | D | 99 | 1 |
| $(CH_3)_2Zn$ | 0.22 | 4.0 | D | No reaction | |
| $LiMg(CH_3)_3$ | 0.37 | 4.0 | D | 99 | 1 |
| $Li_2Mg(CH_3)_4$ | 0.22 | 1.0 | D | 99 | 1 |
| $Li_3Mg(CH_3)_5$ | 0.27 | 4.0 | D | 99 | 1 |
| $LiZn(CH_3)_3$ | 0.39 | 4.0 | D | 99 | 1 |
| $Li_2Zn(CH_3)_4$ | 0.22 | 1.0 | D | 99 | 1 |
| $Li_3Zn(CH_3)_5$ | 0.26 | 4.0 | D | 99 | 1 |

[a] A, 4-*tert*-butylcyclohexanone; B, 3,3,5-trimethylcyclohexanone; C, norcamphor; D, camphor. [b] Normalized as % axial (exo) alcohol + % equatorial (endo) alcohol = 100%. [c] Reaction was carried out in refluxing benzene for 3 days. Total yield of alcohol products was 48%. Reaction in benzene at room temperature was not carried out owing to low solubility of $LiB(CH_3)_4$ in benzene. [d] Methylation products.

age of enolization. Lithium triisobutylmethylaluminate yields even larger percentages of equatorial alcohol *via* methylation, although large amounts of reduction product are formed.

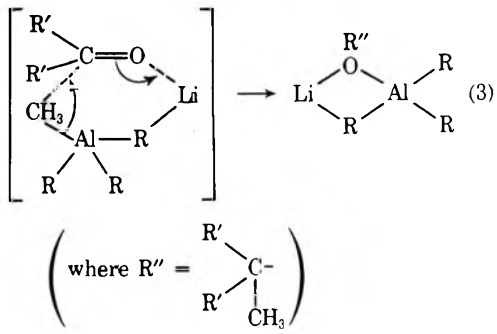
The reason for the unusually high percentage of axial attack in these cases is not immediately obvious. The normal controlling factors of the stereochemistry of alkylation, steric approach control, and torsional strain are not sufficient to explain the observed isomer ratios in these reactions.[12] The "Compression Effect," which was shown to be the controlling factor in the alkylation of 4-*tert*-butylcyclohexanone with excess $(CH_3)_3Al$ in benzene and proposed for the $(CH_3)_2Zn$ and $(CH_3)_2Cd$ reactions,[12] may also be the controlling factor in the $LiAl(CH_3)_4$ reactions. However, nothing is known about the mechanism of ate complex addition to ketones and the exact way in which a compression effect might operate is not clear.

The stereochemistry of addition of aluminum ate complexes to 4-*tert*-butylcyclohexanone in benzene is illustrated in Table III. In 1:1 reactant ratio $LiAl(CH_3)_4$ gives slightly less axial attack on 4-*tert*-butylcyclohexanone in benzene (48%) than in polar solvents (58%). In addition, the observed isomer ratio of the product is dependent on reactant ratio with the percentage of axial attack increasing as the ate complex:ketone ratio increases.

The reaction of $LiAl(i\text{-}C_4H_9)_3CH_3$ with 4-*tert*-butylcyclohexanone in benzene yields no methylation product, whereas in diethyl ether a significant percentage of methylation product (~30%) is observed. In addition, the percentage of equatorial alcohol formed *via* reduction of the ketone increases significantly in going from diethyl ether (52%) to benzene (69%) at the higher reagent:ketone ratios. The mechanism of reduction of ketones by these types of ate complexes is not known, but is expected to be significantly different from that proposed for aluminum alkyls[13] since all primary coordination sites on the aluminum atom are occupied. However, we found that lithium triisobutylmethylaluminate prepared in ether is isolated as the monoetherate $[LiAl(i\text{-}C_4H_9)_3CH_3 \cdot O(C_2H_5)_2]$ even after the liquid compound is subjected to vacuum (100 $\mu$, 24 hr, room temperature). Thus, it appears that one molecule of ether is specifically solvated to each molecule of ate complex and therefore it is possible that complexes such as $LiAl(CH_3)_4$–ketone play an important role in the mechanisms of both alkylation and reduction.

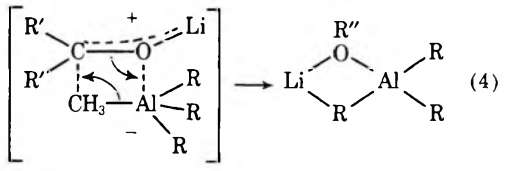
If coordination of the ketone takes place at lithium, it is possible to draw a reasonable transition state for the reaction. Coordination of the carbonyl oxygen atom by lithium followed by a rate-determining carbanionic attack at the carbonyl carbon atom is somewhat reminiscent of the reac-

$$R'_2C{=}O + LiAlR_3CH_3 \longrightarrow$$



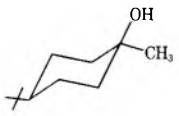
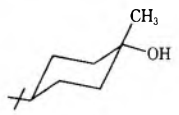

tion of ketones with $R_3Al$ compounds in 1:2 ratio where the first molecule coordinates the carboxyl oxygen and the second attacks the carbonyl carbon. The fact that the stereochemistry of ate complex alkylation reveals predominant axial attack rather than the usual 30:70 (axial:equatorial) ratio observed by those reactions that proceed through a four-center transition lends some support to the proposed mechanism. It is not necessary that the transition state be cyclic; indeed one could picture a consecutive bimolecular reaction in which the lithium ion complexed carbonyl group is then attacked by the tetraalkylaluminate ion.

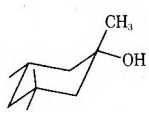
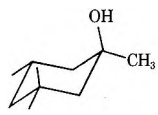
$$R'_2C{=}O + LiAlR_3CH_3 \longrightarrow \left[\begin{matrix} R' \\ R' \end{matrix}\!\!>\!C{=}O \rightarrow Li\right]^+ \xrightarrow{[AlR_3CH_3]}$$

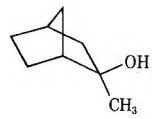
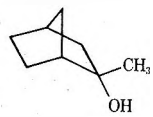


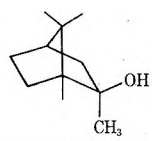
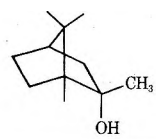

It is possible that coordination takes place through the aluminum atom rather than lithium; however, solvation studies on $LiAl(CH_3)_4$ with ether solvents indicates that the ether is attached to lithium and not aluminum and fur-

**Table II**
**Reaction of Ate Complexes of Aluminum with Ketones in Polar Solvents[a]**

| Reagent | Initial concentration, M | Ratio of reagent:ketone | Ketone | % axial alcohol[b]  | % equatorial alcohol[b]  |
|---|---|---|---|---|---|
| $LiAl(CH_3)_4$ | 0.15 | 1.0 | A | 42 | 58 |
| $LiAl(CH_3)_4$ | 0.21 | 4.0 | A | 42 | 58 |
| $LiAl(CH_3)_4$ | 0.18 | 1.0 | A | 44[c] | 56[c] |
| $LiAl(CH_3)_4$ | 0.37 | 4.0 | A | 43[c] | 57[c] |
| $LiAl(CH_3)_4$ | 0.39 | 1.0 | A | 43[d] | 57[d] |
| $LiAl(CH_3)_4$ | 0.63 | 4.0 | A | 44[d] | 56[d] |
| $LiAl(i\text{-}C_4H_9)_3CH_3$ | 0.10 | 1.0 | A | 18[e] | 82[e] |
| $LiAl(i\text{-}C_4H_9)_3CH_3$ | 0.30 | 3.0 | A | 31[e] | 69[e] |
| $LiAl(i\text{-}C_4H_9)_3CH_3$ | 0.355 | 1.0 | A | 31[e] | 69[e] |
| $LiAl(i\text{-}C_4H_9)_3CH_3$ | 0.461 | 3.0 | A | 33[e] | 67[e] |
| $(n\text{-}C_8H_{17})_3C_3H_7NAl(CH_3)_3Br$ | 0.044 | 1.0 | A | 81 | 19 |
| $(n\text{-}C_8H_{17})_3C_3H_7NAl(CH_3)_3Br$ | 0.132 | 3.0 | A | 77 | 23 |

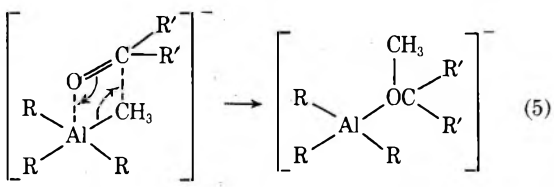
| Reagent | Initial concentration, M | Ratio of reagent:ketone | Ketone | % axial alcohol[b]  | % equatorial alcohol[b]  |
|---|---|---|---|---|---|
| $LiAl(CH_3)_4$ | 0.40 | 1.0 | B | 100 | 0 |
| $LiAl(CH_3)_4$ | 0.54 | 4.0 | B | 100 | 0 |

| Reagent | Initial concentration, M | Ratio of reagent:ketone | Ketone | % exo alcohol  | % endo alcohol  |
|---|---|---|---|---|---|
| $LiAl(CH_3)_4$ | 0.19 | 1.0 | C | 5 | 95 |
| $LiAl(CH_3)_4$ | 0.61 | 4.0 | C | 5 | 95 |

| Reagent | Initial concentration, M | Ratio of reagent:ketone | Ketone | % exo alcohol  | % endo alcohol  |
|---|---|---|---|---|---|
| $LiAl(CH_3)_4$ | 0.36 | 1.0 | D | 99 | 1 |
| $LiAl(CH_3)_4$ | 0.58 | 4.0 | D | 99 | 1 |

[a] Diethyl ether unless otherwise noted. [b] Normalized as % axial (exo) alcohol + % equatorial (endo) alcohol = 100%. [c] Tetrahydrofuran. [d] Dimethoxyethane. [e] Methylation product. The major product of these reactions was the reduction product (66 to 75%). In all cases the reduction product was composed of 48% axial alcohol and 52% equatorial alcohol.

$$R'_2C{=}O + LiAlR_3CH_3 \longrightarrow$$



(5)

thermore the observed stereochemistry is not consistent with this suggestion.

Similar mechanistic suggestions could be made to explain the reduction reactions; however, there is even less justification than exists for the alkylation reactions to discuss these reactions at this time.

As was noted in the ether case, the addition of an equivalent amount of tri-*n*-octylpropylammonium bromide to $(CH_3)_3Al$ in benzene does not alter the stereochemistry observed in the 1:1 $(CH_3)_3Al$-ketone:reactant ratio. However, in a 3:1 reactant ratio, $Al(CH_3)_3$ yields 90% axial attack on 4-*tert*-butylcyclohexanone,[7] whereas $(n\text{-}C_4H_9)_3\text{-}C_3H_7NAl(CH_3)_3Br$ gives 76% equatorial attack, providing strong evidence that the principle species in solution in the latter case is the proposed ate complex. In every case the ate complexes involving the $R_4N^+$ cation attacked 4-*tert*-butylcyclohexanone more from the less hindered equatorial side than the corresponding $Li^+$ cation complexes. This result could be interpreted simply as a steric effect; however, the possibility also exists that the difference is due to the fact that the $Li^+$ cation can complex the carbonyl oxygen, whereas the $NR_4^+$ cation cannot and therefore one might

**Table III**
**Reaction of Ate Complexes of Aluminum with 4-*tert*-Butylcyclohexanone in Benzene**

| Reagent | Initial concentration, *M* | Ratio of reagent:ketone | % axial alcohol[a] | % equatorial alcohol[a] |
|---|---|---|---|---|
| $LiAl(CH_3)_4$ | 0.012 | 1.0 | 52 | 48 |
| $LiAl(CH_3)_4$ | 0.012 | 4.0 | 42 | 58 |
| $LiAl(i\text{-}C_4H_9)_3CH_3$ | 0.085 | 1.0 | Trace[b] | 0[b] |
| $LiAl(i\text{-}C_4H_9)_3CH_3$ | 0.26 | 3.0 | 0[b] | 0[b] |
| $(n\text{-}C_8H_{17})_3C_3H_7NAl(CH_3)_3Br$ | 0.044 | 1.1 | 75 | 25 |
| $(n\text{-}C_8H_{17})_3C_3H_7NAl(CH_3)_3Br$ | 0.132 | 3.1 | 76 | 24 |

[a] Normalized as −% axial alcohol + % equatorial alcohol = 100%. [b] Methylation product. The only product of these reactions was reduction product with no recovered ketone. The reduction product was composed of 39–31% axial alcohol and 61–69% equatorial alcohol at the low and high ratios, respectively.

**Table IV**
**Stereochemistry of Alkylation of 4-*tert*-Butylcyclohexanone by $LiAl(CH_3)_4$ as a Function of Temperature[a]**

| Temp, °C | Solvent | $[LiAl(CH_3)_4]$, *M* | $LiAl(CH_3)_4$/ketone | % yield of alcohol products | % yield of axial products |
|---|---|---|---|---|---|
| 25 | Benzene | 0.012 | 1.0 | 79 | 52 |
| 25 | Benzene | 0.012 | 4.0 | 99 | 42 |
| 5 | Benzene | 0.0093 | 1.0 | 14 | 48 |
| 5 | Benzene | 0.0098 | 4.0 | 20 | 49 |
| 25 | Ether | 0.15 | 1.0 | 87 | 42 |
| 25 | Ether | 0.21 | 4.0 | 97 | 42 |
| 0 | Ether | 0.24 | 1.0 | 40 | 35 |
| 0 | Ether | 0.48 | 4.0 | 61 | 32 |
| −75 | Ether | 0.091 | 1.0 | 8 | 36 |
| −75 | Ether | 0.11 | 4.0 | 11 | 37 |

[a] All reaction times, 20 hr. [b] Normalized as −% ketone + % alcohol = 100%. [c] Normalized as −% axial alcohol + % equatorial alcohol = 100%.

**Table V**
**Per Cent Recovered Ketone from Reaction of a Variety of Metal Alkyls and Ate Complexes with 4-*tert*-Butylcyclohexanone under Identical Reaction Conditions[a]**

| Ate complex | % recovered ketone |
|---|---|
| $Li_3Mg(CH_3)_5$ | 6 |
| $Li_2Mg(CH_3)_4$ | 8 |
| $CH_3Li$ | 10 |
| $LiMg(CH_3)_3$ | 19 |
| $Li_3Zn(CH_3)_5$ | 19 |
| $Li_2Zn(CH_3)_4$ | 22 |
| $(CH_3)_2Mg$ | 28 |
| $LiZn(CH_3)_3$ | 33 |
| $LiAl(CH_3)_4$ | 33 |
| $(CH_3)_3Al$ | 59 |
| $(CH_3)_2Zn$ | 99 |

[a] Conditions: time, 2 hr; temperature, 25°; organometallic reagent concentration, 0.2 *M*; reagent:ketone ratio, 2:1.

expect substantial differences in the respective transition states.

Owing to the unusually high percentage of axial attack observed in the alkylation of 4-*tert*-butylcyclohexanone by $LiAl(CH_3)_4$, a study of the temperature dependence of the observed isomer ratio obtained from this reaction was undertaken. It was felt that, if the activation enthalpies leading to axial and equatorial alcohol were significantly different, the isomer ratio might be controlled simply by controlling the temperature. The results, illustrated in Table IV, demonstrate that temperature has a noticeable, but small, effect on the observed isomer ratio.

Finally, to evaluate various organometallic reagents in terms of their use as alkylating agents, a series of reactions involving reaction of these reagents with 4-*tert*-butylcyclohexanone was carried out to determine their relative yields. The results, shown in Table V, should not be considered a representation of relative reactivities since recovery of ketone occurs *via* enolization as well as *via* lack of addition.

**Registry No.**—$CH_3Li$, 917-54-4; $(CH_3)_2Mg$, 2999-74-8; $(CH_3)_2Zn$, 544-97-8; $LiB(CH_3)_4$, 2169-38-2; $LiMg(CH_3)_3$, 52225-42-0; $Li_2Mg(CH_3)_4$, 15679-76-2; $Li_3Mg(CH_3)_5$, 14040-22-3; $LiMg(C_6H_5)_2CH_3$, 52196-04-0; $LiZn(CH_3)_3$, 52196-05-1; $Li_2Zn(CH_3)_4$, 15691-62-0; $Li_3Zn(CH_3)_5$, 14040-23-4; $KMg(CH_3)_2O\text{-}t\text{-}C_4H_9$, 52196-06-2; $[(n\text{-}C_8H_{17})_3C_3H_7N]Mg(CH_3)_2Br$, 52196-07-3; $LiAl(CH_3)_4$, 14281-94-8; $LiAl(i\text{-}C_4H_9)_3CH_3$, 52196-08-4; $(n\text{-}C_8H_{17})_3C_3H_7NAl(CH_3)_3Br$, 52196-09-5; 4-*tert*-butylcyclohexanone, 98-53-3; 3,3,5-trimethylcyclohexanone, 873-94-9; norcamphor, 497-38-1; camphor, 76-22-2.

## References and Notes


(1) We are indebted to the National Science Foundation (Grant No. GP-31550X) for partial support of this work.
(2) For recent reviews concerning the nature of ate complexes, see (a) T. Tochtermann, *Angew. Chem., Int. Ed. Engl.*, **5**, 351 (1966); (b) G. Wittig, *Quart. Rev.*, **20**, 191 (1966).
(3) P. H. Lewis and R. E. Rundle, *J. Chem. Phys.*, **21**, 986 (1953).
(4) J. F. Ross, anc J. P. Oliver, *J. Organometal. Chem.*, **22**, 503 (1970); (b) J. P. Oliver and C. A. Wilkie, *J. Amer. Chem. Soc.*, **89**, 163 (1967); (c) K. C. Williams and T. L. Brown, *ibid.*, **88**, 4133 (1966).
(5) E. C. Ashby and R. C. Arnott, *J. Organometal. Chem.*, **14**, 1 (1968).
(6) W. S. Johnson and W. P. Schneider, "Organic Syntheses," Collect. Vol. IV, Wiley New York, N. Y., 1963, p 132.
(7) D. T. Hurd, *J. Org. Chem.*, **13**, 711 (1948).
(8) J. Laemmle, E. C. Ashby, and P. V. Roling, *J. Org. Chem.*, **38**, 2526 (1973), and references cited therein.
(9) M. L. Capman W. Chodkiewicy, and P. Cadiot, *Tetrahedron Lett.*, **No. 21**, 1619 (1965).
(10) Special caution should be exercised on acid hydrolysis of $LiB(CH_3)_4$ in any of the solvents mentioned since the $B(CH_3)_3$ released is spontaneously flammable.
(11) P. R. Jones, E. J. Goller, and W. S. Kauffmann, *J. Org. Chem.*, **34**, 3566 (1969).
(12) For a recent review concerning the stereochemistry of alkylation of ketones, see E. C. Ashby and J. Laemmle, *Chem. Rev.*, in press.
(13) E. C. Ashby and S. H. Yu, *J. Org. Chem.*, **35**, 1034 (1970).

# The Synthesis of Alkenes from Carbonyl Compounds and Carbanions α to Silicon. III. A Full Report and a Synthesis of the Sex Pheromone of Gypsy Moth[1,2]

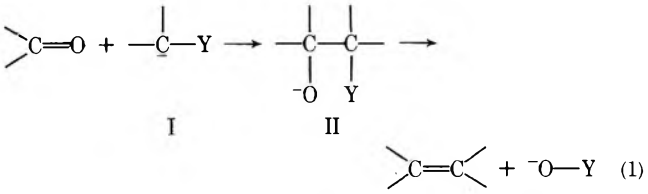
T. H. Chan* and E. Chang

*Department of Chemistry, McGill University, Montreal, Canada*

*Received May 7, 1974*

The synthesis of alkenes from carbonyl compounds and carbanions α to silicon is described. Methylenation of carbonyl compounds was accomplished by their reactions with trimethylsilylmethyl carbanion followed by treatment with thionyl chloride or acetyl chloride. Additions of organolithiums to triphenylvinylsilane were used as a method to generate α-silylalkyllithiums which reacted with carbonyl compounds to give the corresponding alkenes. A simple synthesis of the sex pheromone of gypsy moth by this method is reported.

A general method for the synthesis of alkenes can be represented by eq 1. The Wittig reaction[3] (Y = $PR_3^+$) and its many modifications are based on the key role of phosphorus in the carbanion formation as well as the elimination steps. An interesting alternative is Corey's olefin synthesis from sulfinamide derivatives (Y = $SONR_2$).[4] The use of other sulfur derivatives has subsequently been reported.[5,6] This paper describes our studies in the synthesis of alkenes from reaction of carbonyl compounds with carbanions α to silicon (Y = $SiR_3$).



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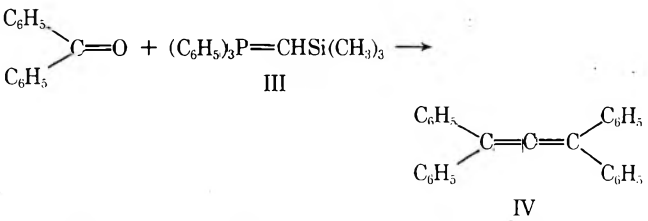
In 1962, Gilman and Tomasi[7] studied the reaction of trimethylsilylmethylenetriphenylphosphorane (III) with benzophenone. They obtained tetraphenylallene (IV), a prod-



III IV

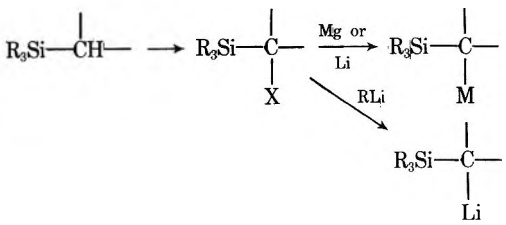
uct which they considered as rather unexpected. It was in 1968 that Peterson,[8] in extending his work on the generation of α-silyl carbanions,[9] demonstrated the alkene synthesis based on eq 1 (Y = $SiR_3$). Thus, the formation of IV from the reaction of III with benzophenone can be viewed as a special case of alkene synthesis *via* α-silyl carbanion.

At about the same time, we initiated our studies on the use of silicon compounds for a variety of organic syntheses.[10-12] This general interest led to a study of the olefination reaction using α-silyl carbanions. We have subsequently reported our preliminary results[1] on this reaction.

## Results and Discussion

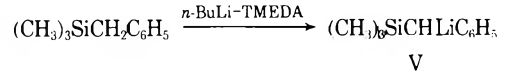
In order for the reaction (eq 1, Y = $SiR_3$) to be a viable method of forming the carbon–carbon double bond, two conditions must be met: first, a facile method of generating carbanions α to silicon must exist; and second, the elimination of the siloxy group from the β-silyl oxyanion adduct (II, Y = $SiR_3$) must occur readily. We shall now examine these two conditions.

**Methods of Generating Carbanions α to Silicon.** One of the simplest ways of preparing α-silyl carbanion is the reaction of α-halosilanes with magnesium[13,14] or lithium. The synthetic utility of this reaction is considerably enhanced by the fact that α-halosilanes can in turn be prepared by free-radical halogenation of alkylsilanes.[15] Alternatively, metal–halogen exchange reactions between α-halosilanes and alkyllithiums can lead also to the formation of α-silylalkyllithium compounds.[15]



M = MgBr or Li

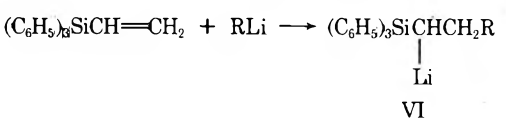
It has recently been shown by Peterson[9,16] that the highly reactive *n*-butyllithium–tetramethylethylenediamine complex (*n*-BuLi–TMEDA) can metalate a number of weakly acidic heteroatom-substituted methanes. This provides a useful method for preparing α-silylakyllithium compounds, especially when the alkyl group is further activated, for example, eq 2. We found that benzyltrimethylsil-



V (2)

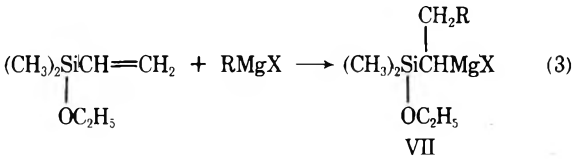
ane can also be metalated by alkyllithium in hexamethylphosphoramide (HMPA). However, neither of these methods can be used to generate carbanions on long-chain alkyl carbon moieties. Peterson metalated *n*-butyltrimethylsilane with *n*-BuLi–TMEDA and found that metalation occurred mainly on the methyl carbons.[17] We have also attempted the metalation of *n*-hexyltriphenylsilane and found the metalation not to occur on the alkyl chain.

A solution to this problem is to take advantage of the discovery by Cason and Brooks that alkyllithium can add across the double bond of triphenylvinylsilane to give a metalated silane.[18] Thus, carbanions of general structure VI can be generated by the reaction of equimolar quantities of organolithium compound and triphenylvinylsilane in ether.



VI

The usefulness of this method may be further extended by the recent report of Buell, *et al.*,[19] which indicated that Grignard reagents can also add to activated vinylsilanes, for example, eq 3. It is therefore apparent that with a judi-

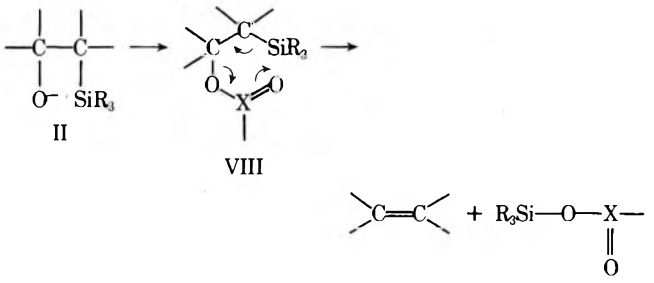


(3)

VII

cious choice of one of the above methods, $\alpha$-silyl carbanions of diverse structures can be synthesized.

**Elimination of the $\beta$-Silyl Oxyanion Adduct II.** The formation of alkene and siloxy anion from the adduct II was found to occur spontaneously when the alkene was nonterminal. Although there is no direct evidence, decomposition is assumed to proceed through a four-membered cyclic transition state.[20,21] When the alkene was terminal, the lithium or magnesium salt of the adduct II did not decompose under the reaction conditions. On working up, the $\beta$-silylcarbinol can be obtained in good yield. While $\beta$-elimination of silylcarbinol under acidic conditions may be effected,[22] the resultant alkene may isomerize and thus it cannot be considered as a good synthetic method. Peterson[8] overcame this problem by converting the $\beta$-silylcarbinol to the corresponding sodium salt, which would then decompose in refluxing tetrahydrofuran to the alkene. He attributed the difference to the more ionic character of the sodium salt. We found that a satisfactory solution to this problem is to treat the adduct II *in situ* with either thionyl chloride or acetyl chloride. The alkene can in general be formed in good yield without contamination of other double-bond isomers. The reaction is assumed to proceed *via* the derivative VIII.[24]

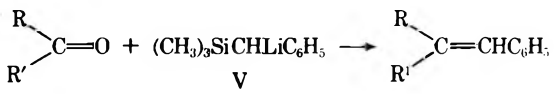


II VIII

**Methylenation.** Trimethylsilylmethylmagnesium chloride or trimethylsilylmethyllithium was prepared in ether by reported procedures.[13-15] The appropriate carbonyl compound in ether was added and the reaction mixture was refluxed for 1–2 hr. To the reaction mixture, a slight excess of thionyl chloride or acetyl chloride was added and stirred for 1 hr. After working up, the product could be isolated in moderately good yield (Table I). The terminal alkene thus obtained was generally free from contamination with other double-bond isomers. Also, an isolated double bond in other parts of the molecule was not affected. Because of the ready availability of chloromethyltrimethylsilane and thus the corresponding organometallics, this method offers an attractively simple way of converting carbonyl compounds to the corresponding methylene derivatives. In certain cases, it is superior to the Wittig reaction.[23]

This method of methylenation is applicable to $\alpha,\beta$-unsaturated ketones. $\beta$-Ionone was converted in reasonable yield to the corresponding methylene derivative. On the other hand, methylenation of cyclohex-2-enone gave only a 20% yield of 3-methylenecyclohexene. It seemed that 1,4-addition as well as polymerization predominated in this case.

**Benzylidene Formation.** The trimethylsilylbenzyl carbanion V was prepared from trimethylbenzylsilane and *n*-



V

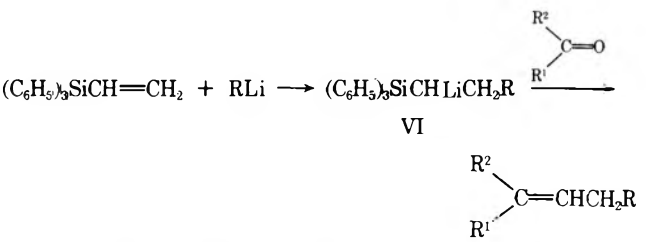
**Table I**
**Methylenation of Carbonyl Compounds**

| Carbonyl compd | Organometallic reagent used | Decompn agent used | Yield of olefin,[a] % |
|---|---|---|---|
| 2-Methylhept-2-en-6-one | $(CH_3)_3SiCH_2MgCl$ | $SOCl_2$ | 57 |
| 2-Methylhept-2-en-6-one | $(CH_3)_3SiCH_2Li$ | $SOCl_2$ | 53 |
| Cyclohexanone | $(CH_3)_3SiCH_2MgCl$ | $CH_3COCl$ | Quant[b] |
| $\beta$-Ionone | $(CH_3)_3SiCH_2MgCl$ | $CH_3COCl$ | 52 |
| Cyclohex-2-enone | $(CH_3)_3SiCH_2Li$ | $CH_3COCl$ | 20[c] |

[a] Isolated yield except where noted. [b] Determined by nmr. [c] By comparison with authentic sample prepared according to W. J. Barley and J. C. Goossens, *J. Amer. Chem. Soc.*, 78, 2804 (1956).

butyllithium or methyllithium in HMPA. The existence of the carbanion was demonstrated by quenching the mixture with $D_2O$ and was recovered and found to be >85% deuterated at the benzyl group by nmr. The red carbanion solution was treated with the appropriate carbonyl compound. The mixture, after stirring at room temperature, gave the alkene directly in reasonable yield. We have obtained stilbene from benzaldehyde and 1,2-diphenylpropene from acetophenone. In both these cases as well as subsequent ones, where *E–Z* isomerism is possible, both isomers were obtained. We have not examined the effect of solvents or additives on the ratio of isomers.[24]

**Substituted Ethylidenes.** Carbanions of structure VI were generated by the reaction of equimolar quantities of



VI

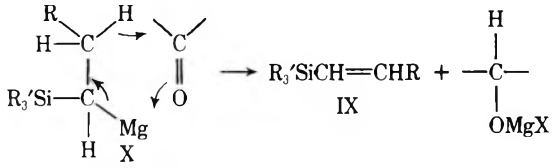
organolithium and triphenylvinylsilane in ether.[18] Quenching experiments with $D_2O$ indicated that the carbanion deteriorated on standing, since the percentage of deuterium incorporation in the isolated substituted ethyltriphenylsilane decreased rapidly. To the carbanion solution, the appropriate carbonyl compound was added. The mixture, on working up, gave the corresponding alkene in good yield. We have prepared 1-phenyl-1-heptene, 2-methyl-6-heptadecene, 2,6-dimethyl-2,6-dodecadiene, and 1,3-diphenylpropene by this method (Table II).

We have also examined the efficacy of the $\alpha$-silylalkylmagnesium halide (VII), prepared by the addition of Grignard reagent ot an activated vinylsilane, in this olefination. In agreement with the report by Buell, *et al.*,[19] we found that isopropylmagnesium chloride indeed added to dimethylvinylethoxysilane to generate the corresponding adduct VII (R = *i*-Pr). When benzaldehyde was added to a solution of adduct VII, a reaction occurred. The reaction mixture was quenched with acetyl chloride. On working up, the products were found to be benzyl acetate and tetramethylbis[1-(3-methyl-1-(*E*)-butenyl)]disiloxane (IX). There was no trace of product which could be identified as due to the addition of the carbonyl compound to the Grignard reagent VII. While the formation of benzyl alcohol (as the acetate) is not entirely unexpected and can be accounted for satisfactorily by the usual hydride transfer mechanism, we are nevertheless surprised by the dominance of reduction over the addition process. This seems to be the common feature of VII on reaction with carbonyl

**Table II**
**Olefination of Carbonyl Compounds by α-Silyl Carbanions Formed from Addition of Organolithium to Vinyltriphenylsilane**

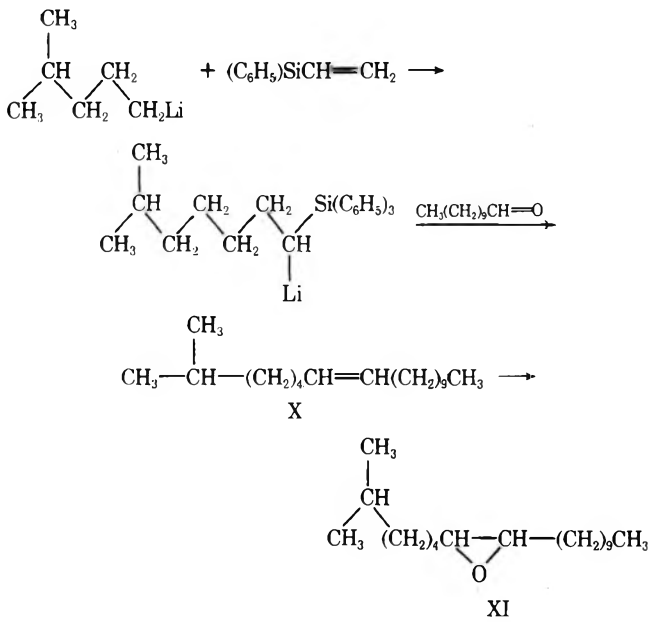
| Carbonyl compd | Organolithium | α-Silyl carbanion | Product | Yield, % (*E*:*Z*) |
|---|---|---|---|---|
| $C_6H_5CHO$ | *n*-BuLi | $CH_3(CH_2)_2CHSi(C_6H_5)_3$ | 1-Phenyl-1-heptene[a] | 50(1:1) |
| $CH_3(CH_2)_9CHO$ | 3-Methylbutyllithium | $(CH_3)_2CH(CH_2)_3CHSi(C_6H_5)_3$ | 2-Methyl-6-heptadecene[b] | 69(1:1) |
| 2-Methylhept-2-en-6-one | *n*-BuLi | $CH_3(CH_2)_4CHSi(C_6H_5)_3$ | 2,6-Dimethyl-2,6-dodecadiene[c] | 34(1:1) |
| $C_6H_5CHO$ | $C_6H_5Li$ | $C_6H_5CH_2CH-Si(C_6H_5)_3$ | 1,3-Diphenylpropene[d] | 40(1:1) |
| $CH_3(CH_2)_9CHO$ | 4-Methylpentyllithium | $(CH_3)_2CH(CH_2)_4CHSi(C_6H_5)_3$ | 2-Methyl-7-octadecene[e] | 50(1:1) |

[a] Reference 34. [b] Bp 111–112° (0.35 nm); nmr ($CDCl_3$) 0.95 (m, 9 H), 1.4 (broad s, 20 H), 2.05 (m, 5 H), 5.45 ppm (m, 2 H); mass spectrum M+ 252. [c] Bp 58–60° (0.1 mm); nmr (neat) 0.95 (t, 3 H), 1.25 (broad, 5 H), 1.58 and 1.62 (s, 9 H), 2.0 (broad, 6 H), 5.05 (t, 2 H); mass spectrum M+ 194. [d] Spectroscopic data in agreement with literature values: E.K. Ramino and W.A. Bonner, *J. Org. Chem.*, **31**, 396 (1966). [e] See Experimental Section.




compounds which we have examined. Thus, acetophenone and 2-methylhept-2-en-6-one also gave the corresponding alcohols, which were characterized as the acetates. The other products in these reactions were the disiloxanes IX. The ease of hydride transfer may be a reflection of the "β effect" of silicon.[25,26] It is known, for example, that carbene insertion into alkylsilanes occurred exclusively at the β position.[27]

**Sex Pheromone of Gypsy Moth.** The structure of the sex pheromone of gypsy moth (Disparlure) has recently been identified as *cis*-7,8-epoxy-2-methyloctadecane[28] (XI).




A simple synthesis of this compound was achieved by the silicon method.[29] 4-Methylpentyllithium, prepared from the corresponding chloro compound, was allowed to react *in situ* with triphenylvinylsilane. Undecanal was added to the reaction mixture. On working up, a 50% yield of 2-methyl-7-octadecenes (X) was obtained. This was converted to the corresponding epoxides by *m*-chloroperbenzoic acid in quantitative yield. The epoxides, on nmr analysis, were found to be a 1:1 mixture of cis and trans isomers. They were identical in all respects with an authentic mixture.[30] Under field test, they showed the appropriate biological activities.[30]

## Experimental Section

All reactions were conducted in glassware that was dried, either overnight in an oven at 130° or by flame drying under nitrogen. The reactions were all conducted under a nitrogen atmosphere up to the hydrolysis step. Stirring was done with magnetic stirring bars unless otherwise noted. HMPA and TMEDA were distilled and stored over molecular sieves. Absolute diethyl ether was stored over sodium ribbon and used without further purification. Boiling and melting points were uncorrected. Spectra were recorded on the following instruments: nmr, Varian T-60 and A-60; ir, Perkin-Elmer 257; uv, Unicam SP-800; mass spectra, AEI MS-902 at 70 eV. Vpc was done on a Hewlett-Packard 7570 gas chromatograph and the columns were 12 ft of UCW-98 or SE-30 unless otherwise noted. Column chromatography was carried out with silica gel, mesh size 100–200, by Grace.

**I. Methylenation. A. Reaction of 2-Methylhept-2-en-6-one–Trimethylsilylmethylmagnesium Chloride Adduct with Thionyl Chloride.** To a stirred solution of trimethylsilylmethylmagnesium chloride, made from 2.5 g (0.02 mol) of chloromethyltrimethylsilane and 0.5 g (0.02 mol) of magnesium turnings in 25 ml of diethyl ether, was added a solution of 2.5 g (0.02 mol) of 2-methylhept-2-en-6-one in 5 ml of diethyl ether.

The addition was done dropwise at such a rate that a gentle reflux of the mixture was maintained. The reaction mixture was refluxed with continued stirring. After 3 hr, the reaction mixture was cooled in an ice bath and 1.8 ml (0.025 mol) of thionyl chloride was added. The ice bath was removed and stirring was continued at room temperature. After 1 hr, the reaction mixture was hydrolyzed by the dropwise addition of a saturated ammonium chloride solution. The coagulated solid was filtered off and washed with diethyl ether. Distillation of the combined filtrate–washings gave 1.4 g (57%) of 2,6-dimethyl-1,5-heptadiene as a clear, colorless liquid: bp 135–136°; $n^{23}D$ 1.4385 [lit.[31] bp 69–70° (80 mm), $n^{18}D$ 1.4461]; nmr (neat) 1.52 (s, 3 H), 1.62 (s, 6 H), 2.06 (m, 4 H), 4.64 (s, 2 H), 5.06 ppm (m, 1H); ir (neat) 3080 (w), 2970, 2925 (s), 2865 (m), 1660 (m), 1460, 1452, 1390 (m), 895 $cm^{-1}$ (s).

**B. Reaction of β-Ionone–Trimethylsilylmethylmagnesium Chloride Adduct with Acetyl Chloride.** To a stirred solution of trimethylsilylmethylmagnesium chloride, made from 1.25 g (0.01 mol) of chloromethyltrimethylsilane and 0.25 g (0.01 mol) of magnesium turnings in 15 ml of diethyl ether, was added dropwise 1.9 g (0.01 mol) of β-ionone in 5 ml of diethyl ether. After the mixture was refluxed with stirring for 3 hr, the reaction mixture was allowed to cool to room temperature and 0.8 g (0.01 mol) of acetyl chloride was added to the stirred solution. Stirring was continued at room temperature for 1 hr, whence the reaction mixture was hydrolyzed by a saturated ammonium chloride solution. The coagulated solid was filtered off and washed with diethyl ether. The combined filtrate–washings were evaporated to remove the solvent to give 2.0 g of pale brown oil. High-vacuum distillation of this oil afforded 1.1 g (52%) of olefin as a clear colorless liquid:[33] bp 46–47° (0.05 mm) [lit.[32] bp 113–115° (15 mm)]; $n^{21}D$ 1.5147; uv (etha-

**Table III**

| Reaction time,[a] hr | Wt crude, g | % starting material left[b] | Wt product recrystd, g | % yield | Mp,[c] °C | Abs[d] at 2160 cm$^{-1}$ |
|---|---|---|---|---|---|---|
| 1.25 | 0.35 | 30.3 | 0.20 | 60 | 74–76 | 0.29 |
| 1.75 | 0.40 | 29.2 | 0.20 | 60 | 74–77 | 0.275 |
| 2.25 | 0.35 | 27.8 | 0.20 | 60 | 74–77 | 0.26 |
| 3.25 | 0.40 | 25.2 | 0.15 | 45 | 73–76 | 0.20 |
| 4.25 | 0.25 | 25.5 | 0.10 | 42 | 73–77 | 0.083 |

[a] Includes time for addition. [b] Calculated from the relative integration per olefinic *vs.* aromatic proton, respectively. [c] Reported mp 77–78° for *n*-hexyltriphenylsilane. [d] For a concentration of 250 mg/cc. Value given is corrected for absorption (0.030) observed for nondeuterated *n*-hexyltriphenylsilane.

nol) 228 nm (ε 10,600), 262 (10,200) [lit.[32] 228 nm (ε 633), 262 (611)]; nmr ($CCl_4$) 0.96 (s, 6 H), 1.6 (s, 3 H), 1.82 (s, 3 H), 2.28 (m, 6 H), 4.8 (s, 2 H), 5.95 ppm (s, 2 H); ir (neat) 3100 (w), 2930, 2940, 2880 (s), 2840 (m), 1612, 1460, 1393, 1381, 1370 (m), 985, 900 cm$^{-1}$ (s).

**II. Benzylidene Formation. Reaction of Trimethylsilylbenzyl Anion with Benzaldehyde.** To a stirred, ice-cooled solution of 1.64 g (0.1 mol) of benzyltrimethylsilane in 10 ml of HMPA was added 0.01 mol of methyllithium in pentane. Stirring was continued for 2 hr, when a solution of 1.1 g (0.01 mol) of benzaldehyde in 5 ml of diethyl ether was added. The ice bath was removed and the reaction mixture was stirred at room temperature. After 1 hr, the mixture was poured into 25 ml of ice-cooled 1% hydrochloric acid. The ether layer was separated and the aqueous layer was extracted with two 10-ml portions of ether. The combined ether extracts was washed with water, dried over sodium sulfate–sodium carbonate, and then film evaporated to give 2.4 g of brown liquid. Recrystallization of the crude material from ethanol gave 0.6 g of *trans*-stilbene, mp 124–125°. The filtrate was evaporated and distillation of the resulting liquid gave 0.3 g of *cis*-stilbene, bp 105–106° (5 mm) (total yield of stilbene, 50%).

**III. Substituted Ethylidenes. A. Quenching Experiments. Reaction of *n*-Butyllithium with Triphenylvinylsilane.** To a stirred solution of 2.5 ml (0.005 mol) of *n*-butyllithium–hexane was added a solution of 1.43 g (0.005 mol) of triphenylvinylsilane in 50 ml of diethyl ether dropwise over 1.25 hr. At the completion of addition, 10 ml of the reaction mixture was withdrawn and added to 2 ml of frozen $D_2O$. The ether layer was separated, dried over sodium sulfate, and evaporated to give *n*-hexyltriphenylsilane. Similar samples were taken at intervals of additional stirring of 0.5, 1, 2, and 3 hr. The nmr ($CCl_4$) of the crude product was recorded in each instance. The samples were then purified by recrystallization (absolute ethanol) and dried, and the ir ($CCl_4$) was recorded from 1900 to 2800 cm$^{-1}$ for C–D absorption (~2160 cm$^{-1}$). The results are given in Table III. The 1.25-hr sample showed 77% D incorporation by mass spectrometry.

**B. Olefination. Reaction of 1-Triphenylsilyl-1-hexyllithium with Benzaldehyde.** To a stirred solution of 2.2 ml (0.005 mol) of *n*-butyllithium–ether was added a solution of 1.43 g (0.005 mol) of triphenylvinylsilane in 50 ml of diethyl ether dropwise over 1.75 hr. After 5 min, to the stirred mixture was added 0.53 g (0.005 mol) of benzaldehyde over 15 min. The reaction mixture was stirred under reflux for 30 hr. The cooled mixture was poured into 50 ml of 10% aqueous ammonium chloride solution and the ether layer was separated. The aqueous layer was extracted with two 25-ml portions of ether. The ether fractions were combined, dried over sodium sulfate, and evaporated to give 2.2 g of a mixture of pale yellow oil and white solid. Treatment with *n*-pentane and filtration afforded 0.6 g of triphenylsilanol, mp 156–157.5°. The filtrate was evaporated to an oil, which was distilled to give 0.4 g (46%) of 1-phenylheptene (1:1 *E*:*Z* by vpc): bp 46° (0.01 mm) [lit.[34] bp 90–94° (3–4 mm)] ir (neat) 2910 (w), 2830 (s), 2770 (m), 1610 (w), 1502 (m), 1478, 1458 (m), 973 (s), 772 (m), 747 (s), 704, 697 cm$^{-1}$ (s); nmr ($CCl_4$) 0.9 (t, 3 H), 1.48 (m, 6 H), 2.2 (m, 2 H), 6.13 (m, 2 H), 7.23 ppm (s, broad, 5 H); mass spectrum M$^+$ *m/e* 174.

**C. Sex Pheromone of Gypsy Moth. 1. Reaction of 1-Triphenylsilyl-6-methylheptyllithium with Undecanal.** To a stirred, ice-cooled solution of 13 ml (0.01 mol) of 4-methylpentyllithium and 1.2 g (0.01 mol) of tetramethylethylenediamine was added a solution of 2.8 g (0.01 mol) of triphenylvinylsilane in 50 ml of diethyl ether dropwise over 3 hr. The reaction mixture was stirred for 30 min more and a solution of 1.6 g (0.01 mol) of undecanal in 10 ml of diethyl ether was added over 15 min. The ice bath was removed and the mixture was refluxed for 45 hr. The cooled reaction mixture was poured into 50 ml of 10% aqueous ammonium chloride solution, the ether layer was separated, and the aqueous layer was extracted with two 25-ml portions of ether. The combined ether extracts were washed successively with 1 *N* hydrochloric acid and water, and dried over sodium sulfate–sodium carbonate. The dried ether solution was evaporated to give 4.75 g of a mixture of white solid and liquid. The mixture was treated with 50 ml of *n*-hexane, cooled, and filtered to give 1.02 g of triphenylsilanol, mp 149–153°. The filtrate was film evaporated to give 3.57 g of light brown liquid, which was column chromatographed (hexane and hexane–chloroform) to give 1.82 g of crude product and 0.46 g (0.0016 mol) of unreacted triphenylvinylsilane. Distillation of the crude material gave 1.2 g (50%, based on silane) of 2-methyl-7-octadecene (*E*–*Z* mixture): bp 101–103° (0.09 mm); $n^{25}$D 1.4444; nmr ($CDCl_3$) 0.93 (m, 9 H), 1.33 (s, broad, 22 H), 2.01 (m, 5 H), 5.46 ppm (m, 2 H); ir (neat) 3002 (w) 2920, 2862, 2843 (s), 1468 (m), 1386, 1380, 1369 (w), 970 (m), 728 cm$^{-1}$ (w); mass spectrum M$^+$ *m/e* 266.[28]

**Table IV**

| Compd | μg/trap | Insects trapped |
|---|---|---|
| 6,7-Epoxy-2-methylheptadecane | 20 | 23 |
| | 2 | 16 |
| | 0.2 | 6 |
| 7,8-Epoxy-2-methyloctadecane | 20 | 40 |
| | 2 | 30 |
| | 0.2 | 25 |
| Disparlure (85% cis) | 20 | 71 |
| | 2 | 36 |
| | 0.2 | 28 |

**2. Biological Activities.** Two compounds, 6,7-epoxy-2-methylheptadecane (cis:trans 1:1) and 7,8-epoxy-2-methyloctadecane (cis:trans 1:1), synthesized by the silicon method, were tested for activity toward gypsy moth[30] with the following results (Table IV). Insects trapped were the total in three replecates. Chemicals were formulated with 2 mg keeper/trap.

**D. Reaction of Benzaldehyde–1-(Dimethylethoxysilyl)-3-methylbutylmagnesium Chloride Adduct with Acetyl Chloride.** A solution of isopropylmagnesium chloride [made from 1.57 g (0.2 mol) of isopropyl chloride and 0.5 g (0.2 mol) of magnesium turnings in 5 ml of diethyl ether] and 2.6 g (0.2 mol) of vinyldimethylethoxysilane was refluxed with stirring for 20 hr. To the stirred, cooled (to room temperature) reaction mixture was added a solution of 2.1 g (0.02 mol) of benzaldehyde in 5 ml of diethyl ether dropwise over 15 min. After stirring for 1 hr more, 1.45 ml (0.02 mol) of acetyl chloride was added and the mixture was stirred at reflux. After 5 hr, heating was discontinued and the mixture was left standing at room temperature. After 43 hr, the reaction mixture was hydrolyzed by dropwise addition of saturated ammonium chloride solution. The combined filtrate–washings were evaporated to give 4.5 g of brown liquid. Attempted distillation gave mixtures as evidenced by vpc. Further purification by column chromatography (hexane and hexane–$CHCl_3$ mixtures) gave 1.3 g (50%, based on silane used) of tetramethylbis[1-(3-methyl-1-(*E*)-butenyl)]disiloxane [bp 67.5° (6 mm); nmr ($CCl_4$) 0.13 (s, 6 H), 0.96 (d, $J$ = 7 Hz, 6 H), 2.11 (m, 1 H), 5.17 (d, $J$ = 17.5 Hz, 1 H), 5.73 ppm (d of d, $J$ = 17.5 and 5 Hz, 1 H); ir (neat) 2960 (vs), 2876 (s), 1630 (s), 15 (m), 1415, 1388, 1370, 1325 (w), 1260 (vs), 1225, 1175 (w), 1080 (s), 1050 (vs), 995 (s), 840, 805, 790 cm$^{-1}$ (vs); mass spectrum M$^+$ *m/e* 270] and 1.5 g (50%) of benzyl acetate, bp 82–83° (5 mm).

**Registry No.**—2-Methylhept-2-en-6-one, 110-93-0; chloromethyltrimethylsilane, 2344-80-1; thionyl chloride, 7719-09-7; 2,6-dimethyl-1,5-heptadiene, 6709-39-3; β-ionone, 14901-07-6; acetyl chloride, 75-36-5; β-ionone methylene derivative, 52260-01-2; benzyltrimethylsilane, 770-09-2; benzaldehyde, 100-52-7; *trans*-stilbene, 103-30-0; *cis*-stilbene, 645-49-8; triphenylvinylsilane, 18666-68-7; *n*-hexyltriphenylsilane, 18751-09-2; (*E*)-1-phenylheptene, 10201-58-8; (*Z*)-1-phenylheptene, 10201-59-9; undecanal, 112-44-7; 1-triphenylsilyl-6-methylheptyllithium, 52260-02-3; (*Z*)-2-methyl-7-octadecene, 35354-39-3; (*E*)-2-methyl-7-octadecene, 40302-56-5; *cis*-6,7-epoxy-2-methylheptadecane, 52260-03-4;

*trans*-6,7-epoxy-2-methylheptadecane, 52260-04-5; *cis*-7,8-epoxy-2-methyloctadecane, 29804-22-6; *trans*-7,8-epoxy-2-methyloctadecane, 42991-03-7; vinyldimethylethoxysilane, 5356-83-2; isopropyl chloride, 75-29-6; tetramethylbis[1-(3-methyl-1-(*E*)-butenyl)]disiloxane, 52260-05-6.

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# Notes

## Products and Rates of Reaction of Trifluoroacetic Anhydride with Aldehydes. A Nuclear Magnetic Resonance Study


A. L. Ternay, Jr.*, D. Deavenport, and G. Bledsoe

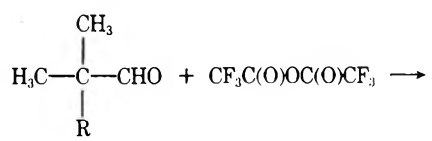
*Department of Chemistry, The University of Texas at Arlington, Arlington, Texas 76019*


*Received April 2, 1974*

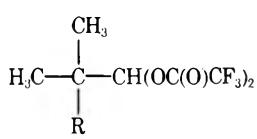
The reaction of carboxylic acid anhydrides with carbonyl compounds has been known since the beginning of this century.[1] These reactions appear to involve initial formation of a *gem*-bisester, $RC[OC(O)R']_2$, but may proceed to form other compounds, including enol esters.[2] While studies[3] have appeared on the synthetic aspects of this reaction, comparatively little has been done to elucidate the mechanism(s) of these reactions. The most extensive study to date appears to be that of Mazur and coworkers[4] on the reaction of ketones with trichloroacetic anhydride.

The broad application of trifluoroacetic anhydride (TFAA) to synthetic organic chemistry,[5] the greater reactivity of TFAA compared to trichloroacetic anhydride, TCAA, and the suitability of TFAA as an nmr solvent have prompted our investigation into the reaction(s) of TFAA with carbonyl compounds.[6] This report deals with the reaction of nonenolizable aliphatic and aromatic carboxaldehydes with TFAA.

**Aliphatic Carboxaldehydes.** Nonenolizable aliphatic carboxaldehydes were selected for study because they could not readily lose trifluoroacetic acid and would, therefore, lead to stable adducts.[7] The aldehydes selected for examination were 2,2-dimethylpropanol (pivalaldehyde, **1**), 2-methyl-2-phenylpropanal (**2**), and 2-methyl-2-*p*-methoxyphenylpropanal (**3**). These aldehydes reacted with excess TFAA to yield the anticipated 1,1-bis(trifluoroacetoxy)-2,2-dimethylpropane (**4**), 1,1-bis(trifluoroacetoxy)-2-methyl-2-phenylpropane (**5**), and 1,1-bis(trifluoroacetoxy)-2,2-dimethylpropane (**4**), 1,1-bis(trifluoroacetoxy)-tively. No other products could be detected by nmr; these products appear to be stable indefinitely in TFAA at 25°.



**1**, R = $CH_3$
**2**, R = $C_6H_5$
**3**, R = *p*-$CH_3OC_6H_4$



**4**, R = $CH_3$
**5**, R = $C_6H_5$
**6**, R = *p*-$CH_3OC_6H_4$

The rate of adduct formation was followed by integration of both the decreasing carboxaldehyde resonance and the new methine resonance in the product. The reaction exhibited pseudo-first-order behavior. The half-lives, $t_{1/2}$, for the reactions are similar but suggest some steric hindrance to adduct formation in going *from* **1** *to* **2** and **3** ($t^1_{1/2}$ = 20 min, $t^2_{1/2}$ = 125 min, $t^3_{1/2}$ = 130 min).[8]

The pmr spectra of these adducts are included in Table I. It is noteworthy that adduction "shifts" the aldehydic resonance upfield by *ca.* 2 ppm, since this, when necessary, can serve as a useful diagnostic tool for the presence of the carboxaldehyde group.

**Aromatic Carboxaldehydes.** Benzaldehydes, like the nonenolizable aliphatic carboxaldehydes, react with TFAA to produce *gem*-bis(trifluoroacetates). Again, these esters

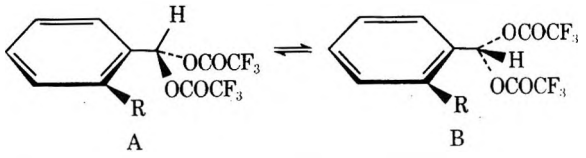
**Table I**
**Proton Chemical Shifts for *gem*-Bis(trifluoroacetates)[a]**

R = $(CF_3CO_2)_2CH$– R′ = $(CF_3CO_2)_2CHC(CH_3)_2$–

| Compd | Registry no. | X | Chemical shifts | | | | |
|---|---|---|---|---|---|---|---|
| | | | $(CF_3CO_2)_2CH$-[b] | C-2, 6H[c] | C-3, 5H[c, d] | Others | |
| 1-R-4-X-Benzenes | 52195-50-3 | H | 7.82 | 7.35–7.65 | | | |
| | 52195-51-4 | F | 7.87 | 7.66 | 7.16 | | |
| | 52195-52-5 | Cl | 7.83 | 7.58 | 7.43 | | |
| | | Cl[e] | 7.80 | 7.52 | 7.46 | | |
| | 52195-53-6 | Br | 7.82 | 7.51 | 7.61 | | |
| | 52195-54-7 | CN[f] | 7.97 | 7.80 | 7.80 | | |
| | 52195-55-8 | $NO_2$ | 7.96 | 7.88 | 8.36 | | |
| | 52195-56-9 | $OCH_3$ | 7.80 | 7.53 | 6.94 | $OCH_3$ | 3.71 |
| | 52217-40-0 | $CH_3$ | 7.79 | 7.48 | 7.25 | $CH_3$ | 2.33 |
| | 52195-57-0 | $N(CH_3)_2$ | 7.72 | 7.43 | 6.75 | $N(CH_3)_2$ | 2.92 |
| | | | $(CF_3CO_2)_2CH$– | C-2,4,5,6 H | | | |
| 1-R-3-X-Benzenes | 52195-58-1 | $OCH_3$ | 7.80 | 6.90–7.35 | | $OCH_3$ | 3.80 |
| | 52195-59-2 | $CH_3$ | 7.75 | 7.21–7.45 | | $CH_3$ | 2.31 |
| | 52195-60-5 | $NO_2$ | 8.01 | 7.70–8.60 | | | |
| | | | $(CF_3CO_2)_2CH$– | C-3,4,5,6 H | | | |
| 1-R-2-X-Benzenes | 52195-61-6 | $OCH_3$ | 8.25 | 6.95–7.60 | | $OCH_3$ | 3.88 |
| | 52195-62-7 | $CH_3$ | 8.02 | 7 10–7.65 | | $CH_3$ | 2.60 |
| | | | $(CF_3CO_2)_2CH$– | C-3,5 H | C-2,6 $CH_3$ | C-4 $CH_3$ | |
| 1-R-2,4,6-X-Benzene | 52195-63-8 | $CH_3$ | 8.29 | 6.87 | 2.55 | 2.24 | |
| | | | $(CF_3CO_2)_2CH$– | | | | |
| 1-R-2,3,4,5,6-X-Benzene | 52195-64-9 | F | 8.13 | | | | |
| | | | $(CF_3CO_2)_2CH$– | C-10 H | C-1,8 H | C-2,7 H | C-3,6 H | C-4,5 H |
| 9-R-Anthracene | 52195-65-0 | F | 9.40 | 8.21 | 8.54 | 7.50 | 7.30 | 7.72 |
| | | | $(CF_3CO_2)_2CH$– | C-2,6 H | C-3,5 H | | | |
| 1-R′-4-X-Benzenes | 52195-66-1 | H | 7.08 | 7.15–7.50 | | R′$CH_3$ | 1.55 |
| | 52195-67-2 | $OCH_3$[c] | 7.02 | 7.36 | 6.86 | R′$CH_3$ | 1.53 |
| | | | | | | $OCH_3$ | 3.68 |
| | | | $(CF_3CO_2)_2CH$– | Others | | | |
| R-X | 52195-68-3 | $CH_3$ | 7.13 q ($J$ = 5.5 Hz) | $CH_3$ | 1.74 | | |
| | 52195-69-4 | $C_2H_5$ | 6.97 t ($J$ = 5.5 Hz) | $CH_3$ | 1.11 | $-CH_2-$ | 2.08 |
| | 52195-70-7 | $C(CH_3)_3$ | 6.76 s | $CH_3$ | 1.12 | | |

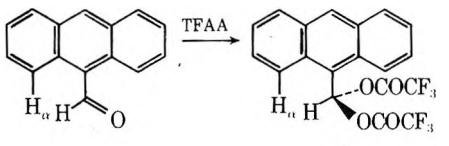
[a] All chemical shifts are reported in parts per million ($\delta$) downfield from internal tetramethylsilane. [b] The methine proton, $(CF_3CO_2)_2CH$–, is a singlet except where indicated. [c] The aromatic chemical shifts in the *para*-substituted compounds were estimated by analyzing the spectrum as a two-spin AB system. [d] Verification of the aromatic assignments was obtained by plotting the C-3,5 H chemical shifts *vs.* the semiempirical parameter, $Q$, as shown by W. B. Smith and J. L. Roark, *J. Amer. Chem. Soc.*, **89**, 5018 (1967). [e] These chemical shifts were taken from the isolated compound in $CDCl_3$. [f] The reaction between 4-cyanobenzaldehyde and TFAA is complex and will be discussed in a future communication.

exhibit the benzylic methine resonance, Ar**C**H[O-C(O)$CF_3$]$_2$, *ca.* 2 ppm upfield from the resonance of the corresponding aldehyde (Table I). Although the chemical shift of the benzylic methine proton is not readily correlated with the electronic nature of the ring, it is at lower field when a given substituent is ortho to the carboxaldehyde group than when it is para or meta. For example, this resonance occurs at $\delta$ 7.79 for the *p*-tolualdehyde adduct but at $\delta$ 8.02 for the *o*-tolualdehyde adduct. This suggests a conformational change which places that proton, on the average, closer to the aromatic plane in the ortho-substituted benzaldehyde (B favored at the expense of A, below). Such an alteration should reduce the repulsion between the ortho substituent and the trifluoroacetoxy groups.




A B

When 9-anthraldehyde is dissolved in trifluoroacetic anhydride it rapidly forms the corresponding bis(trifluoroacetate) (7). The pmr spectrum of this adduct contains a




7

methine resonance at $\delta$ 9.4. This resonance undergoes an 18% nuclear Overhauser enhancement[9] when the aryl protons adjacent to it (C-$H_\alpha$) are irradiated. Observation of the NOE suggests an average conformation for the adduct which is similar to that of the parent aldehyde[10] and which possesses its "benzylic" hydrogen close to, or in, the aryl plane. Furthermore, these results are consistent with the ortho effect noted above.

The rate of reaction of aryl carboxaldehydes, studied by pmr, followed pseudo-first-order kinetics. While some compounds (*e.g.*, *p*-$CH_3OC_6H_4CHO$) reacted too rapidly for accurate kinetic study, the logarithm of the observed half-lives (Table II) produced a straight line when plotted against the $\sigma$ constant for the substituent but not when plotted against $\sigma^+$. The $\rho$ value for the reaction was found to be $-2.5$.[11]

While the *gem*-bis(trichloroacetates) are reported[4] to be comparatively stable and capable of purification by distil-

**Table II**
**Reactivity of Aldehydes with Trifluoroacetic Anhydride[a,b]**

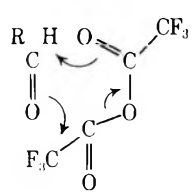
| Compd | $t_{1/2}$ (32°), min | Registry no. |
|---|---|---|
| *p*-Anisaldehyde | <1 | 123-11-5 |
| *o*-Anisaldehyde | <1 | 135-02-4 |
| *p*-Dimethylaminobenzaldehyde | <1[c] | 100-10-7 |
| *p*-Tolualdehyde | 9 | 104-87-0 |
| *o*-Tolualdehyde | 10 | 529-20-4 |
| *m*-Tolualdehyde | 17 | 620-23-5 |
| Benzaldehyde | 34 | 100-52-7 |
| *p*-Fluorobenzaldehyde | 35 | 459-57-4 |
| *m*-Anisaldehyde | 41 | 591-31-1 |
| *p*-Chlorobenzaldehyde | 70 | 104-88-1 |
| *p*-Bromobenzaldehyde | 84 | 1122-91-4 |
| *m*-Nitrobenzaldehyde | 800 | 99-61-6 |
| *p*-Nitrobenzaldehyde | 1970 | 555-16-8 |
| Pentafluorobenzaldehyde | ~7 days | 653-37-2 |

[a] In each instance the product was identified as the bis(trifluoracetate) by proton and fluorine magnetic resonance spectroscopy. [b] Registry no., 407-25-0. [c] Amide formation prevented use of the isomeric aminobenzaldehydes.

lation, *gem*-bis(trifluoroacetates) are easily converted to carbonyl compounds and TFAA. Thus, attempts at removal of TFAA from solutions of these esters in TFAA by distillation (bp 40°) normally afforded only starting aldehyde. However, diesters could be isolated by removing the excess of TFAA at reduced temperature (below 0°) and pressure. For example, $\alpha,\alpha$-bis(trifluoroacetoxy)-*p*-chlorotoluene could be separated from TFAA and dissolved in deuteriochloroform to afford an nmr spectrum consistent with the assigned structure (Table I).

**Mechanism.** There are two mechanisms which could account for *gem*-bisester formation. One (A, below) involves a

$$RCHO + [CF_3C(O)]_2O \longrightarrow [R^+CHOC(O)CF_3CF_3CO_2^-] \longrightarrow RCH[OC(O)CF_3]_2 \quad (A)$$



$$\rightleftharpoons RCH(OCOCF_3)_2 \quad (B)$$

nucleophilic attack by the carbonyl group upon TFAA to form a carbocation and a trifluoroacetate anion. While not discussed by Mazur[4] in their study of TCAA, this could not be ruled out, *a priori*, for reactions of TFAA because trifluoroacetate is a better leaving group than is trichloroacetate. However, the absence of rearrangement during the reaction of **1**, **2**, *and* **3** and the virtually identical rates of reaction of **2** and **3** would appear to rule this mechanism out. One might have imagined that even a moderate increase in positive charge at the carbonyl carbon would have resulted in participation by the *p*-methoxyphenyl group in **3**. Furthermore, if a free carbocation were involved one would have anticipated that the rate of reaction of substituted benzaldehydes would have followed $\sigma^+$ rather than $\sigma$.

These data argue in favor of a fairly concerted addition, one which may be viewed as a cycloaddition reaction of TFAA across the carbonyl group (B).

## Experimental Section

**Instruments and Techniques.** Spectra were recorded on a Varian HA-100 spectrometer. The nuclear Overhauser enhancement experiments were performed using a Hewlett-Packard 200CD oscillator. The per cent enhancement was determined by comparing the intensity of the enhanced spectra to the intensity of the spectrum during off-resonance irradiation. An average of ten values was used to calculate the NOE.

All samples were prepared in an excess of TFAA (*ca.* 10:1 v/w). Trifluoroacetic anhydride and tetramethylsilane were vacuum distilled from calcium hydride into the nmr tube containing the sample. The tubes were then sealed under vacuum. Progress of the reaction was followed by integrating the aldehydic and the adduct proton resonances at appropriate intervals. The initiation time, $t_0$, was obtained by extrapolating the linear plot (per cent reaction *vs.* time) back to 0% reaction. The half-life, $t_{1/2}$, was taken from the plot at the point where the reaction was 50% complete. Reactions were normally followed through 3 half-lives.

**Syntheses.** Most of the aldehydes were available commercially and were purified by recrystallization or distillation. Solid samples were dried *in vacuo* over phosphorus pentoxide; liquids were dried over calcium hydride. All commercial samples were homogeneous (nmr) after such treatment.

**2-*p*-Methoxyphenyl-2-methylpropanal.** The procedure of Kuntzel, Wolf, and Schaffner[12] was used to prepare 2-*p*-methoxyphenyl-2-methylpropanoic acid in 44% yield. (The work-up was altered slightly by refluxing the crude product in 10% sodium hydroxide to saponify residual ester.)

A solution of 12.2 g (0.0628 mol) of 2-*p*-methoxyphenyl-2-methylpropanoic acid in 20 ml of thionyl chloride was refluxed for 20 min. After removal of volatiles, vacuum distillation afforded 11.1 g (0.0515 mol) of 2-*p*-methoxyphenyl-2-methylpropanoyl chloride, bp 125–135° (0.1 Torr). Reduction of the acid chloride was accomplished by slowly adding a cooled (0°) solution of 12.5 g of lithium aluminum tri-*tert*-butoxyhydride in 40 ml of tetrahydrofuran to 11.0 g of acid chloride dissolved in 120 ml of cold (−68°) tetrahydrofuran. After addition was completed, the reaction mixture was allowed to warm to 10°. The desired product was isolated by pouring the reaction mixture over an equal volume of ice, acidifying with 50 ml of dilute hydrochloric acid, and extracting with methylene chloride (2 × 100 ml). Drying of the extract, followed by removal of solvent, afforded 7.9 ml of yellow oil shown (nmr) to be 70% aldehyde and 30% alcohol. Distillation yielded 4.9 g (0.0275 mol, 53% yield) of 2-*p*-methoxyphenyl-2-methylpropanal, bp 90–95° (0.1 Torr) [lit.[12] bp 143–148° (10 Torr)].

**2-Phenyl-2-methylpropanal.** The preparation of 2-phenyl-2-methylpropanal was similar to that used to prepare 2-*p*-methoxyphenyl-2-methylpropanal. The desired product was obtained in about 50% yield, based upon the acyl halide, bp 92–96° (0.2 Torr) [lit.[12] bp 105–120° (10 Torr)].

**Acknowledgment.** We are grateful to the Robert A. Welch Foundation for the support of this research through Grant Y-484 (including a postdoctoral fellowship for Dennis Deavenport). The nmr spectrometer used in this research was purchased with the aid of a grant from the Research Corporation.

**Registry No.**—**2**, 3805-10-5; **3**, 32454-14-1; 2-*p*-methoxyphenyl-2-methylpropanoic acid, 2955-46-6; 2-*p*-methoxyphenyl-2-methylpropanoyl chloride, 40919-14-0; 2-phenyl-2-methylpropanoyl chloride, 36293-05-7.

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(5) J. M. Tedder, *Chem. Rev.*, **55**, 787 (1955).
(6) In our initial report we described the reaction of thioxanthone and some derivatives with TFAA: A. L. Ternay, Jr., and D. W. Chasar, *J. Org. Chem.*, **33**, 3641 (1968).
(7) Aldehydes possessing $\alpha$ hydrogens react as do these compounds but the first-formed bisesters may undergo loss of trifluoroacetic acid to enol esters. Under proper conditions these may react further (unpublished results). See also ref 4, and references cited therein.
(8) Pivaladehyde reacts at a rate comparable to that of propanal ($t_{1/2}$ = 11 min), suggesting that, in general, the reaction of aldehydes with acid anhydrides is not subject to *severe* steric requirements.

(9) Related NOE's have been observed for 9,10-dihydroanthracene and thioxanthene derivatives: A. W. Brinkmann, M. Grodon, R. G. Harvey, P. W. Rabideau, J. B. Stothers, and A. L. Ternay, Jr., *J. Amer. Chem. Soc.*, **92**, 5912 (1970); A. L. Ternay, Jr., and S. A. Evans, *J. Org. Chem.*, in press.
(10) J. B. Stothers, "Carbon-13 NMR Spectroscopy," Vol. 24 of Organic Chemistry Monographs, A. T. Blomquist and H. Wasserman, Ed., Academic Press, New York, N. Y., 1972, pp 282–285.
(11) In his study of the reaction of ketones with TCAA, Mazur[3] noted that added trichloroacetic acid (20%) diminished the reaction rate, suggesting that ". . . the carbonyl in its protonated form does not react with anhydride." We have noted, by way of contrast, that the addition of trifluoroacetic acid (as much as 20%) to solutions of aldehydes in TFAA does not appear to have a significant effect upon the rate of adduct formation. For example, $t_{1/2}$ (32°) for *m*-anisaldehyde in TFAA and in 90% TFAA–10% TFA are within experimental error of one another (41 ± 1 min).
(12) H. Kuntzel, H. Wolf, and K. Schaffner, *Helv. Chim. Acta*, **54**, 868 (1971).

## Phase Transfer Catalysis. The Acetoacetic Ester Condensation

H. Dupont Durst* and Lanny Liebeskind

*Department of Chemistry, State University of New York at Buffalo, Buffalo, New York 14214*

*Received November 13, 1973*

Great interest has developed in recent years in phase transfer processes, especially liquid–liquid phase transfer.[1,2] The elegant paper of Starks[1] on the usefulness of several liquid–liquid phase transfer catalysts gives several examples of how the process may be used as a routine synthetic tool. We have extended this work to a solid–liquid phase transfer process using the acetoacetic ester condensation as a representative example of this principle.

The catalyst used in this study was a long-chained aliphatic quaternary ammonium salt, "Alaquat 336,"[1,3] which consists of mixed trialkylmethylammonium chlorides (average molecular weight 503[1]). It is insoluble in water and soluble in all common organic solvents. The basic process was to generate a solid reactive anion which is normally insoluble in organic solvents, use the phase transfer catalyst to transport this anion into the organic phase, then allow this anion to react in the organic phase. The reactive anion generated in this study was the methyl acetoacetate anion. Once dissolved by the phase transfer catalyst in the organic solvent, this anion reacted with an alkylating agent to give the traditional acetoacetic ester alkylated product.

There have been numerous studies[4,5] directed at the alkylation pattern of ambident ions in both protic solvents (usually alcohols) and polar aprotic solvents. The major difference in these two systems seems to be that carbon alkylation is favored in protic solvents while O-alkylation is favored in polar aprotic solvents [especially in hexamethylphosphoramide[4a] (HMPA)]. In our study it was found that alkylation of the acetoacetate anion in benzene using benzyl chloride as the alkylation reagent gave predominantly (>99%) carbon alkylation with no detectable oxygen alkylation.[6] Thus, this process offers a reversal of the usually observed results in aprotic solvents in that carbon alkylation is favored, thereby giving an alternative to the usual procedure of using protic solvents to favor carbon alkylation. It also offers the advantage that no solvolysis products arising from alkylating reagent–solvent interactions are possible, thus eliminating a major side product of reactions run in protic solvents. This advantage is especially important when small amounts of valuable alkylating reagents are required, such as geranyl bromide.

The experimental conditions using this solid–liquid phase transfer process are exceedingly simple. The concentration of catalyst has an effect on the rate of reaction.

**Table I**
**Catalyst Concentration Using Benzyl Chloride as the Alkylating Reagent**

| Ratio[a,b] | Yield,[c,d] % |
|---|---|
| No catalyst | 25 |
| 25:1 | 61 |
| 20:1 | 70 |
| 10:1 | 85 |

[a] Standard conditions consist of benzene as solvent; 8-hr reflux; sodium methyl acetoacetate/benzyl chloride ratio 2:1; the reaction was protected from moisture during the reaction. [b] Molar ratio of catalyst to alkylating agent. Catalyst av mol wt 503. [c] Isolated yields by distillation. [d] Gc analysis shows only one peak >99% purity by integration.

**Table II**
**Solvent Effects on Alkylation Yields**

| Solvent[a] | Yield,[b] % |
|---|---|
| Benzene | 85 |
| Toluene | 82 |
| Chloroform | 56 |
| Carbon tetrachloride | 42 |
| Hexane | 40 |

[a] Standard conditions: 8-hr reflux, sodium methyl acetoacetate/benzyl chloride/catalyst ratio 20:10:1. [b] Isolated monoalkylated yields by distillation.

**Table III**
**Alkylation Products**

| Alkylating agent[a] | Product,[b,c] % |
|---|---|
| Allyl bromide | 85 |
| Benzyl chloride | 85 |
| Geranyl bromide | 85 |
| Dimethylallyl chloride | 37 |
| Allyl chloride | 30 |

[a] Standard conditions: 8-hr reflux, benzene solvent; sodium methyl acetoacetate/alkylating agent/catalyst ratio 20:10:1. [b] Product isolated by distillation. [c] Only monocarbon alkylation observed.

Using benzene as a solvent and 8-hr reflux as a standard condition, we found that a 10:1 alkylating reagent/catalyst molar ratio gave consistently high yields. All reactions with catalyst were accelerated over control experiments without catalyst. These results are tabulated in Table I. We also found that benzene was not the only solvent one could use. In effect, all commonly used solvents ranging from benzene to hexane may be used. These results are tabulated in Table II. One might note that in hexane the monocarbon alkylated product was obtained in 40% yield. The alkylation in hexane, without added catalyst, gave essentially no alkylation product (<5%). The reaction using different alkylating reagents is shown in Table III.

It is interesting to speculate on the anion species in solution. The initial transfer would give a quaternary ammonium methyl acetoacetate species which is soluble in nonpolar solvents because of the large hydrophobic properties and symmetry of the transfer reagent.[7] In our system, we looked for not only oxygen alkylation but dialkylation, both carbon–carbon and carbon–oxygen. Again we found very little, if any, of either product.[4,6] In the studies of alkylation in aprotic solvents two factors seem to control the alkylation pattern, that of the nature of the alkylating reagent and the tightness of the generated ion pair. The latter[4] seems to be most important in the control of these reactions. For example, in solvents like HMPA very loose ion pairs are formed, thus favoring the formation of O-al-

kylated products. This process has been used in several synthetic sequences[8] where O-alkylated material was the desired product. From our work it would seem to us that we are dealing with a very tight ion pair, thus the resulting carbon, instead of oxygen, alkylation. While it is true that activated alkylating agents tend to alkylate on carbon, the shift from polar protic solvents to polar aprotic solvents gives a much higher percentage of oxygen alkylation. Thus, le Noble[4a] reports a 13% yield of O-alkylated product, a 51% yield of C-alkylated product, and a 36% yield of di-C-alkylated product when methyl acetoacetate anion is alkylated with benzyl chloride in HMPA. le Noble[4a] also reports that allyl chloride alkylation of methyl acetoacetate anion gives 17% O-alkylation, 45% C-alkylation, and 38% di-C-alkylation. le Noble[4a] reports that, in a series of activated alkylating reagents (substituted benzyl chlorides), he obtains O-alkylated products ranging from 10 to 40% when HMPA was used as the solvent. These ratios of oxygen *vs.* carbon alkylation are almost never seen when these alkylations are carried out in polar protic solvents.[9]

le Noble, as well as others,[4b,c] also reports high yields of O-alkylated product when ethyl bromide was used as the alkylating agent with HMPA as solvent (*i.e.*, 45% yield). Kurz,[4b,c] *et al.*, observed the same trend with similar nonactivated alkylating reagents. We used *n*-butyl bromide as the alkylation reagent in our system and obtained less than 5% O-alkylated product. This result thus mimicks the alkylation pattern found in polar protic solvents. The reaction, however, had to be run for a longer time period than with our activated alkylating reagents to obtain a reasonable yield. When nonactivated halides are used in the traditional acetoacetic ester condensation (using absolute alcohol as a solvent), very little solvolysis of the alkylating reagent is observed. Thus, our system does not offer any substantial advantage in either yield or product distribution from the traditional procedure when nonactivated halides are used as alkylating reagents. However, when using activated alkylating reagents, an advantage in both alkylation products and suppression of side reactions is achieved by using the solid–liquid phase transfer process. This is especially true when small quantities of radioactive alkylating reagents[10] are used in the synthesis of biogenetic precursor molecules such as geraniol, farnesol, etc.

It is also known that aggregate formation can contribute to the reactivity of an anion[4a,11,12] in solution. We do not know what the aggregate properties of our system are nor how it affects the alkylation distribution. From the alkylating pattern we can only say that our species seems different from most other aprotic ion pairs and that this property may be used synthetically to give carbon alkylation almost exclusively.

## Experimental Section

Boiling points and melting points are uncorrected. Nmr spectra were recorded on a Varian A-60 and a Joelco HA-100 nmr spectrometer. Infrared spectra were recorded on a Perkin-Elmer Model 457 grating spectrophotometer. Mass spectral data were obtained on a Hitachi Perkin-Elmer RMU-6E spectrometer. Gas chromatograms were run on a Varian Model 1400 gas chromatograph using a flame ionization detector.

**Reaction of Methyl Acetoacetate with Benzyl Chloride. General Procedure.** Sodium hydride (5.0 g of a 50% dispersion in mineral oil, 0.104 mol) was added to a 500-ml three-neck flask fitted with a mechanical stirrer (good stirring is essential), reflux condenser, and addition funnel fitted to provide an inert atmosphere. The sodium hydride was washed free of mineral oil with small portions of anhydrous benzene, 200 ml of anhydrous benzene being added as solvent after the mineral oil was removed. With stirring, methyl acetoacetate (11.6 g, 0.100 mol) was added dropwise with the evolution of hydrogen. The solution was stirred until no more evolution of hydrogen was observed. At this point "Alaquat 336" (2.5 g, 0.005 mol, dried by benzene azeotrope and diluted to a 0.001 mol/ml standard solution in benzene) was added and the solution was brought to reflux. At reflux benzyl chloride (6.3 g, 0.050 mol), dissolved in a few milliliters of benzene, was added at a reasonable rate and the solution was refluxed for 8 hr after the addition was completed. The solution was then cooled and acidified with 1 *N* HCl, the organic layers were separated (small amounts of ether may be added to break any emulsion formed at this point), the organic phase was washed with 5% sodium bicarbonate and brine, and the resulting organic phase was dried over magnesium sulfate. The solvent was removed on a rotary evaporator at 16 mm and the resulting oil was distilled to give 8.77 g of 3-carbomethoxy-4-phenylbutanone as a clear oil, bp 98–109° (0.05 mm) (85% yield). The catalyst remained as a dark residue in the distillation flask and was discarded. Gc analysis on a 10 ft 5% FFAP column showed only one peak which was >99% pure by integration. Infrared spectral analysis showed that the 1685- and 1630-$cm^{-1}$ peaks (O-alkylated product) were missing and only those attributed to carbon alkylated acetoacetic esters were present. The nmr showed no absorption at $\tau$ 4.8–5.2 (characteristic of vinyl protons). A small portion of the clear oil was hydrolyzed, decarboxylated, and shown to consist of only 4-phenyl-2-butanone.

An alternative procedure for the work-up was to remove the methyl acetoacetate, after removal by solvent, by vacuum evaporation at 0.05 mm pressure and room temperature. The resulting oil was chromatographed, using benzene as solvent, over either alumina or silica gel. This removes the catalyst from the product and the resulting oil was distilled using a Kuhlrohr apparatus after removal of benzene, to give the same product obtained above. This work-up procedure is more convenient when working on a small amount ($\simeq$1–2 g) than the distillation procedure above.

**Reaction of Methyl Acetoacetate with Allyl Bromide.** The general procedure described above was used. Obtained was a clear oil, 4-carbomethoxy-1-hexen-5-one, bp 38–43° (0.1 mm) (94.7% yield). Ir and nmr analysis showed no peaks characteristic of O-alkylated material.[6] Gc analysis showed only one peak of >99% purity.

**Reaction of Methyl Acetoacetate with Allyl Chloride.** The general procedure described above was used. Obtained was a clear oil, 4-carbomethoxy-1-hexen-5-one, bp 36–39° (0.05 mm) (30% yield). Ir and nmr analysis showed no peaks characteristic of O-alkylated material.[6] Gc analysis showed only one peak of >99% purity.

**Reaction of Dimethylallyl Chloride with Methyl Acetoacetate.** Dimethylallyl chloride was synthesized from isoprene according to the procedure of Roux and Kotzanevas.[13] The chloride was kept at −20° until used. The general procedure described above was used for the alkylation. Obtained was a clear oil, 3-carbomethoxy-6-methyl-5-hepten-2-one, bp 55–60° (0.6 mm) (36.8% yield). Ir and nmr analysis showed no peaks characteristic of O-alkylated material. Gc showed one peak of >98% purity with a minor unidentified peak ($\simeq$2%).

**Reaction of Geranyl Bromide with Methyl Acetoacetate.** Geranyl bromide was synthesized according to the procedures of Meyers.[14] The material was used immediately after synthesis. The standard procedure described above was used. Obtained was a slightly yellow oil, 3-carbomethoxy-6,10-dimethyl-5,9-undecadien-2-one, Kuglrohr distillation, bp 120–130° (0.5 mm) (85.1% yield). Ir and nmr analysis showed no absorptions characteristic of O-alkylated material.[6] Gc analysis showed only one peak of >99% purity.

One gram of the above oil was hydrolyzed using KOH in methanol at room temperature for 48 hr. Acidification using glacial acetic acid and removal of solvent gave an oil which was distilled by Kuglrohr distillation at 100° (0.1 mm). The resulting oil was taken up in ether and washed with 5% $NaHCO_3$. The ether was dried ($MgSO_4$) and solvent was removed to yield geranyl acetone which gc analysis showed to be >95% of the trans product. The trans stereochemistry showed that very little isomerization occurred during the reaction.

The 85.1% yield reported above represents our best yield. The synthesis of geranyl bromide gave variable yields depending on how the bromide was generated[14] from the alcohol. Yields of geranyl bromide were estimated to-range from 55 to 85%, several synthetic procedures being tried.

**Acknowledgment.** We would like to thank Mr. J. E. House of General Mills Chemical Co. for his generous gift of "Alaquat 336" for this project and Drs. F. Wudl, C. D. Ritchie, and J. J. Tufariello for helpful discussions on

ion pair alkylations. One of us (L. L.) would like to thank the Undergraduate Research Fund as administered by the State University of New York at Buffalo Student Association for a grant in support of this work. The National Science Foundation provided financial aid in the purchase of the nmr spectrometer used in this research.

**Registry No.**—Methyl acetoacetate, 105-45-3; benzyl chloride, 100-44-7; 3-carbomethoxy-4-phenylbutanone, 3666-82-8; 4-phenyl-2-butanone, 2550-26-7; allyl bromide, 106-95-6; 4-carbomethoxy-1-hexen-5-one, 3897-04-9; allyl chloride, 107-05-1; dimethylallyl chloride, 503-60-6; 3-carbomethoxy-6-methyl-5-hepten-2-one, 20962-72-5; geranyl bromide, 5389-87-7; 3-carbomethoxy-6,10-dimethyl-5,9-undecadien-2-one, 51933-45-0; geranyl acetone, 3796-70-1.

## References and Notes

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(6) Reaction products were examined by ir, nmr, and gc. The $\beta$-alkoxy-$\alpha,\beta$-unsaturated ester absorptions at 1685 and 1630 $cm^{-1}$ were missing. There were no nmr absorptions at $\tau$ 4.8–5.15 characteristic of vinyl protons. Gc analysis showed only one major peak (99% by intergration) which corresponds to monoalkylated methyl benzylacetoacetate. This product was hydrolyzed, decarboxylated, and shown to consist of only 4-phenyl-2-butanone. See Experimental Section.
(7) D. Picker and A. W. Herriott, First Fall Organic Conference, Cape Cod, Mass., Oct , 1973; *Tetrahedron Lett.*, 4521 (1972).
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(12) Zaugg, *et al.*,[11b] reports using nonpolar solvents, such as benzene, in a malonic ester type alkylation. In this case the solution, although visually homogeneous, was determined to be a colloidal suspension. The molecular weight of these colloidal particles was calculated to be at least 10,000. Thus, the solubility of alkali metal salts in hydrocarbon solvents is relatively low. Although we performed the benzyl chloride alkylations using the phase transfer catalyst in several nonpolar solvents, we only checked the reactivity of the methyl acetoacetate anion without added catalyst in two solvent systems, benzene and hexene. In both cases substantial enhancement of product formation was observed using the phase transfer procedure (25 *vs.* 85% using benzene; <5 *vs.* 40% using hexane as a solvent). We presume that the same trend will be followed with the other solvents.
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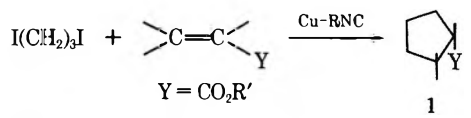
# Synthetic Reactions by Complex Catalysts. XXXVI. A New Synthesis of Cyclopentanecarboxylates. Cyclization of 1,3-Diiodopropane with $\alpha,\beta$-Unsaturated Esters by a Copper–Isonitrile Complex

Yoshihiko Ito, Kiyoshi Nakayama, Kazuya Yonezawa, and Takeo Saegusa*

*Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Kyoto, Japan*

*Received March 26, 1974*

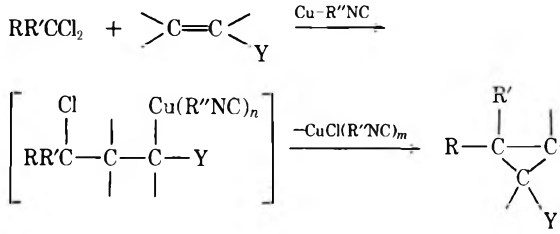
The present paper describes a new synthetic method for cyclopentanecarboxylates (1) by the reaction of 1,3-diiodopropane with an $\alpha,\beta$-unsaturated ester in the presence of copper and isonitrile (RNC) (Table I). This reaction was




(1)

1

found in the course of exploratory studies on the synthetic reactions caused by Cu–RNC mixture. Previously we have found[1] that an aliphatic halide reacts with metallic copper in the presence of RNC to form the corresponding organocopper–isonitrile complex, which then adds to $\alpha,\beta$-unsaturated carbonyl and nitrile compounds in the manner of a conjugate addition. Moreover, an organocopper–isonitrile complex bearing a halogen atom in the same molecule readily undergoes cyclization by the intramolecular elimination of copper halide–isonitrile complex. The following cyclopropane syntheses, for example, have been based upon this interesting reactivity of organocopper–isonitrile complex.




(2)

i, R = Ph, $CO_2R'''$, and CN; R' = Cl[2]
ii, R = $CH_2$=CH; R' = H[3]

The reaction described in the present paper (eq 1) affords a five-membered ring. For this reaction the transient formation of a 3-iodopropylcopper–isonitrile complex may be proposed, which is followed by the subsequent addition to an $\alpha,\beta$-unsaturated carbo ester and the final cyclization through the intramolecular elimination of the copper halide–isonitrile complex.

## Results and Discussion

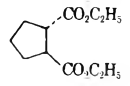
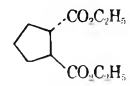
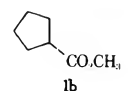
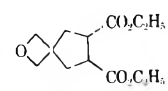
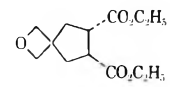
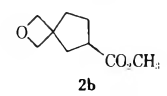
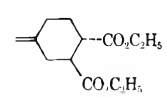
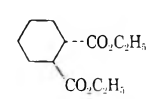
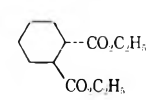
On heating a mixture of 1,3-diiodopropane, diethyl fumarate, cyclohexyl isocyanide, and metallic copper in refluxing toluene under nitrogen, *trans*-1,2-dicarbethoxycyclopentane was produced in a high yield and high selectivity. Also the reaction of 1,3-diiodopropane with diethyl maleate by an identical procedure gave the same product. Since it has been found by us that maleate is readily isomerized to fumarate by the Cu–RNC system,[1] and that cyclopropane-, cyclopentane-, and cyclohexane-*cis*-1,2-dicarboxylates are isomerized to the corresponding trans isomers, respectively, under the present reaction conditions, it is conceivable that diethyl maleate is converted to diethyl fumarate prior to the cyclization reaction and/or that *cis*-1,2-dicarbethoxycyclopentane once formed is converted to *trans*-1,2-dicarbethoxycyclopentane.

Similarly, the reaction of 1,3-diiodopropane with methyl acrylate afforded cyclopentanecarboxylic acid methyl ester in 58% yield. Use of electron-deficient olefins other than fumarate, maleate, and acrylate in the present reaction, however, gave rise to decreased yields and selectivities of the corresponding cyclopentane derivatives.

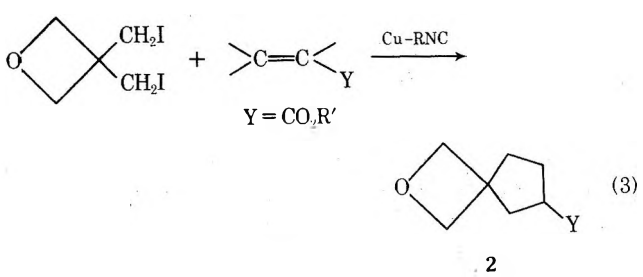
3,3-Bis(iodomethyl)oxetane can be used in place of 1,3-diiodopropane. The product is the corresponding oxaspirane carboxylate (2). Cyclization of tetraiodoneopentane with fumarate gave **3** instead of the spirocyclononanetetracarboxylate. Compound **3** is supposed to be produced through intermediate **4**.[4]

Employment of iodides in the present reaction is essen-

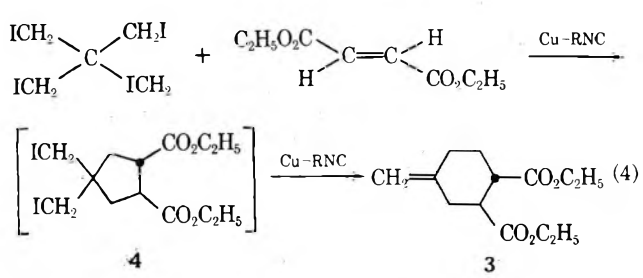
**Table I**
**Reaction of Diiodopropane with the Cu(0)–Isonitrile Complex in the Presence of α,β-Unsaturated Esters**

| Halide (registry no.) | Olefin (registry no.) | Conditions | Product (%)[a,b] | | Registry no. |
|---|---|---|---|---|---|
| $I(CH_2)_3I$ (627-31-6) | *trans*-$C_2H_5O_2CCH{=}CHCO_2C_2H_5$ (623-91-6) | 110°, 13 hr |  1a | (90)[c] | 30689-38-4 |
| $I(CH_2)_3I$ | *cis*-$C_2H_5O_2CCH{=}CHCO_2C_2H_5$ (141-05-9) | 110°, 13 hr |  1a | (89)[c] | |
| $I(CH_2)_3I$ | $CH_2{=}CHCO_2CH_3$ (96-33-3) | 80°, 12 hr |  1b | (58)[d] | 4630-80-2 |
|  (2402-82-6) | *trans*-$C_2H_5O_2CCH{=}CHCO_2C_2H_5$ | 110°, 14 hr |  2a | (46)[c,e] | 52239-59-5 |
|  | *cis*-$C_2H_5O_2CCH{=}CHCO_2C_2H_5$ | 110°, 14 hr |  2a | (23)[c,e] | |
|  | $CH_2{=}CHCO_2CH_3$ | 80°, 15 hr |  2b | (66)[d] | 52239-60-8 |
| $(ICH_2)_4C$ (1522-88-9) | *trans*-$C_2H_5O_2CCH{=}CHCO_2C_2H_5$ | 110°, 12 hr |  3 | (50)[c] | 52239-61-9 |
| $I(CH_2)_4I$ (628-21-7) | *trans*-$C_2H_5O_2CCH{=}CHCO_2C_2H_5$ | 110°, 15 hr |  7 | (37)[c] | 17357-22-3 |
| $I(CH_2)_4I$ | *cis*-$C_2H_5O_2CCH{=}CHCO_2C_2H_5$ | 110°, 13 hr |  7 | (55)[c] | |

[a] All new compounds in the table gave satisfactory elemental analyses. [b] The yields of products are not necessarily optimum, since only one or two experiments have been done for each combination. [c] Cyclohexyl isocyanide was used. [d] *tert*-Butyl isocyanide was used. [e] Stereochemistry of **2a** has not been definitely determined. However, the trans configuration was deduced from the following reasons: either diethyl fumarate or maleate react with 3,3-bis(iodomethyl)oxetane to yield the same product, and *cis*-1,2-dicarbethoxycyclopentane is readily isomerized to the trans isomer under the present reaction conditions.




(3)




(4)

tial. 1,3-Dichloro- and 1,3-dibromopropane gave the cyclopentane products only in low yields.

The present cyclization may be explained by a scheme involving an intermediate of 3-iodopropylcopper–isonitrile complex (**5**) which is initially formed by the reaction of diiodopropane with Cu–RNC.[1,2] The addition of **5** to α,β-unsaturated ester gives the second organocopper species (**6**), which in turn undergoes the cyclization by the intramolecular 1,5-elimination of CuI–RNC complex (Scheme I).

**Scheme I**

$$ICH_2CH_2CH_2I + Cu\text{-}RNC \longrightarrow ICH_2CH_2CH_2Cu(RNC)_n$$

**5**

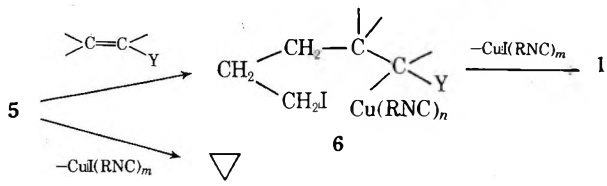


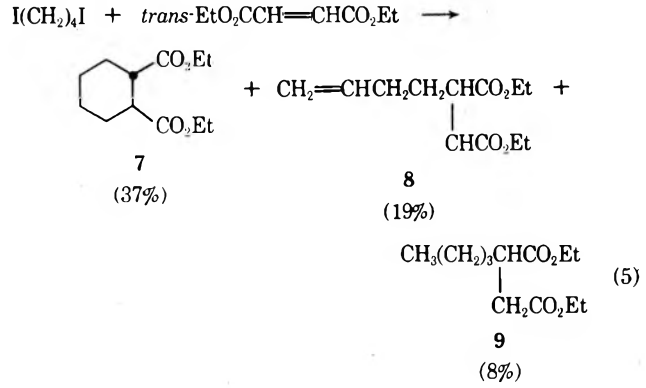
**Table II**
**Characterization of Products[c]**

| | Ir, $cm^{-1}$ [a] | Nmr, $\tau$ [b] | Mass, m/e |
|---|---|---|---|
| **1a** | 1733 | 5.84 (q, 4 H, $J$ = 7.5 Hz), 6.68–7.06 (m, 2 H), 7.62–8.92 (m, 6 H), 8.74 (t, 6 H, $J$ = 7.5 Hz) | |
| **1b** | 1735 | 6.30 (s, 3 H), 6.90–7.50 (m, 1 H), 7.92–8.47 (m, 6 H) | 128 ($M^+$) |
| **2a** | 1730 | 5.49 (s, 4 H), 5.90 (q, 4 H, $J$ = 6.5 Hz), 6.62–7.10 (m, 2 H), 7.58–7.90 (m, 4 H), 8.79 (t, 6 H, $J$ = 6.5 Hz) | |
| **2b** | 1735 | 5.41 and 5.42 (two s, 4 H), 6.30 (s, 3 H), 6.90–7.50 (m, 1 H), 7.75–8.20 (m, 6 H) | |
| **3** | 3060, 1732, 1650, 895 | 5.24 (s, 2 H), 5.84 (q, 4 H, $J$ = 7.0 Hz), 7.10–8.25 (m, 8 H), 8.77 (t, 6 H, $J$ = 7.0 Hz) | 240 ($M^+$) |
| **7** | 1732, 890 | 5.87 (q, 4 H, $J$ = 7.0 Hz), 7.25–7.60 (m, 2 H), 7.85–9.00 (m, 8 H), 8.81 (t, 6 H, $J$ = 7.0 Hz) | |

[a] Neat. [b] $CDCl_3$ solution with TMS. [c] Satisfactory analytical data were reported for all compounds in the table.

The intermediacy of 3-iodopropylcopper–isonitrile complex **5** is supported by the formation of cyclopropane in the treatment of 1,3-diiodopropane with the Cu–RNC system in the absence of olefin at about 100°. In the presence of an $\alpha,\beta$-unsaturated carboester, however, the formation of cyclopropane as a by-product was almost negligible.

The reaction of 1,4-diiodobutane with fumarate by the Cu–RNC system produced acyclic compounds **8** and **9** along with the desired product, *trans*-1,2-cyclohexanedicarboxylate (**7**).




## Experimental Section

**Reagents.** Metallic copper was prepared by reducing[5] $CuSO_4$ with zinc powder and dried under nitrogen. *tert*-Butyl and cyclohexyl isocyanide were prepared by Ugi's procedure.[6] Olefins such as fumarate, maleate, and acrylate were commercial reagents and purified by distillation under nitrogen prior to use. Trimethylene diiodide and 3,3-bis(iodomethyl)oxetane were synthesized by the reaction of the corresponding dichloride and NaI in acetone.[7] Pentaerythrityl tetriodide[8] was prepared by iodination of pentaerythrityl tetrabromide, which was synthesized by the reaction of pentaerythritol and $PBr_3$.[9] Tetramethylene diiodide was prepared by the reaction of tetrahydrofuran with KI, orthophosphoric acid, and phosphoric anhydride.[10]

**Reaction of Trimethylene Diiodide with Diethyl Fumarate by the Copper–Isonitrile System.** Under nitrogen, 1.48 g (5 mmol) of trimethylene diiodide in 4 ml of toluene was added dropwise with stirring over 30 min, to a preheated mixture of 1.27 g (20 mg-atoms) of metallic copper, 4.40 g (40 mmol) of cyclohexyl isocyanide, 1.72 g (10 mmol) of diethyl fumarate, and 6 ml of toluene at 110°. After the reaction mixture was heated for 12 hr at 110°, it was treated with ether to remove copper iodide–isonitrile complex. The extract was concentrated and distilled *in vacuo*. *trans*-1,2-Diethoxycarbonylcyclopentane was isolated in a yield of 90% by preparative glpc. The structure of the product was confirmed by spectral data and elemental analysis. These data are shown in Table II.

**Reaction of Trimethylene Diiodide with Methyl Acrylate by Copper–Isonitrile System.** A mixture of 1.48 g (5 mmol) of trimethylene diiodide, 1.72 g (20 mmol) of methyl acrylate, and 4 ml of benzene was added with stirring to a mixture of 1.27 g (20 mg-atoms) of metallic copper, 3.32 g (40 mmol) of *tert*-butyl isocyanide, and 6 ml of benzene at 80°. After the reaction mixture was heated for an additional 12 hr at 80°, the mixture was extracted with ether. The extract was concentrated and analyzed by glpc. Methyl cyclopentanecarboxylate was isolated in a yield of 58%. Reactions of 3,3-bis(iodomethyl)oxetane and tetramethylene diiodide with olefins by the copper–isonitrile system were carried out by similar ways.

**Reaction of Pentaerythrityl Tetriodide with Diethyl Fumarate by the Copper–Isonitrile System.** A mixture of 2.30 g (4 mmol) of pentaerythrityl tetriodide, 1.72 g (10 mmol) of diethyl fumarate, 1.27 g (20 mg-atoms) of metallic copper, 4.40 g (40 mmol) of cyclohexyl isocyanide, and 20 ml of toluene was stirred at 110° for 12 hr. The reaction mixture was extracted with ether. The extract was concentrated and distilled *in vacuo*. 3,4-*trans*-Diethoxycarbonylmethylenecyclohexane was isolated in a yield of 50%.

**Registry No.**—Copper, 7440-50-8; cyclohexyl isocyanide, 931-53-3; *tert*-butyl isocyanide, 7188-38-7.

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## Aqueous Sulfolane as Solvent for Rapid Oxidation of Higher α-Olefins to Ketones Using Palladium Chloride

Darryl R. Fahey* and Ernest A. Zuech

*Research and Development, Phillips Petroleum Company, Bartlesville, Oklahoma 74004*

*Received April 26, 1974*

As the chain length and substitution of olefins are increased, an overall decrease in the rate of their $PdCl_2$-catalyzed oxidation occurs.[1] Long-chain α-olefins are oxidized to methyl ketones only very slowly in entirely aqueous solutions of $PdCl_2$. Clement and Selwitz[2] found that oxidation rates of higher olefins are increased in aqueous *N,N*-dimethylformamide (DMF) solution while double-bond isomerizations are decreased. In a study of α-olefin oxidations with the Clement–Selwitz system, we consistently experienced DMF hydrolysis during oxidations. This resulted in the evolution of $CO_2$ (from formic acid oxidation[3]) and the formation of $PdCl_2(HNMe_2)_2$. Eventually, the $PdCl_2$ catalyst becomes completely poisoned.

As illustrated by the results given in Table I for the oxidation of 3,3-dimethylbut-1-ene, rapid oxidation can be achieved in aqueous 3-methylsulfolane (3-methyltetramethylenesulfone). Of the four solvent combinations listed in Table I, the aqueous 3-methylsulfolane system is clearly

**Table I**
**Solvent Dependence on 3,3-Dimethylbut-1-ene Oxidation[a]**

| Solvent (50 ml) | $H_2O$, ml | Reaction time, hr | Alkene conversion, %[b] | 3,3-Dimethylbutan-2-one yield, %[c] |
|---|---|---|---|---|
| 3-Methylsulfolane | 7 | 1.4 | ~100 | 91 |
| NMP | 7 | 7.5 | ~100 | 79 |
| DMF | 7 | 8.0 | ~70 | 33 |
| DMF | 0 | 8.0 | ~70 | 58 |

[a] All solutions contained 200 mmol of 3,3-dimethylbut-1-ene, 20 mmol of $PdCl_2$, and 20 mmol of $CuCl_2 \cdot 2H_2O$. Reactions were conducted at 70–80° under 40–99 psig $O_2$. [b] Estimated by glpc as $wt_{ketone}/(wt_{alkene} + wt_{ketone}) \times 100\%$. [c] Distilled yield based on 200 mmol of 3,3-dimethylbut-1-ene.

superior with respect to reaction rate and product yield. Sulfolanes are chemically very stable, and their low volatility allows easy product recovery. Sulfolane and 3-methylsulfolane can be used interchangeably, but sulfolane is less expensive and more readily available. Aqueous *N*-methylpyrrolidone (NMP) is an improved solvent compared to the corresponding DMF system, but its performance is less satisfactory than sulfolane's. The oxidation is very much slower in entirely aqueous media.

At high alkene to $PdCl_2$ mole ratios, high selectivities to the ketone are obtained only at moderate olefin conversions (*e.g.*, entry 1 in Table II). In oxidations with similar turnover numbers of Pd, the highest selectivity to the ketone occurs at the highest alkene to $PdCl_2$ ratio (Table II).

**Table II**
**Selectivity to Ketone at High Alkene to $PdCl_2$ Ratios**

| Mole ratio of 3,3-dimethylbut-1-ene to $PdCl_2$ | Alkene conversion, % | Number of Pd turnovers | Selectivity to 3,3-dimethylbutan-2-one, % |
|---|---|---|---|
| 421 | 24 | 101 | 96 |
| 211 | 59 | 123 | 81 |
| 100 | 100 | 100 | 77 |

When low selectivities are observed, they are a result of further reactions of the ketone. Two by-products which have been isolated are 1-chloro-3,3-dimethylbutan-2-one and 2,2-dimethylpropanoic acid.

### Experimental Section

3,3-Dimethylbut-1-ene and the sulfolanes were Phillips Petroleum Co. products and were used without purification. Palladium chloride was purchased from Engelhard Industries. Other reagents were obtained commercially in high purity.

**Small-Scale 3,3-Dimethylbut-1-ene Oxidations.** Solvent studies were performed in a 6-oz (177 ml) aerosol compatibility bottle equipped with a stainless steel cap and sealed by a neoprene rubber ring. The cap was fitted with a pressure gauge and a valve connected to an oxygen source. After the bottle was charged with the desired reactants, as described in Table I, the bottle was pressured to 30–45 psig with $O_2$ and was then immersed in an oil bath held at 70–80°. The mixture was magnetically stirred, and whenever the pressure dropped to 40 psig, oxygen was added to increase the pressure to *ca.* 80 psig. After completion of the reaction, the reaction mixture was distilled, and all the material distilling up to 106° was collected. The organic portion of the distillate was redistilled, and 3,3-dimethylbutan-2-one was collected at 100–106°. This fraction and its immediate forerun were analyzed by glpc on a 6 ft × 0.125 in. column packed with 10% SP-1200–1% $H_3PO_4$ on 80/100 Chromosorb W AW temperature programmed from 80 to 140°. Each yield shown in Table I is the sum of the ketone product contained in these two fractions. The 100–106° fraction was 96–99% 3,3-dimethylbutan-2-one.

In the third entry in Table I, a glpc analysis of the gas phase in the bottle after completion of the reaction showed it to be 28% $CO_2$. The analysis was performed on a 20 ft × 0.25 in. column packed with 20% bis(2-methoxyethoxy)ethyl ether on 35/80 Chromosorb P at 40°. Filtration of this reaction mixture before distillation gave 2.40 g (37%) of gold $PdCl_2(HNMe_2)_2$ contaminated with a small amount of a green solid (a copper complex?). The complex has an ir spectrum identical with that of dimethylamine. Recrystallization of the sample from $CH_2Cl_2$–pentane afforded yellow crystals, mp 213–215° dec.

*Anal.* Calcd for $C_4H_{14}Cl_2N_2Pd$: C, 17.96; H, 5.28; Cl, 26.50; N, 10.48; Pd, 39.80. Found: C, 17.85; H, 4.93; Cl, 27.2; N, 10.48; Pd, 40.5.

**Large-Scale 3,3-Dimethylbut-1-ene Oxidation.** A similar procedure was used for the three reactions, so only a representative example is given. 2,2-Dimethylbutane, bp 49°, was present as an inert internal standard to monitor losses of 3,3-dimethylbut-1-ene, bp 41°, due to evaporation. A 300-ml 316-S.S. stirred autoclave with a glass cup insert was charged with 67.2 g (800 mmol) of 3,3-dimethylbut-1-ene, 0.34 g (1.9 mmol) of $PdCl_2$, 0.66 g (3.9 mmol) of $CuCl_2 \cdot 2H_2O$, 6 ml of 0.4 *N* HCl, 50 ml of sulfolane, and 16.8 g of 2,2-dimethylbutane. The autoclave was pressured to 220 psig with $O_2$ and was then heated to 120–130°. Heatup required 0.5 hr. The oxidation was allowed to proceed for 2.5 hr, and each time the pressure fell to 250 psig, oxygen was added until the pressure was 310 psig. The reactor was cooled to 25° over 2.5 hr. The product mixture was distilled at 1 mm with a pot temperature of 80°, and the distillate was trapped at −78°. The organic portion of the distillate was redistilled at atmospheric pressure, collecting 3,3-dimethylbut-1-ene and 2,2-dimethylbutane at 40–49° and 3,3-dimethylbutan-2-one at 95–106°. The alkane–alkene fraction was analyzed by glpc on a 20 ft × 0.125 in. column packed with 20% tris-1,2,3-(2-cyanoethoxy)propane on 60/80 Chromosorb P. The alkane recovery was 14.0 g (83.5%), and the alkene recovery was 42.9 g (63.9%). Assuming that the rate of evaporation is the same for both the alkane and the alkene, the actual 3,3-dimethylbut-1-ene conversion is calculated to be 23.5%. The total yield of 3,3-dimethylbutan-2-one was 18.0 g (95.8% selectivity based on 23.5% alkene conversion).

In a separate high-conversion alkene oxidation, two of the more prevalent by-products were isolated by preparative glpc and were identified by their ir, nmr, and mass spectra. 2,2-Dimethylpropanoic acid was confirmed by comparison of its ir spectrum with Sadtler[4] Spectrum No. 6355. The ir and nmr spectra of 1-chloro-3,3-dimethylbutan-2-one compare favorably with published[5] spectral information. Both compounds have the appropriate molecular ions in their mass spectra.

**Acknowledgment.** Experimental assistance by Mr. W. K. Clem is gratefully acknowledged.

**Registry No.** —3,3-Dimethylbut-1-ene, 558-37-2; 3,3-dimethyl-

butan-2-one, 75-97-8; $PdCl_2$, 7647-10-1; $CuCl_2$, 7447-39-4; $PdCl_2(HNMe_2)_2$, 52217-23-9.

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## A New Synthesis of the Benzothiazole Ring *via* Imidoyl Chlorides and Chloroformamidines


Kurt Pilgram* and R. D. Skiles

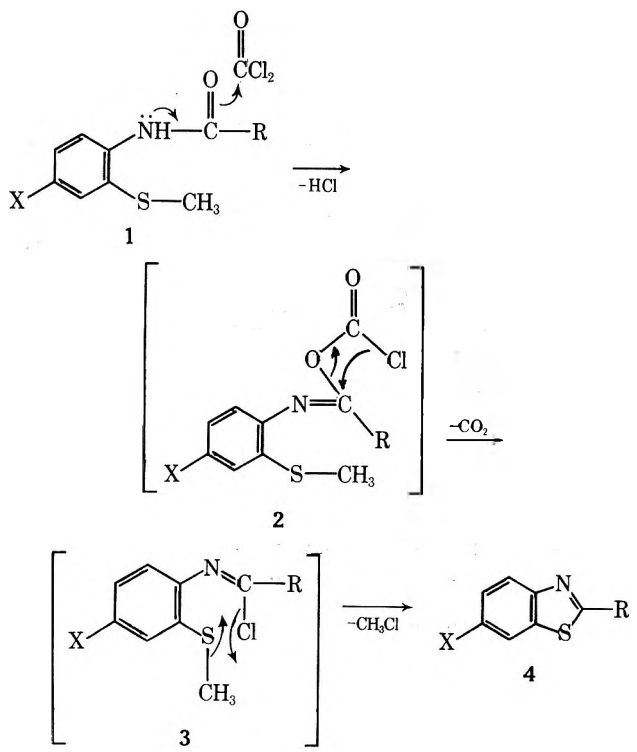
*Biological Sciences Research Center, Shell Development Company, Modesto, California 95352*


*Received June 14, 1974*

In an attempt to prepare a series of aromatic imidoyl chlorides as intermediates, 2′-(methylthio)acylanilides (**1**) were treated with phosgene in a manner similar to that reported for the preparation of imidoyl chlorides.[1] Although our attempt did not produce the desired imidoyl chlorides, *e.g.*, **3**, we did discover a convenient method of preparing 2-substituted benzothiazoles, **4**.

### Results and Discussion

As a model compound, 2′-(methylthio)acetanilide (**1a**) was converted with phosgene into 2-methylbenzothiazole (**4a**) in 86% yield. In a convenient procedure, the reactants were heated (80°) and stirred in *p*-dioxane. After 0.5 to 1 hr, the hydrochloride of 2-methylbenzothiazole was isolated. Prolonged heating (8 hr at 80–98°) brought about evolution of hydrogen chloride to give **4a** as the only detectable reaction product.




**1** **2** **3** **4**

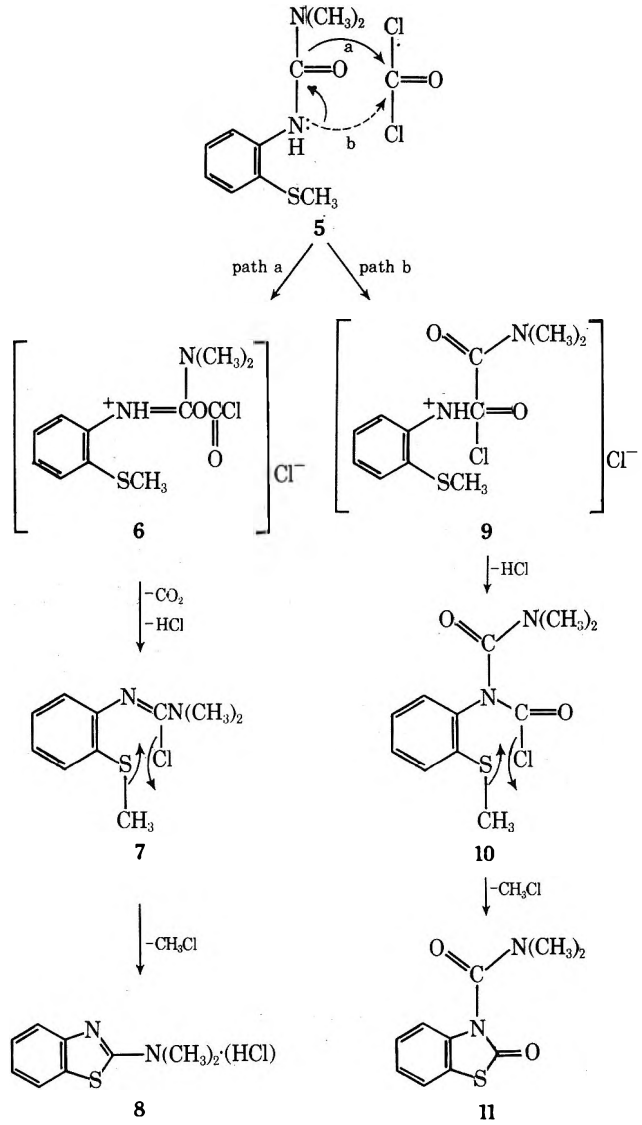
a, R = $CH_3$; X = H
b, R = ; X = Cl
c, R = $CF_3$; X = H

4′-Chloro-2′-(methylthio)cyclopropanecarboxanilide (**1b**) reacted with phosgene in ethyl acetate at 50–55° (8 hr). Under these conditions, **4b** was obtained in 10% yield. No attempt was made to optimize the yield. The nmr spectrum of **4b** showed the expected proton count, shifts of three aromatic protons at 7–8 ppm, and the five cyclopropyl protons at $\delta$ 1.2 ($CH_2CH_2$) and 2.4 ppm (CH). Consistent with the structure of **4b**, the mass spectrum shows the correct molecular ion at *m/e* 209, 211 ($M^+$, base peak), indicating the presence of one chlorine atom in the molecule.

When 2′-(methylthio)trifluoroacetanilide (**1c**) was treated with phosgene under similar conditions, starting material, **1c**, was recovered unchanged after 96 hr at 80°. Attempted reaction with phosgene in refluxing toluene containing catalytic amounts of dimethylformamide was also unsuccessful. It was not possible to obtain 2-(trifluoromethyl)benzothiazole (**4c**) by either procedure.

The formation of benzothiazoles, **4**, from **1** and phosgene suggests that phosgene is attacked by the oxygen rather than the nitrogen of the anilide. O-Acylation of amides has been demonstrated.[2,3] Thus, the O-acylated intermediate, **2**, initially formed from **1** and phosgene apparently loses carbon dioxide and hydrogen chloride with formation of reactive imidoyl chloride,[1] **3**, which is converted into the benzothiazole, **4**, by loss of methyl chloride.

In a similar manner, the reaction of 1,1-dimethyl-3-(2′-(methylthio)phenyl)urea (**5**) with phosgene in *p*-dioxane was found to give the hydrochloride of the known 2-(di-




**5** **6** **7** **8** **9** **10** **11**

methylamino)benzohiazole[4] (8) in 39.7% yield in addition to 3-(dimethylcarbamoyl)benzothiazolin-2-one (11) in 60.2% yield. The structure of 11 is supported by elemental analysis, infrared spectroscopy, nmr and mass spectrum. Evidence for the structural assignment of 11 includes C=O absorption at 1755 $cm^{-1}$ in the infrared spectrum. The nmr spectrum contains two unsplit methyl signals at 3.05 and 3.15 ppm, whereas the aromatic region displays a multiplet at 7.1 ppm. In the mass spectrum of 11, the molecular ion is observed at *m/e* 222 ($M^+$). The initial fragmentation pattern is characterized by the loss from the parent ion of a carbonyl (C=O) and dimethylcarbamoyl group, $(CH_3)_2NCO$ (base peak), to give *m/e* 122.

The reaction of urea 5 with phosgene follows two major pathways. Initial attack by the urea oxygen (path a), similar to that which occurs in the anilide–carbonyl chloride reaction, gives chloroformamidine 7, as an intermediate *via* 6, which cyclocondenses to give 2-(dimethylamino)benzothiazole (8). Alternately, attack of phosgene by the urea nitrogen atom ($N^3$) affords the intermediate allophanoyl chloride 10 by way of 9; loss of methyl chloride from 10 gives 11 directly. The formation of intermediates analogous to 7 and 10 is well documented in the literature.[1,5]

## Experimental Section

**2′-(Methylthio)acetanilide (1a).** This compound was prepared in 90.1% yield from 2-aminothioanisole and acetyl chloride in tetrahydrofuran in the presence of triethylamine as acceptor for hydrogen chloride; colorless crystalline solid, mp 111–113° (lit.[6] mp 114–115°).

**4′-Chloro-2′-(methylthio)cyclopropanecarboxanilide (1b).** This compound was prepared in 95% yield from 2-amino-5-chlorothioanisole[7] and cyclopropanecarbonyl chloride as outlined above for 1a: mp 117–119°; ir (KBr) 3260 (NH) and 1655 $cm^{-1}$ (C=O); nmr ($CDCl_3$) δ 0.7–1.8 (5, m, cyclopropyl), 2.4 (3, s, $CH_3$), and 7–9 ppm (3, m, $C_6H_3$); mass spectrum (70 eV) *m/e* 243 ($M^+$), 196, 194 ($M^+ - CH_3S$), 175, 173 ($M^+ - C_3H_5CO$), 69 ($C_3H_5CO$), 41 ($C_3H_5$).

*Anal.* Calcd for $C_{11}H_{12}ClNOS$: C, 54.7; H, 5.0; N, 5.8. Found: C, 54.5; H, 5.4; N, 5.6.

**2′-(Methylthio)-2,2,2-trifluoroacetanilide (1c).** This compound was prepared analogously in 89.4% yield from 2-aminothioanisole and trifluoroacetyl chloride in the presence of 1 molar equiv of triethylamine: mp 45–47°; ir (KBr) 3220 (NH) and 1740 $cm^{-1}$ (C=O); nmr (DMSO-$d_6$) δ 2.4 (3, s, $CH_3$), 7.3 (4, q, $C_6H_4$), and 11.0 ppm (1, s, NH).

*Anal.* Calcd for $C_9H_8F_3NOS$: C, 46.0; H, 3.4; N, 6.0. Found: C, 45.7; H, 3.3; N, 5.7.

**2-Methylbenzothiazole Hydrochloride and 2-Methylbenzothiazole (4a).** To a stirred solution of 13.5 g (0.075 mol) of 1a in 200 ml of *p*-dioxane was added dropwise a solution of 30.0 g (0.30 mol) of phosgene (*caution: highly toxic*) in 50 ml of *p*-dioxane. The resulting yellow solution was heated to reflux (80–85°). After 3.5 hr, a sample was withdrawn, cooled, filtered, and dried to give a crystalline solid: mp 180–183°; ir (KBr) 2600 $cm^{-1}$ (HX-salt); nmr (DMSO-$d_6$) δ 2.9 (3, m, $CH_3$), 7–8.2 (4, m, aromatic H), and 12.2 ppm (1, m, HCl); mass spectrum (70 eV) *m/e* 149 ($M^+ - HCl$, base peak), 121, 117 ($M^+ - S$), 108 ($C_6H_4S^+$), 82, 75, 69, 63, 50, 45, 39.

*Anal.* Calcd for $C_8H_8ClNS$: C, 51.8; H, 4.3; N, 7.5; Cl, 19.1. Found: C, 51.4; H, 4.2; N, 7.3; Cl, 19.1.

After a heating period of 8 hr at 80–98°, thin layer chromatography indicated the complete disappearance of starting material, and hydrogen chloride evolution had ceased. The reaction mixture was concentrated under reduced pressure, washed with water, dissolved in ether, dried ($MgSO_4$), concentrated, and distilled to give 9.5 g (86%) of a colorless liquid: bp 128–130° (35 mm); bp 236° (760 mm) (lit.[8] bp 238°); nmr ($CDCl_3$) δ 2.8 (3, s, $CH_3$), and 7–8 ppm (4, m, aromatic H).

*Anal.* Calcd for $C_8H_7NS$: C, 64.4; H, 4.7; N, 9.4. Found: C, 64.4; H, 4.7; N, 9.4.

**6-Chloro-2-cyclopropylbenzothiazole (4b).** A solution of 19.0 g (0.079 mol) of 1b in 200 ml of ethyl acetate containing 30.0 g (0.30 mol) of phosgene was refluxed at 50–55° for 8 hr. In order to contain the low-boiling phosgene in the reaction flask, the reflux condenser was topped with a Dry Ice–acetone condenser. The solvent and excess phosgene were removed by distillation leaving a residue which crystallized from ethyl acetate to give 2.0 g (10%) of 4b, a colorless crystalline solid: mp 65–67°; nmr ($CDCl_3$) δ 1.2 [4, s, $(CH_2)_2$ cyclopropyl], 2.4 (1, m, CH cyclopropyl), and 7–8 ppm (3, m, CH aromatic); mass spectrum (70 eV) *m/e* 211, 209 ($M^+$, base peak), 210, 208 ($M^+ - H$), 196, 194, 185, 183 ($M^+ - HCl$), 142 ($ClC_6H_4S^+$), 107, 92, 75, 69, 63, 45, 41, 39; ir (KBr) no carbonyl bands, mostly phenyl bands.

*Anal.* Calcd for $C_{10}H_8ClNS$: C, 57.3; H, 3.8; N, 6.7. Found: C, 57.4; H, 3.9; N, 6.6.

**1,1-Dimethyl-3-(2′-(methylthio)phenyl)urea (5).** Reaction of 2-(methylthio)phenyl isocyanate with dimethylamine in benzene afforded 5 in 97% yield, mp 98–100°.

*Anal.* Calcd for $C_{10}H_{14}N_2OS$: N, 13.3; S, 15.3. Found: N, 13.5; S, 15.5.

**2-(Dimethylamino)benzothiazole (8) and 3-(Dimethylcarbamoyl)benzothiazolin-2(3*H*)-one (11).** A solution of 15.7 g (0.075 mol) of 5 in 200 ml of *p*-dioxane containing 30.0 g (0.30 mol) of phosgene was refluxed at 70° with stirring. After approximately 15 min, a colorless solid began to precipitate. After 12 hr, the mixture was cooled to 20° and filtered to give 6.4 g (39.7%) of the hydrochloride of 8: mp 234–235°; ir (KBr) 3500, 3420 (NH or OH), 2800 $cm^{-1}$ (bonded OH, NH, HX); nmr (DMSO-$d_6$, TFA-$d$) δ 3.6 [6, s, $(CH_3)_2$], and 7.5 ppm (4, m, aromatic H).

*Anal.* Calcd for $C_9H_{11}ClN_2S$: C, 50.3; H, 5.2; Cl, 16.5; N, 13.1. Found: C, 47.9; H, 5.4; Cl, 16.0; N, 12.5.

The above salt was dissolved in 50 ml of water and the solution was made basic by addition of aqueous sodium hydroxide to give 6.0 g (37.5%) of 8, a colorless crystalline solid: mp 82–83° and 88–90° (lit.[4] mp 87°); ir (KBr) bands at 1560, 1570, and 1605 $cm^{-1}$ (aromatic H); nmr ($CDCl_3$) δ 3.2 [6, s, $(CH_3)_2$], and 6.8–7.7 ppm (4, m, aromatic H).

*Anal.* Calcd for $C_9H_{10}N_2S$: C, 60.7; H, 5.6; N, 15.7. Found: C, 60.6; H, 5.7; N, 15.8.

The original filtrate was concentrated to dryness and triturated with hexane to give 10.0 g (60.2%) of 11, as a colorless crystalline solid: mp 80–82°; ir (KBr) 1600 (C=) and 1755 $cm^{-1}$ (C=O); nmr ($CDCl_3$) δ 3.05 and 3.15 [6, s, $(CH_3)_2$], and 7.1 ppm (4, m, aromatic H); mass spectrum (70 eV) *m/e* 222 ($M^+$), 150 [$M^+ - (CH_3)_2NCO$], 122 ($C_6H_4NS$), 106, 95, 78, 72 [$(CH_3)_2NCO$, base peak], 69, 56, 51, 45, 44, 42, 38, 15.

*Anal.* Calcd for $C_{10}H_{10}N_2SO_2$: C, 54.1; H, 4.5; N, 12.6. Found: C, 53.8; H, 4.5; N, 12.3.

**Registry No.**—1a, 6310-41-4; 1b, 52260-23-8; 1c, 52260-24-9; 4a, 120-75-2; 4a HCl, 52260-25-0; 4b, 52260-26-1; 5, 52260-27-2; 8, 4074-74-2; 8 HCl, 52260-28-3; 11, 52260-29-4; 2-aminothioanisole, 2987-53-3; acetyl chloride, 75-36-5; cyclopropanecarbonyl chloride, 4023-34-1; trifluoroacetyl chloride, 354-32-5; 2-(methythio)phenyl isocyanate, 52260-30-7; dimethylamine, 124-40-3.

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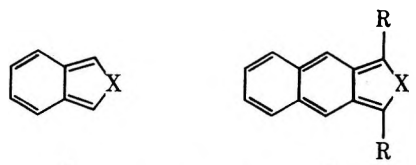
# Syntheses of Some Derivatives of Pyrrolo- and Thieno[2,3-*c*]quinoxaline and -quinoline

Makhluf J. Haddadin,* Nabil C. Chelhot, and Maria Pieridou

*Department of Chemistry, American University of Beirut, Beirut, Lebanon*

*Received March 19, 1974*

The recent isolation of the elusive isobenzofuran (1a) and isoindole (1b) rounds out the identification of all the parent benzo[c] heterocycles 1.[1-3] In contrast, none of the parent naphtho[2,3-*c*] heterocycles 2 has been reported, although transient formation of 2b (R = H) and 2c (R = H) was demonstrated by trapping them with *N*-phenylmaleimide.[4,5] 1,3-Diphenylnaphtho[2,3-c]furan (2a, R = Ph)



1 2

a, X = O
b, X = NH
c, X = S

and 1,3-diphenylnaphtho[2,3-*c*]thiophene (**2c**, R = Ph) were synthesized by Cava and Van Meter.[6] **2a** (R = Ph) was found to be rather unstable and quite reactive in Diels–Alder reactions.

We report the syntheses of some analogs of **2** containing more than one heteroatom (**3c–f**). Key intermediates in these syntheses were 2,3-dibenzoylquinoxaline (**7a**) and 2,3-dibenzoylquinoline (**7b**), whose preparations are described below.

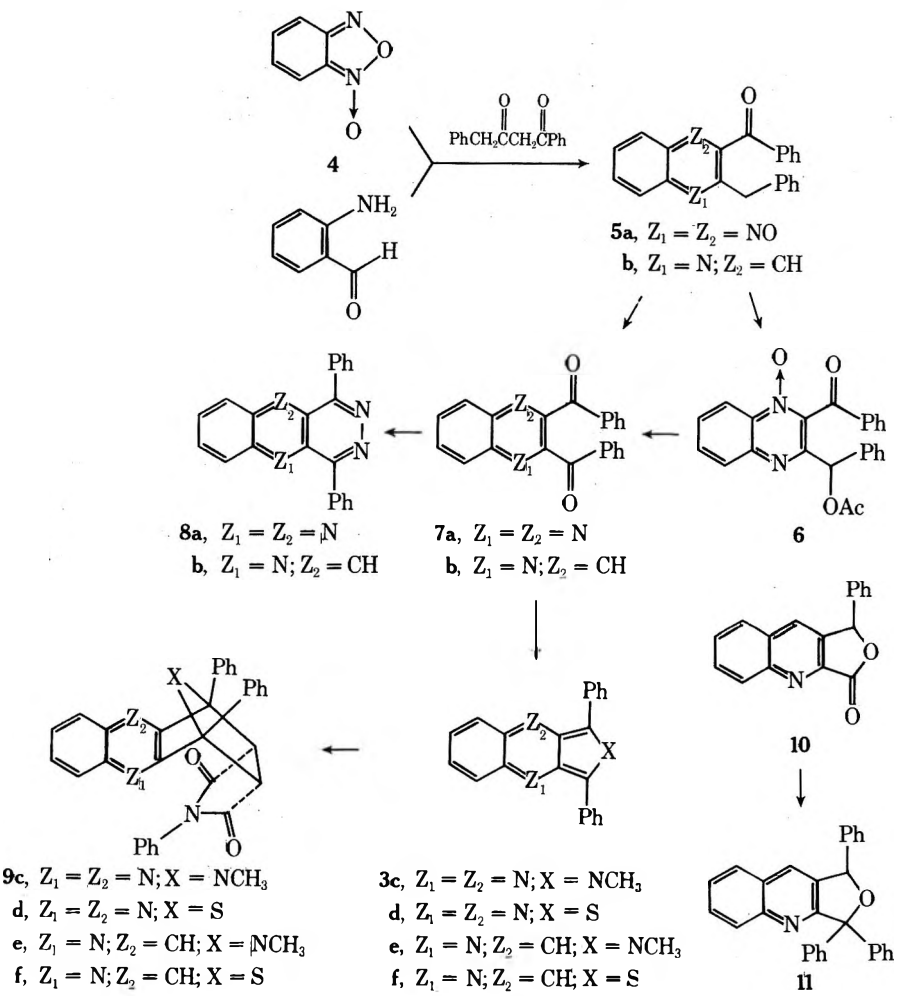
Treatment of benzofurazan oxide (**4**) with phenylacetylacetophenone in triethylamine gave 2-benzyl-3-benzoylquinoxaline 1,4-dioxide (**5a**), which was converted by refluxing acetic anhydride into 2-benzoyl-3-α-acetoxybenzylquinoxaline 1-oxide (**6**) in 50% yield. Hydrolysis of **6** in hot methanolic potassium hydroxide gave 2,3-dibenzoylquinoxaline (**7a**) in 63% yield. The rearrangement of **6** into **7a** is analogous to that reported recently for quinoxaline 1,4-dioxides with an α-methylene group.[7] The identity of **7a** was established by comparison with an authentic sample prepared by photolysis of 1,3-diphenylfuro[2,3-*c*]quinoxaline in the presence of oxygen.[8] As expected, **7a** reacted readily with hydrazine to give 1,4-diphenylpyridazino[4,5-*b*]quinoxaline (**8a**).[9]

Friedlander condensation of o-aminobenzaldehyde with phenylacetylacetophenone gave in good yield 2-benzyl-3-benzoylquinoline (**5b**) from which **7b** could be obtained by oxidation with chromic oxide in acetic anhydride. Quinoline **7b** was also obtained by adaptation of the recent method of Potts and Elliot.[10] The structure of **7b** was confirmed by its reaction with hydrazine to give 1,4-diphenylpyridazino[4,5-*b*]quinoline (**8b**).

Treatment of a hot methanolic solution of **7a** and methylamine with sodium borohydride or sodium dithionite brought about swift development of a blue color and subsequent precipitation of blue 1,3-diphenyl-2-methylpyrrolo[2,3-*c*]quinoxaline (**3c**) in 90% yield. Similarly, 1,3-diphenyl-2-methylpyrrolo[2,3-*c*]quinoline (**3e**)[11] was obtained as a red solid in high yield from **7b**. These reactions are essentially an adaptation of the Leuckart reductive amination of an *o*-dibenzoyl aromatic system which was employed by Emmett and Lwowski in the synthesis of 1,3-diphenylisoindoles.[12]

The reaction of **7a** in pyridine with phosphorus pentasulfide[13] gave, after chromatography, 1,3-diphenylthieno[3,4-*b*]quinoxaline (**3d**) as a blue solid. Similarly, red 1,3-diphenylthieno[3,4-*b*]quinoline (**3f**) was obtained from **7b** in 55% yield.

The products are formulated as **3c–f** on the basis of their elemental analyses, spectroscopic properties, and addition reactions to *N*-phenylmaleimide. The Diels–Alder adducts (**9c–f**), which partially reversed to starting materials before melting, were predominantly endo as inferred from their nmr signals in the 3.70–4.0 ppm region.[14] Adduct formation occurred at room temperature with **3e** (4 min) and **3c** (5 hr), but required prolonged heating at 78° with **3f** (50 hr) and **3d** (150 hr).



The *N*-methyl protons of **3c** ($\tau$ 5.82) and **3e** ($\tau$ 5.92) are deshielded compared with those of 1,3-diphenyl-2-methylisoindole ($\tau$ 6.25). The deshielding is apparently due to the electron-withdrawing effect of the nitrogen atoms in the adjacent six-membered ring and is, therefore, more pronounced in **3c** (quinoxaline ring) than in **3e** (quinoline ring). Electron withdrawal by the two nitrogen atoms in **3c** is also responsible for the observed sluggishness of the diene to react with *N*-phenylmaleimide.

Finally, in an effort to synthesize 1,3-diphenylfuro[2,3-*c*]quinoline we treated lactone[7] **10** with phenylmagnesium bromide. Acidification of the reaction product yielded furan **11**.

## Experimental Section[15]

**2-Benzyl-3-benzoylquinoxaline 1,4-Dioxide (5a).** A warm solution of benzofurazan oxide (**4**, 16.3 g) in triethylamine (50 ml) was mixed with a warm solution of phenylacetylacetophenone[16] (29 g) in triethylamine (50 ml). The solution was allowed to stand at room temperature for 5 days, during which a dark brown oil appeared. The supernatant liquid was decanted and the oily residue was rubbed with methanol to yield **5a** as a yellow solid. Recrystallization from methanol furnished yellow needles that melted at 167–168: 8.4 g (20%); ir 1670, 1350, 1040, 950, 765, 700, and 680 $cm^{-1}$; nmr $\tau$ 1.55 (m, 2 H), 2.5 (m, 12 H), 5.8 (s, 2 H).

*Anal.* Calcd for $C_{22}H_{16}N_2O_3$: C, 74.14; H, 4.53; N, 7.86. Found: C, 74.11; H, 4.50; N, 7.73.

**2-Benzoyl-3-α-acetoxybenzylquinoxaline 1-Oxide (6).** 2-Benzyl-3-benzoylquinoxaline 1,4-dioxide (5 g) was dissolved in acetic anhydride–acetic acid (10:5 ml) and the solution was refluxed for 0.5 hr. The cold solution was poured onto ice–water and the resulting brownish solid was purified by chromatography on an alumina column (benzene elution). Recrystallization from methanol yielded colorless prisms (2.5 g, 45%): mp 150–152; ir 1740, 1670, 1400, 1350, 1230, 1030, 960, 770, 750, 720, 700, and 690 $cm^{-1}$; nmr $\tau$ 1.6 (m, 1 H) 2.5 (m, 13 H), 3.1 (s, 1 H), 8.25 (s, 3 H).

*Anal.* Calcd for $C_{24}H_{18}N_2O_4$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.63; H, 4.57; N, 7.02.

**2,3-Dibenzoylquinoxaline (7a).** 2-Benzoyl-3-α-acetoxybenzylquinoxaline 1-oxide (2 g) was placed in 10% methanolic potassium hydroxide (40 ml). The solution was heated until all the solid dissolved, after which it was cooled and diluted with water. The precipitate was collected and recrystallized from methanol: 1.2 g (63%); mp 169–170; ir 1660, 1595, 1450, 1320, 1280, 1240, 930, 920, 880, 760, and 720 $cm^{-1}$; nmr $\tau$ 2.3 (m). The product was identical with that obtained from the photolysis of 1,3-diphenylfuro[2,3-*c*]quinoxaline in the presence of oxygen. 1,4-Diphenylpyridazino[4,5-*b*]quinoxaline obtained from the reaction of **7a** with hydrazine melted at 237–238° (lit.[9] mp 239–240°).

**2-Benzyl-3-benzoylquinoline (5b).** *o*-Aminobenzaldehyde (6.2 g) and phenylacetylacetophenone (12.2 g) were dissolved in absolute ethanol (100 ml). Piperidine (0.5 ml) was added and the solution was refluxed for 48 hr. The solution was concentrated to half its volume and cooled in an ice–salt bath. The product appeared as a yellowish solid which was recrystallized from ethanol, 7 g (43%), mp 79–80°. In some cases where the product appeared as an oil, prolonged cooling resulted in a solid which was purified by chromatography on alumina and benzene elution: ir 1660, 1615, 1590, 1560, 1485, 1440, 1410, 1280, 1260, 1245, 1200, 1100, 1070, 940, 910, 870, 790, 775, 760, 720, 710, and 700 $cm^{-1}$; nmr $\tau$ 2.6 (m, 15 H), 5.55 (s, 2 H).

*Anal.* Calcd for $C_{23}H_{17}NO$: C, 85.42; H, 5.30; N, 4.33. Found: C, 84.95; H, 5.31; N, 4.34.

**2,3-Dibenzoylquinoline (7b).** 2-Benzyl-3-benzoylquinoline (3.3 g) was dissolved in acetic anhydride (10 ml). Concentrated sulfuric acid (2 ml) was added and the solution was cooled in an ice bath. A solution of chromic oxide (3 g) in water (2 ml) and acetic anhydride (13 ml) was cooled to 0° and added to the above solution. The mixture was allowed to stand at room temperature for 1 hr and poured onto ice–water. The resulting solid was chromatographed on alumina (benzene elution). Product **7b** (2 g, 58%) was recrystallized from methanol: mp 118–120°; ir 1665, 1450, 1405, 1330, 1235, 960, 935, 920, 870, 760–750, 710, and 700 $cm^{-1}$; nmr $\tau$ 2.38 (s, 1 H), 2.8 (m, 14 H).

*Anal.* Calcd for $C_{23}H_{15}NO_2$: C, 81.88; H, 4.48; N, 4.15. Found: C, 81.84; H, 4.52; N, 4.12.

Product **7b** was identical with a sample prepared by the condensation of dibenzoylacetylene with *o*-aminobenzaldehyde (30%).[10]

**1,4-Diphenylpyridazino[4,5-*b*]quinoline (8b).** 2,3-Dibenzoylquinoline (100 mg) was dissolved in hot methanol (10 ml). Addition of 80% hydrazine hydrate (3 ml) brought about the precipitation of **8b** which was recrystallized from methanol: 50 mg (50%); mp 232–233°; ir 1450, 1380, 1370, 920, 780, 765, 750, and 700 $cm^{-1}$.

*Anal.* Calcd for $C_{23}H_{15}N_3$: C, 82.86: H, 4.54; N, 12.61. Found: C, 82.84; H, 4.33; N, 12.55.

**1,3-Diphenyl-2-methylpyrrolo[3,4-*b*]quinoline (3e).** 2,3-Dibenzoylquinoline (100 mg) was dissolved in hot methanol (10 ml). An aqueous solution of 40% methylamine (5 ml) was added. Heating was continued for another minute. Sodium borohydride was added (30 mg) and a deep red color developed. On cooling **3e** separated as a red solid which was recrystallized from methanol: 75 mg (75%); mp 196–198°; ir 1600, 1480, 1450, 1280, 1220, 760, and 750 $cm^{-1}$; nmr $\tau$ 2.3 and 2.7 (m, 15 H), 5.92 (s, 3 H).

*Anal.* Calcd for $C_{24}H_{18}N_2$: C, 86.20; H, 5.43; N, 8.38. Found: C, 86.09; H, 5.37; N, 8.03.

**1,3-Diphenyl-2-methylpyrrolo[3,4-*b*]quinoxaline (3c).** The above procedure was applied to the synthesis of **3c.** 2,3-Dibenzoylquinoxaline (100 mg) yielded 90 mg of blue **3c** which was recrystallized from methanol: mp 224–225°; ir 1600, 1470, 1420, 760, and 700 $cm^{-1}$; nmr $\tau$ 2.2 and 2.6 (m, 14 H), 5.82 (s, 3 H).

*Anal.* Calcd for $C_{23}H_{17}N_3$: C, 82.38; H, 5.11; N, 12.53. Found: C, 81.46; H, 5.07; N, 12.33.

**1,3-Diphenylthieno[3,4-*b*]quinoxaline (3d).** 2,3-Dibenzoylquinoxaline (100 mg) was dissolved in pyridine (5 ml). Phosphorus pentasulfide (70 mg) was added and the mixture was refluxed for 2 hr. Evaporation of the solvent gave a solid which was extracted with benzene and chromatographed on alumina (benzene elution). Evaporation of the blue fractions gave **3d,** which was recrystallized from acetic acid: 60 mg (60%); mp 174–175°; ir 1590, 1530, 1500, 1470, 1430, 1410, 1300, 760, 710, 690, and 660 $cm^{-1}$.

*Anal.* Calcd for $C_{22}H_{14}N_2S$: C, 78.09; H, 4.17; N, 8.28; S, 9.46. Found: C, 77.83; H, 4.17; N, 8.05; S, 9.59.

**1,3-Diphenylthieno[3,4-*b*]quinoline (3f).** The above procedure was used to prepare **3f.** 2,3-Dibenzoylquinoline (200 mg) gave 110 mg (55%) of **3f,** which was recrystallized from methanol: mp 162–163°; ir 1600, 1500, 1470, 1450, 1420, 900, 750, and 700 $cm^{-1}$.

*Anal.* Calcd for $C_{23}H_{15}NS$: C, 81.88; H, 4.48; N, 4.15; S, 9.49. Found: C, 81.25; H, 4.56; N, 4.08; S, 9.44.

**Adducts with *N*-Phenylmaleimide. General Procedure.** The specific diene was dissolved in benzene and an equimolar quantity of *N*-phenylmaleimide was added to the solution. The reaction mixture was worked up when the color of diene disappeared. The adducts (Table I) did not melt sharply owing to dissociation to starting materials.

**1,3-Dihydro-1,3,3-triphenylfuro[3,4-*b*]quinoline (11).** Treat-

**Table I**

| Adduct | Time and temp, °C | Ir, $cm^{-1}$ | Nmr, $\tau$ | Mp, °C |
|---|---|---|---|---|
| **9e** | 4 min, room temp | 1715, 770, 700, 770, 700 | 4 (m, 2 H), 5.5 (s, 2 H), 8 (s, 3 H) | 215–222 |
| **9c** | 5 hr, 78 | 1710, 770, 700 | 3.92 (m, 2 H), 5.55 (s, 2 H), 8 (s, 3 H) | 205–242 |
| **9f** | 50 hr, 78 | 1715, 770, 700 | 3.92 (m, 2 H) 5.12 (s, 2 H) | 235–242 |
| **9d** | 150 hr, 78 | 1720, 770, 700 | 3.65 (m, 2 H), 4.95 5.87 (s, 2 H) | 217–225 |

ment of 1,3-dihydro-1-phenylfuro[3,4-*b*]quinolin-3-one[7] (**10**) with phenylmagnesium bromide according to the procedure of Cava and Van Meter[6] gave the title compound in 48% yield: mp 210–211° (from ethanol); ir 1625, 1600, 1025, 770, 750, and 700 $cm^{-1}$; nmr $\tau$ 2.5 (m, 20 H), 3.8 (s, 1 H).

*Anal.* Calcd for $C_{29}H_{21}NO$: C, 87.19; H, 5.30; N, 3.51. Found: 87.39; H, 5.24; N, 3.48.

**Acknowledgment.** We thank Professors C. H. Issidorides and M. Nazer for stimulating discussions.

**Registry No.**—**3c,** 52260-31-8; **3d,** 52260-32-9; **3e,** 52260-33-0; **3f,** 52260-34-1; **4,** 480-96-6; **5a,** 52260-35-2; **5b,** 52260-36-3; **6,** 52260-37-4; **7a,** 19029-35-7; **7b,** 52260-38-5; **8b,** 52260-39-6; **9c,** 52260-40-9; **9d,** 52260-41-0; **9e,** 52341-46-5; **9f,** 52260-42-1; **10,** 52260-43-2; **11,** 52260-44-3; phenylacetylacetophenone, 3442-15-7; *o*-aminobenzaldehyde, 529-23-7; hydrazine, 302-01-2; *N*-phenylmaleimide, 941-69-5.

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(15) Melting points were determined on a Fisher-Johns apparatus and are uncorrected. All products were homogenous on tlc. Infrared spectra were recorded on a Perkin-Elmer 257 spectrophotometer using potassium bromide disks. Nmr spectra, reported in $\tau$ values, were taken on a Varian A-60D spectrometer in $CDCl_3$ with TMS as internal reference. Elemental analyses were performed by F. Pascher, Bonn, Germany.
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# A New Synthesis of Maltol[1]

Rajender K. Chawla*[2] and William E. McGonigal

*School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30322*

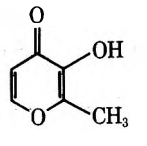
*Received May 14, 1974*

Maltol (2-methyl-3-hydroxy-4*H*-pyran-4-one), **1**, is known to exist in several plants, *e.g.*, fern leaves and larch bark, and in food materials, *e.g.*, roasted chicory, coffee, caramel, and corn.[3] Streptomycin on alkaline hydrolysis also yields up to 30% maltol.[4,5] It was isolated in 1894 by Brand and its structure was established by Peratoner and Tamburello in 1905.[3]

Although maltol is of great value as a flavoring agent in food industry, its reported laboratory syntheses proceed in poor yields and under severe experimental conditions.[6,7]

The purpose of this work was to provide a facile synthesis of 1 from readily available materials in reasonable yields under mild experimental conditions.

Oxidation of methyl 2,3-*O*-isopropylidene-$\alpha$-L-rhamnopyranoside (**2**)[8,9] with chromium trioxide–pyridine complex, prepared at room temperature, according to the procedure of Poos and coworkers,[10] gave a syrupy material, identified as methyl 2,3-*O*-isopropylidene-6-deoxy-$\alpha$-L-*lyxo*-hexopyranos-4-ulose (**3**) in 55% yield. Its ir and nmr spectra and the elemental analysis of its crystalline oxime confirmed its structure.



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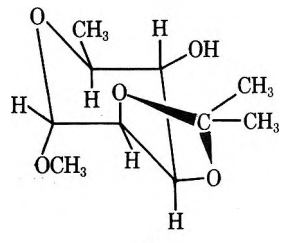

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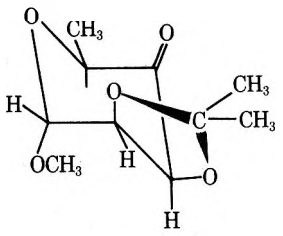


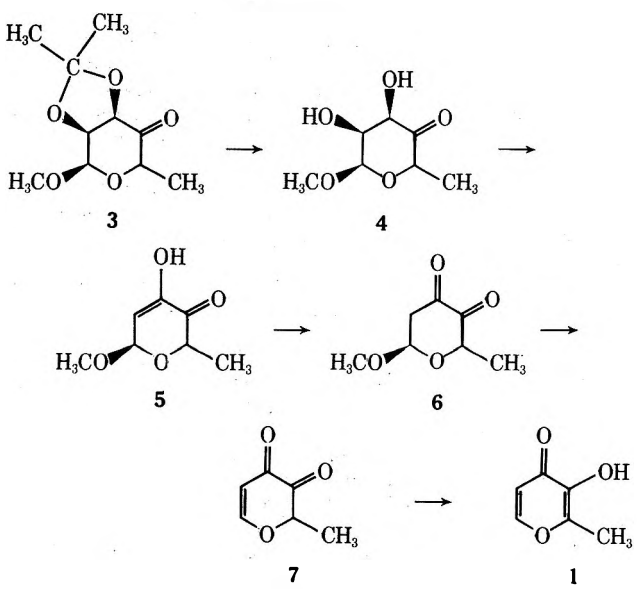
3

Compound **3** was heated on a steam bath with Dowex 50 ($H^+$) and Dowex 1 ($OH^-$) ion exchange resins, in water and in benzene, and the appearance of maltol was determined colorimetrically at 540 nm at given intervals.[11] Maximum yields were obtained by hydrolysis of **3** in aqueous medium by means of Dowex 50 ($H^+$) ion exchange resin: 72% in 60 hr. The final product was characterized as maltol (**1**) by its nmr and ir spectra, its elemental analysis, and by comparison of its tlc behavior with a commercial sample of maltol.

The yield of maltol by reaction of **3** with Dowex 1 ($OH^-$) ion exchange resin in aqueous medium was poor (15% yield). In benzene, the hydrolysis did not proceed to any significant extent (<1% yield) in the presence of acidic or basic ion exchange resins.

The following pathway is suggested for the degradation of **3** to maltol under the conditions of hydrolysis (Scheme I). The pathway involves elimination of acetone under the

**Scheme I**



influence of Dowex 50 ($H^+$) ion exchange resin (known lability of the isopropylidene group to mild acid conditions),[12] followed by $\beta$ elimination of water in which H atom $\alpha$ to the carbonyl function is lost (**4** and **5**). After tau-

tomerization to a dione (6), which loses methanol by a $\beta$ elimination, compound 7 is obtained. In the last step, a keto–enol tautomerization gives maltol (1). Fried,[12] in his mechanism for degradation of streptomycin to maltol, has proposed analogous intermediates, as arising from rearrangement of streptose moiety of streptomycin.

The low yield of maltol from hydrolysis of **3**, when aqueous Dowex 1 ($OH^-$) ion exchange resin is employed, can be explained in part by the relative stability of ketals under conditions of alkaline hydrolysis. An additional likely factor is instability of maltol to basic conditions of hydrolysis. When a known amount of maltol was heated with aqueous Dowex 1 ($OH^-$) ion exchange resin (conditions of hydrolysis of **3**), more than 50% maltol was lost within 72 hr.

## Experimental Section

Melting points were observed on Köfler hot stage and are corrected. The nmr spectra were recorded on Varian A-60 spectrophotometer; the ir spectra were taken on Perkin-Elmer Model 137 recording infracord spectrophotometer. Spectronic 20 Bausch and Lomb colorimeter was used for colorimetric analyses. All solvents and reagents were of reagent grade. Anhydrous pyridine was prepared by distilling analytical grade pyridine over KOH pellets and was stored over KOH pellets.

**Methyl, 2,3-*O*-Isopropylidene-6-deoxy-$\alpha$-L-*lyxo*-hexopyranos-4-ulose (3).** Chromium trioxide (97 g, 970 mmol) was gradually added to 1 l. of anhydrous pyridine at room temperature and under constant stirring. A solution of 21.4 g (98.1 mmol) of methyl 2,3-*O*-isopropylidene-$\alpha$-L-rhamnopyranoside (**2**)[8,9] in 200 ml of anhydrous pyridine was added to the above mixture and the stirring was continued for 16 hr at room temperature. Pyridine was then evaporated *in vacuo* and the residue was extracted with chloroform. The chloroform extract was washed with 2 *N* HCl (3 × 400 ml), dried over anhydrous $MgSO_4$, and evaporated to give 15 g of dark syrupy residue. It was immediately chromatographed on a column packed with silicic acid that had previously been kept in a water-saturated desiccator for 24 hr. The column (25 cm × 4 cm) was eluted with $CHCl_3$ (volume of each fraction, 50 ml). The first 600 ml of effluent was discarded; the next 1500 ml contained 11.362 g (52.6 mmol; 55% yield) of **3**. This compound was chromatographically homogeneous. Its ir spectrum (liquid film) showed $\nu_{max}$ 3.40, 5.74, 6.91, 7.25, 8.15, 9.20, 10.21, and 11.66 $\mu$ among other absorptions. The elemental analysis of its crystalline oxime was consistent with its composition.

*Anal.* Calcd for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.41; N, 6.06. Found: C, 51.73; H, 7.28; N, 6.11.

**Maltol (1). A. Exploratory.** To a solution of 3 (21.710 mg, 0.1 mmol) in 7–8 ml of water (or benzene) was added about 100 mg of dry ion exchange resin. The mixture was heated on a steam bath under reflux, the reflux condenser for benzene being fitted with a drying tube. At specified intervals, 1–2 ml of reaction mixture was withdrawn and treated with ferric ammonium sulfate reagent.[11] The blue color, fully developed at 10 min, was monitored at 540 nm; maltol content in the reaction mixture was determined from a standard curve.

**B. Preparative.** A mixture containing 4.610 g (21.34 mmol) of **3** in 60 ml of water and 1 g of dry Dowex 50 ($H^+$) ion exchange resin was heated on a steam bath for 60 hr. Resin was removed by filtration and the aqueous solution was extracted with $CHCl_3$ for 6 hr. Solvent was evaporated *in vacuo* and the residue was crystallized from cyclohexane. Resulting tan-colored crystals were further purified by sublimation at 100° under reduced pressure (40 $\mu$). The product weighed 1.916 g (72% yield) and showed a corrected mp 159.5° (lit.[3] 159°). Melting point of a mixture of synthetic and commercial samples of maltol remained unchanged. Tlc analysis and ir spectra of the synthetic material were identical with those for the commercial sample. The nmr spectrum (saturated $CDCl_3$ solution) of the compound showed absorptions at $\tau$ 7.63 (3 H, s), 3.55 (1 H, d, $J$ = 5.8 Hz), 2.84 (1 H, broad, s), and 2.33 (1 H, d, $J$ = 5.8 Hz). The ir spectrum (8% solution in $CHCl_3$, 0.1-mm cell path), showed $\nu_{max}$ 3.04, 3.31, 6.17, 6.40, 7.93, 8.42, 10.82, and 11.78 $\mu$ among others.

*Anal.* Calcd for $C_6H_6O_3$: C, 57.14; H, 4.79. Found: C, 57.27; H, 4.81.

**Acknowledgment.** The late Dr. John R. Dyer, School of Chemistry, provided valuable help and guidance throughout this study. We are thankful to Dr. Drury S. Caine, School of Chemistry, for many useful suggestions, and to Dr. Daniel Rudman, Department of Medicine, and Dr. David Goldsmith, Department of Chemistry, both of Emory University, for help in preparation of the manuscript.

**Registry No.**—**1**, 118-71-8; **2**, 14133-63-2; **3**, 2592-53-2; 3 oxime, 35010-57-2.

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# Electrophilic Substitution on Porphin. I. Nitration

John E. Drach and Frederick R. Longo*

*Department of Chemistry, Drexel University, Philadelphia, Pennsylvania 19104*

*Received January 9, 1974*

Previous studies of electrophilic substitution on the porphyrin periphery have used porphyrins which were substituted on most or all of the $\beta$ positions (*viz.*, positions 2, 3, 7, 8, 12, 13, 17, 18, Figure 1A).[1-12] Therefore, the results of such efforts could not be used to determine the difference, if any, between the $\beta$ and meso positions during electrophilic attack. To examine any reactivity differences on the porphyrin periphery, we have studied the nitration of porphin, the parent porphyrin. We have also studied the nitration of nitroporphin to find any directive effects which may be operating. It was found that porphin gave a mono-nitro derivative upon nitration with a stoichiometric amount of nitric acid at 0°. The nitrated product, shown to be a single compound by tlc, exhibited an etio-type visible spectrum. Its nmr spectrum showed that it was meso substituted

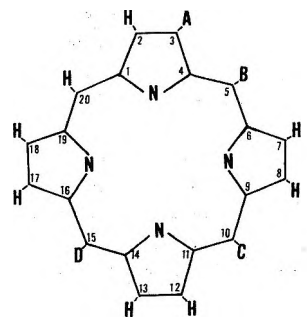


**Figure 1. (A)** A = B = C = D = H; **(B)** A = C = D = H and B = $NO_2$; **(C)** A = D = H; B = C = $NO_2$.

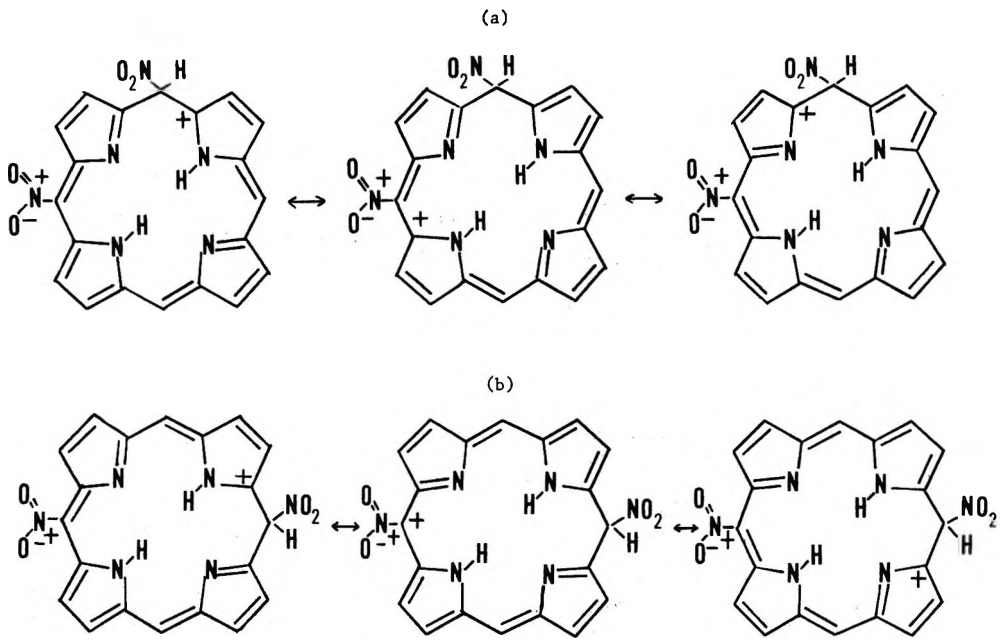


**Figure 2.** Important resonance forms for attack at (a) the β-meso position and (b) the γ-meso position of nitroporphin

(Figure 1B) since the β/meso proton ratio was equal to 2.60 and the meso protons appeared as two separate peaks with a relative area of 2:1. The same ratio for a β-substituted porphin would be 1.75. Chemical degradation afforded additional structural verification. No β-nitromaleimide was found among the degradation products of the nitrated porphin, The main degradation product was maleimide. If the nitro group were on the β position up to 25% β-nitromaleimide would be formed.

To determine the existence of a directive effect which may be operating in the porphyrin ring system, dinitroporphin was prepared by nitrating nitroporphin. Tlc analysis affirmed that it was a single compound. Its visible spectrum was also of the etio type but shifted bathochromically relative to nitroporphin. Analysis of its nmr spectrum showed that it was di-meso substituted since the meso proton absorption had collapsed to a singlet and the β/meso proton ratio was equal to 4. In addition since the β proton absorption pattern was unsymmetrical we concluded that the isomer obtained was the 5,10-dinitroporphin (Figure 1C). The 5,15-dinitroporphin would be expected to be quite symmetric. Chemical degradation again furnished evidence for the di-meso substitution assignment.

## Discussion

Fleischer[13,14] has proposed on the basis of X-ray data that the electronic structure of porphin exhibits an inner π ring of 12 carbon and four nitrogen atoms; each carbon and two of the nitrogen atoms contribute one electron to the π system of this ring while the imine nitrogens (–C=N–) each contribute two electrons, making a total of 18-π electrons, a number consistent with Hückel's rule for aromaticity. The conclusion is that the main path of conjugation is the inner 16-membered ring with the outer pyrrole bonds being olefinic.

Caughey[15] has reported a $^{13}C$ Fourier transform nmr study of deuterioporphyrin IX dimethyl ester which lends supporting evidence to Fleischer's theory of porphin electronic structure. It was found that the $^{13}C$ chemical shifts were in the same range for all the protonated carbons except the meso carbons. Caughey concludes that the meso positions experience strong resonance effects owing to delocalization *via* the inner 16-membered ring with the β–β carbon bonds left as pure double bonds. It is interesting to note that the X-ray data show no single-bond character in the β-carbon–β-carbon bonds.

A mechanism for the meso substitution of porphin can be advanced by considering that the free base prophin (although initially present in very small concentrations in the highly acidic nitration medium) is attacked by the nitronium ion at the aromatic portion of the porphin periphery, the inner 16-membered ring. A true electrophilic substitution occurs involving an initial π-complex formation, collapse to a σ complex and rearomatization *via* proton loss. The apparent directive effect of the nitro group on the position of nitration of nitroporphin can be rationalized by considering the relative stabilities of the σ complexes leading to the respective nitration products.

An examination of Figure 2a and 2b reveals that the 5,10-disubstituted product should be favored because no resonance structures can be written that will place a positive charge on the carbon atom bearing the nitro group; such a transition state possesses a lower relative energy than that of the 5,15-disubstituted product whose transition state has one resonance form with a positive charge on the nitro-substituted carbon atom. The results show, under the conditions described herein, that the meso position of porphin is preferentially nitrated. It has also been demonstrated that the nitro group directs the course of subsequent nitration to the 10 position.

## Experimental Section

**General.** Porphin was synthesized by the method of Adler and Beitchman.[16] Melting points were taken on a Mel-Temp melting point apparatus and are uncorrected. Visible spectra were taken on a Cary 14 recording spectrophotometer. Nmr spectra were obtained with a Varian 220-MHz spectrometer with TMS as an internal standard. The porphyrins were dissolved in a solvent consisting of 33% $CDCl_3$ and 66% $CF_3CO_2D$ at a concentration ≃0.7 *M*.

**Nitroporphin.** To a stirred, ice-cooled solution containing 200 mg of porphin ($6.4 \times 10^{-4}$ mol) and 6 ml of concentrated $H_2SO_4$ was added over a 3-min period a 1.33% $HNO_3$ in $H_2SO_4$ solution which had been pre-cooled to 0°. During the addition of the $HNO_3$ solution the reaction mixture turned from red to blue-green, the porphin dication color. After all the $HNO_3$ solution had been added, the reaction mixture was allowed to stir at 0° for 5 min, whereupon it was poured into 600 ml of ice water containing 10 g of sodium acetate. The brown-black precipitate which formed im-

mediately was filtered and dried in a 100° oven for 2 hr. After drying, the solid was dissolved in $CHCl_3$ and chromatographed on alumina. The nitroporphin was eluted with a chloroform–benzene (50:50, v/v) mixture yielding 151 mg of product: 70% yield; extinction coefficients at maxima $\epsilon_{628}$ 6000, $\epsilon_{572}$ 6860, $\epsilon_{540}$ 8770, $\epsilon_{499}$ 13,120, $\epsilon_{406}$ 200,000.

*Anal.* Calcd for $C_{20}H_{13}N_5O_2$: C, 67.6; H, 3.68; N, 19.nd C, 67.44; H, 3.67; N, 19.64.

**Dinitroporphin.** Dinitroporphin was prepared in the same manner as mononitroporphin except that it was eluted with chloroform after a small amount of unreacted mononitroporphin was eluted with the chloroform–benzene mixture. A 56% yield of dinitroporphin was obtained (20% of the unreacted mono-nitroporphin was recovered): extinction coefficients at maxima $\epsilon_{632}$ 4820, $\epsilon_{578}$ 5400, $\epsilon_{543}$ 7000, $\epsilon_{504}$ 10,800, $\epsilon_{407}$ 145,000.

*Anal.* Calcd for $C_{20}H_{12}N_6O_4$: C, 60.02; H, 3.02; N, 20.99. Found: C, 59.98; H, 3.00; N, 20.89.

**Oxidative Degradation of Nitro- and Dinitroporphin.** The degradations were accomplished according to the method of Neuberger and Muir[17] for the degradation of mesoporphyrin. The porphin in question was dissolved in a 50% aqueous $H_2SO_4$ solution at 0°. To this solution was added dropwise an ice-cold 10% aqueous $CrO_3$ solution. The mixture was then stirred at 0° for 2 hr and an additional 2 hr at room temperature. The solution was then diluted with 50 ml of distilled water and extracted four times with anhydrous ether. The ether extracts were washed once with 50 ml of water and dried over anhydrous $CaSO_4$. The ether was evaporated leaving a white solid. In all cases, the solid melted at 90–92° and was shown to be identical with an authentic sample of maleimide. The maleimide degradation product was analyzed *via* tlc for the presence of nitromaleimide. The tlc analysis was accomplished using a developing solvent consisting of ethyl acetate–carbon tetrachloride–cyclohexane (10:5:1) with a development distance of 10 cm. The plate was removed from the chromatography chamber, dried, and exposed to $Cl_2$ for 5 min. It was then heated to 100° for 5 min. The locating reagent is a 0.5% benzidene solution in ethanol containing a 10% aqueous KI solution per 100 ml of the benzidene solution.[18] No evidence of the presence of nitromaleimide was ever observed.

**4-Nitro-2-pyrrolecarboxaldehyde.** The preparation of 4-nitro-2-pyrrolecarboxaldehyde followed the procedure of Fournari and Tirouflet[19] except that the 4-nitro isomer was extracted from a saturated aqueous $NaHCO_3$ solution containing the 4- and 5-nitro isomers with ether. Typically, 10 g of the isomer mixture is dissolved in 500 ml of a saturated aqueous $NaHCO_3$ solution. This solution is extracted six times with 100-ml portions of anhydrous ether. The extracts are dried over $CaSO_4$ and decolorized. The ether was evaporated leaving 3.5 g of a yellow solid, 4-nitro-2-pyrrolecarboxaldehyde, which was recrystallized from alcohol–water, mp 135–136° (lit.[20] 142°).

**Nitromaleimide.** To an ice-cooled solution containing 5 g of 4-nitro-2-pyrrolecarboxaldehyde in 20 ml of acetone was added with stirring 150 ml of a 50% aqueous $H_2SO_4$ solution. After the acid addition was completed, a solution containing 40 g (0.136 mol) of $K_2Cr_2O_7$ in 100 ml of $H_2O$ was added slowly so that the reaction temperature did not exceed 10°. After the dichromate addition was finished, the reaction mixture was heated to 60° for 30 min; then it was poured into 200 ml of ice water. The aqueous solution was extracted four times with 100-ml portions of anhydrous ether. The ether extracts were dried, decolorized, and stripped leaving a white yellow solid which was recrystallized from water, mp 205° dec.

*Anal.* Calcd for $C_4H_2N_2O_4$; C, 42.86; H, 2.87; N, 19.99. Found: C, 42.50; H, 2.80; N, 19.85.

**Registry No.**—Porphin, 101-60-0; nitroporphin, 52358-25-5; dinitroporphin, 52358-26-6; maleimide, 541-59-3; 4-nitro-2-pyrrolecarboxaldehyde, 19611-63-3; nitromaleimide, 52358-27-7.

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## $\mu$-Truxinic Acid

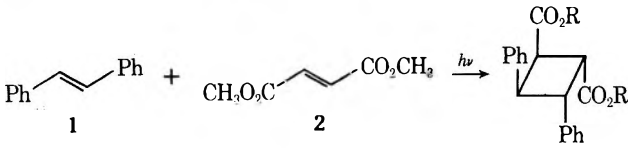

Bernard S. Green* and Miriam Rejtö

*Department of Structural Chemistry, The Weizmann Institute of Science, Rehovot, Israel*


*Received May 3, 1974*

The photoaddition of *trans*-stilbene to fumaric acid would seem to be a straightforward approach to the synthesis of $\mu$-truxinic acid since both stilbene[1] and fumaric acid derivatives[2] undergo photodimerization to cis-anti-cis configurated dimers. However, a previous approach along these lines was reported to be unsuccessful.[3]

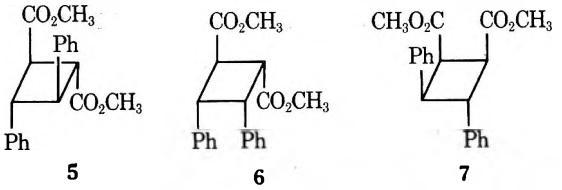
We have repeated this method, irradiating *trans*-stilbene with an excess of dimethyl fumarate in benzene solution, and find that dimethyl $\mu$-truxinate (**3**) is formed




smoothly in acceptable yields. The nmr spectrum uniquely fits that anticipated for **3**: a single carbomethoxyl signal is present at $\delta$ 3.33, shifted upfield as a result of the shielding *cis*-$\beta$-phenyl groups.[4]

Although the diphenylcyclobutanedicarboxylic (truxillic and truxinic) acids are often presented as classical examples of configurational isomerism where all 11 possible isomers are known,[5] the melting point of $\mu$-truxinic acid, **4**, obtained by acid hydrolysis of **3**, differs from that reported by Shemiakin for this material.[6] Ettlinger had earlier questioned the structure assignment to Shemiakin's $\mu$-truxinic acid and suggested that this material was a lactonic acid.[7] Reesterification of **4** with methanol affords **3**; we thus report the first synthesis of $\mu$-truxinic acid and its dimethyl ester.

It is noteworthy that **3** is the major isomer produced; dimethyl $\delta$-truxinate (**5**), presumably the thermodynamically more stable isomer[8] which could *a priori* also have been produced, is formed in only trace quantities, if at all. Dimethyl *neo*-truxinate (**6**) is formed as a side product, while dimethyl $\zeta$-truxinate (**7**) is not found in the irradiation




products. These results are accommodated by a mechanism involving the addition of excited singlet state *trans*-stilbene to dimethyl fumarate *via* a nonconcerted pathway.[9]

## Experimental Section

**The Photoaddition of *trans*-Stilbene to Dimethyl Fumarate.** A solution of **1** (2.50 g, 0.014 mol) and **2** (20 g, 0.14 mol) in 500 ml of benzene was deaerated with a stream of dry, oxygen-free nitrogen and then irradiated (450-W Hanovia immersion lamp, Pyrex) for 24 hr while passing through nitrogen. The benzene was evaporated and the residue sublimed (bulb-to-bulb, on a Büchi rotary evaporator at 2 mm pressure; heating bath at 70–80°; collecting flask cooled in Dry Ice–2-propanol bath). The sublimate consisted of dimethyl fumarate and dimethyl maleate. The residue was chromatographed on 200 g of Merck 0.05–0.20 mm silica gel. Elution with 2% ethyl acetate in *n*-hexane gave traces of stilbene and stilbene dimers. Further elution gave a total of 1.1 g of oily material. Further elution with the same mixture of solvents gave 2.0 g (46% yield) of dimethyl-$\mu$-truxinate (**3**) which was crystallized from methanol to give 1.6 g of analytically pure material: mp 121–123°; $\delta$ ($CDCl_3$) 7.21 (10 H, s, Ph), 4.5–4.7, 3.8–4.2 (4 H, AA'BB' multiplet, cyclobutane hydrogens), and 3.33 (6 H, s, $OCH_3$).

*Anal.* Calcd for $C_{20}H_{20}O_4$: C, 74.05; H, 6.22. Found: C, 73.90; H, 6.11.

Elution with 3% and then 5% ethyl acetate in *n*-hexane afforded 0.20 g of oily material whose nmr spectrum and tlc chromatogram, by comparison with an authentic sample,[10] indicate the presence of a mixture containing dimethyl $\delta$-truxinate (**5**). Elution with 10% ethyl acetate in *n*-hexane gave 0.28 g (6% yield) of dimethyl neotruxinate (**6**) which was crystallized from methanol to give 0.15 g of material with mp 131–132° (lit.[11] mp 127.5°): $\delta$ ($CDCl_3$) 6.71–7.35 (10 H, m, Ph), 3.91–4.43 (4 H, unsymmetrical m, cyclobutane hydrogens), 3.75 (3 H, s, $CO_2CH_3$ trans to $\beta$-Ph), and 3.28 (3 H, s, $CO_2CH_3$ *cis* to $\beta$-Ph). Further elution with increasing proportions of ethyl acetate afforded oily mixtures which were not investigated further.

Dimethyl $\mu$-truxinate can also be isolated in lower yields directly after the sublimation step by several crystallizations from methanol. The first compound to crystallize is an unknown material with mp 218–220° (this substance can also be crystallized from the later chromatographic fractions) which is removed by filtration. The mother liquor then deposits dimethyl $\mu$-truxinate.

**$\mu$-Truxinic Acid (4).** A mixture of **3** (500 mg) and an aqueous HCl solution (75 ml, 1:2) was refluxed while stirring for 137 hr. The product was filtered (390 mg, 85% yield) and crystallized from aqueous acetic acid to give **4** (226 mg) with mp 252–254°: $\delta$ (DMSO) 7.20 (10 H, s, Ph), 4.58–4.26, 3.90–3.56 (4 H, AA'BB', cyclobutane hydrogens).

*Anal.* Calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.86; H, 5.52.

A mixture of the acid **4** (50 mg) in methanol (20 ml) was treated with several drops of thionyl chloride and warmed overnight. Evaporation of solvent left **3** having an nmr spectrum identical with that of the irradiation-derived sample. Crystallization from methanol gave 34 mg of **3**, mp 118–121°.

**Acknowledgment.** We are grateful to Miss Edna Gati for performing some preliminary experiments.

**Registry No.**—**1**, 103-30-0; **2**, 624-49-7; **3**, 52306-38-1; **4**, 528-35-8; **6**, 52305-39-2.

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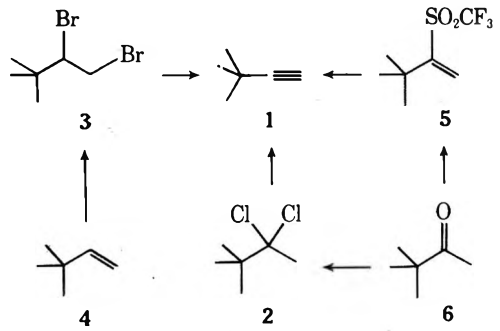
# Facile Synthesis of *tert*-Butylacetylene

P. J. Kocienski

*Department of Chemistry, State University of New York at Binghamton, Binghamton, New York 13901*

*Received July 8, 1974*

Until recently, *tert*-butylacetylene (**1**) was prepared by the method of Bartlett and Rosen[1] which entails the dehydrochlorination of pinacolone dichloride (**2**) in a sodium hydroxide melt. This reaction is difficult to control to the point of being hazardous on a large scale and affords only a moderate yield of **1**. With these limitations in mind, alternate preparations have recently appeared. Collier and Macomber[2] prepared the *vic*-dibromide **3** by the addition of $Br_2$ to *tert*-butylethylene (**4**) which was subsequently dehydrobrominated to **1**. However, the bromination must be carried out at −78° to avoid contamination of the product with substantial amounts of rearranged products. Hargrove and Stang[3] prepared the vinyl triflate **5** from pinacolone (**6**) and subsequently effected a base-catalyzed elimination of $CF_3SO_3H$ to afford **1**. The latter procedure is disadvantaged by the expense of the $(CF_3SO_2)_2O$ required to prepare **5**.




With emphasis on experimental facility and economy, a modification of the Bartlett–Rosen procedure has been developed which permits the synthesis of **1** on a mole scale without recourse to low temperatures or expensive reagents. Pinacolone dichloride (**2**), readily prepared by reaction of pinacolone (**6**) with $PCl_5$,[1,4] was added to a mixture of *t*-BuOK in DMSO while maintaining the temperature below 40°. The product was isolated in 95% yield (from **2**) by direct distillation from the reaction mixture in ≥95% purity by vpc analysis. By this procedure, **1** has been prepared repeatedly in >90% yield in quantities ranging from 5–100 g.

## Experimental Section

Boiling points are uncorrected. The nmr spectra were recorded on a Varian A-60A spectrometer using TMS as an internal standard; infrared spectra were recorded on a Perkin-Elmer 337 spectrometer in $CCl_4$ solution. Gas–liquid chromatographic analyses were performed on a Varian Model 90 chromatograph using ¼-in. × 12-ft columns packed with 10% SE-30 on Chrom W. Freshly opened bottles of *tert*-BuOK from MSA Corporation were employed and the DMSO, obtained from Fisher, was used without further purification.

***tert*-Butylacetylene.** A flame-dried 250-ml three-necked flask fitted with a thermometer, condenser, magnetic stirrer, and addition funnel was charged with 50 g (0.45 mol) of *t*-BuOK and 110 ml of DMSO. With magnetic stirring, pinacolone dichloride (35 g

0.22 mol) in 20 ml of DMSO was added at a rate sufficient to maintain the temperature below 40°. After addition was complete, the mixture was allowed to stir under nitrogen at ambient temperature for 2 hr. The reflux condenser was replaced by a distilling head and the reaction flask heated in an oil bath with the bath temperature gradually increased to 110° while material boiling up to 80° was collected. Redistillation through an 8-in. tantalum spiral column into a dry ice–acetone cooled receiver afforded 17.2 g (95%) of *tert*-butylacetylene, bp 36.5–38.5° (lit.[1] bp 36.4–37.8°) identical by ir, nmr, and vpc with an authentic sample prepared by the method of Bartlett and Rosen.[1]

**Registry No.**—**1**, 917-92-0; **2**, 594-84-3; *t*-BuOK, 865-47-4.

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(4) Insufficient care in maintaining efficient stirring and adequate temperature control is responsible for the fluctuating yields frequently observed in the preparation of the sensitive pinacolone dichloride (**2**) which undergoes facile monodehydrochlorination to the corresponding vinyl chloride. However, the vinyl chloride by-product can be used with equal success in the above procedure. In fact, we have frequently used mixtures of the vinyl chloride and dichloride to afford an overall yield of 70–75% of **1** from pinacolone.

# Leaving Group Effect in the Reaction of 2-Thiophenesulfonyl Halides with Anilines in Methanol

E. Maccarone,* G. Musumarra, and G. A. Tomaselli

*Istituto di Chimica Industriale dell'Università, Viale A. Doria 8, 95125 Catania, Italy*

*Received May 7, 1974*

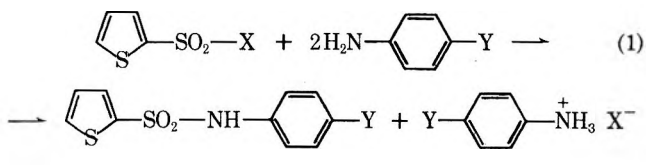
Previously the reaction kinetics of 2-thiophenesulfonyl chloride with several substituted anilines[1,2] was investigated and a study on the ultraviolet and infrared spectroscopic behavior of 2-thiophenesulfonanilides, reaction products, was carried out.[3]

The results of the kinetic measurements showed that 2-thiophenesulfonyl chloride is less reactive than the corresponding benzene derivative,[4] probably owing to the greater conjugative effect of the thiophene ring, but they gave no useful indications about the reaction mechanism.

The Hammett and Brønsted coefficient values for 2-thiophenesulfonyl chloride reactions with anilines in methanol[1] are almost coincident to those for the analogous reactions of benzenesulfonyl chloride.

For the latter reaction have been proposed both a one-step synchronous process, SN2,[4] and a two-step addition–elimination mechanism involving the formation of a metastable intermediate, $S_AN$.[5]

In order to give a further contribution to this question, in this paper we report a kinetic study on the leaving group effect in the reaction of 2-thiophenesulfonyl halides with aniline and *p*-anisidine, eq 1.




X = Cl, Br, F; Y = H, $OCH_3$

## Results and Discussion

The reaction of 2-thiophenesulfonyl halides with a large excess of aniline or *p*-anisidine in methanol solution is pseudo-first-order with respect to the sulfonyl halide. It was followed potentiometrically by titration of the acid produced with sodium hydroxide (see Experimental Section).

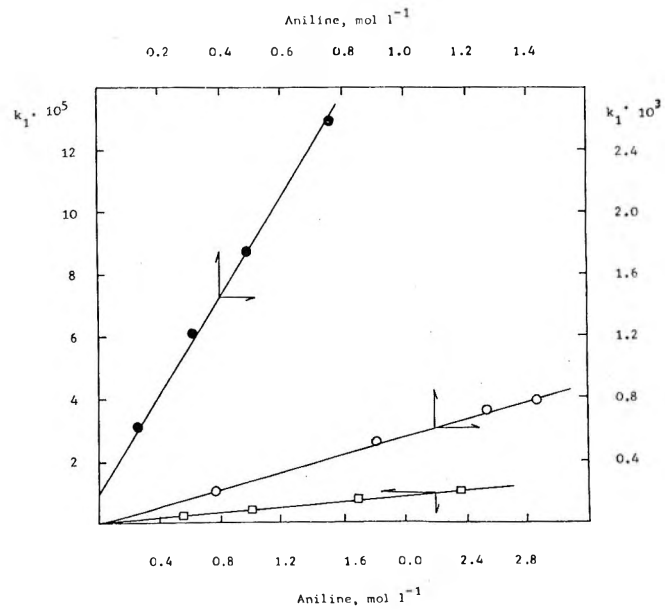



**Figure 1.** Pseudo-first-order rate constants at 25° against aniline concentration for the reaction of 2-thiophenesulfonyl halides: ●, 2-thiophenesulfonyl bromide; ○, 2-thiophenesulfonyl chloride; □, 2-thiophenesulfonyl fluoride.

The reaction of 2-thiophenesulfonyl bromide was followed to at least 80% completion, while that of 2-thiophenesulfonyl fluoride was followed to 25% completion, since it is very slow. The reaction yielded sulfonanilides, since the solvolysis of 2-thiophenesulfonyl halides in methanol is negligible.

Pseudo-first-order rate constants against aniline concentrations give linear plots, indicating that the reaction is first order also with respect to aniline (Figure 1).

The reactions were studied at different temperatures and the second-order rate constants, reported in Table I, together with the standard deviations and the linear correlation coefficients, were obtained by eq 2,[6] using the least-squares method.

$$k_{psl} = k_{solv} + k_2[\text{aniline}] \qquad (2)$$

The value of $k_{solv}$ is almost null for the reactions of 2-thiophenesulfonyl fluoride and chloride and negligible, with respect to $k_2$, for that of 2-thiophenesulfonyl bromide (Figure 1).

The activation parameters are reported in Table II, together with the linear correlation coefficients and the standard deviations.

2-Thiophenesulfonyl bromide reacts *ca.* five times faster than 2-thiophenesulfonyl chloride[1] with both aniline and *p*-anisidine, and respectively *ca.* 7200 and 35,700 times faster than 2-thiophenesulfonyl fluoride. The observed rate sequence follows the halogen polarizability sequence (Br > Cl ≫ F) and is inverse with respect to the S–Hal bond energy sequence.[7]

In order to distinguish between SN2 and $S_AN$ mechanisms we determined the relative amount of bond formation and bond breaking, respectively, for S–N and S–Hal bonds in the transition state, using the Brønsted coefficients[8] obtained from the plots of log $k_2$ against the $pK_a$ of protonated anilines and hydrogen halides ones (Figure 2).

The Brønsted coefficient values ($\beta$) for the leaving group for the reactions of 2-thiophenesulfonyl halides are −0.31 and −0.38, respecitvely, with aniline and *p*-anisidine. The $\beta$

**Table I**
**Second-Order Rate Constants for the Reaction of 2-Thiophenesulfonyl Halides with Aniline and *p*-Anisidine in Methanol**

| $C_4H_3SSO_2X$ X = | $H_2NC_6H_4Y$ Y = | Temp, °C | $k_2$, l. mol$^{-1}$ sec$^{-1}$ | $r$[a] | No. of runs |
|---|---|---|---|---|---|
| F[c] | H[d] | 25 | 0.4250 ± 0.044[b] × $10^{-5}$ | 0.995 | 4 |
| F | H | 35 | 1.036 ± 0.027 × $10^{-5}$ | 0.999 | 3 |
| F | H | 45 | 2.543 ± 0.249 × $10^{-5}$ | 0.995 | 3 |
| F | $OCH_3$[e] | 25 | 0.4629 ± 0.046 × $10^{-5}$ | 0.995 | 4 |
| F | $OCH_3$ | 35 | 1.056 ± 0.101 × $10^{-5}$ | 0.995 | 3 |
| F | $OCH_3$ | 45 | 2.469 ± 0.320 × $10^{-5}$ | 0.992 | 3 |
| Br[f] | H | 15 | 1.370 ± 0.098 × $10^{-2}$ | 0.997 | 3 |
| Br | H | 25 | 3.063 ± 0.064 × $10^{-2}$ | 0.999 | 4 |
| Br | H | 30 | 4.274 ± 0.366 × $10^{-2}$ | 0.996 | 3 |
| Br | H | 35 | 5.338 ± 0.435 × $10^{-2}$ | 0.997 | 3 |
| Br | $OCH_3$ | 15 | 9.802 ± 1.138 × $10^{-2}$ | 0.987 | 4 |
| Br | $OCH_3$ | 25 | 16.53 ± 1.48 × $10^{-2}$ | 0.988 | 5 |
| Br | $OCH_3$ | 35 | 28.27 ± 0.96 × $10^{-2}$ | 0.999 | 3 |

[a] $r$ = linear correlation coefficient. [b] Standard deviations. [c] Registry no. 382-99-0. [d] Registry no. 62-53-3. [e] Registry no. 104-94-9. [f] Registry no., 52259-99-1.

**Table II**
**Activation Parameters for the Reaction of 2-Thiophenesulfonyl Halides with Aniline and *p*-Anisidine in Methanol**

| $C_4H_3SSO_2X$ X = | $H_2NC_6H_4Y$ Y = | $r$[a] | $E_A$, kcal mol$^{-1}$ | Log $A$ | $-\Delta S^*$, cal mol$^{-1}$ °K$^{-1}$ |
|---|---|---|---|---|---|
| F | H | 0.998 | 15.7 ± 1.0[b] | 6.2 ± 0.7[b] | 32 ± 3[b] |
| F | $OCH_3$ | 0.999 | 15.8 ± 0.4 | 6.2 ± 0.3 | 32 ± 1 |
| Cl[c,d] | H | 0.999 | 12.6 ± 0.1 | 7.0 ± 0.1 | 28.5 ± 0.5 |
| Cl[c] | $OCH_3$ | 0.999 | 9.3 ± 0.1 | 5.4 ± 0.1 | 35.8 ± 0.5 |
| Br | H | 0.995 | 12.2 ± 0.8 | 7.4 ± 0.6 | 27 ± 3 |
| Br | $OCH_3$ | 0.999 | 9.4 ± 0.2 | 6.1 ± 0.2 | 33 ± 1 |

[a] $r$ = linear correlation coefficient. [b] Standard deviations. [c] Reference 1. [d] Registry no., 16629-19-9.

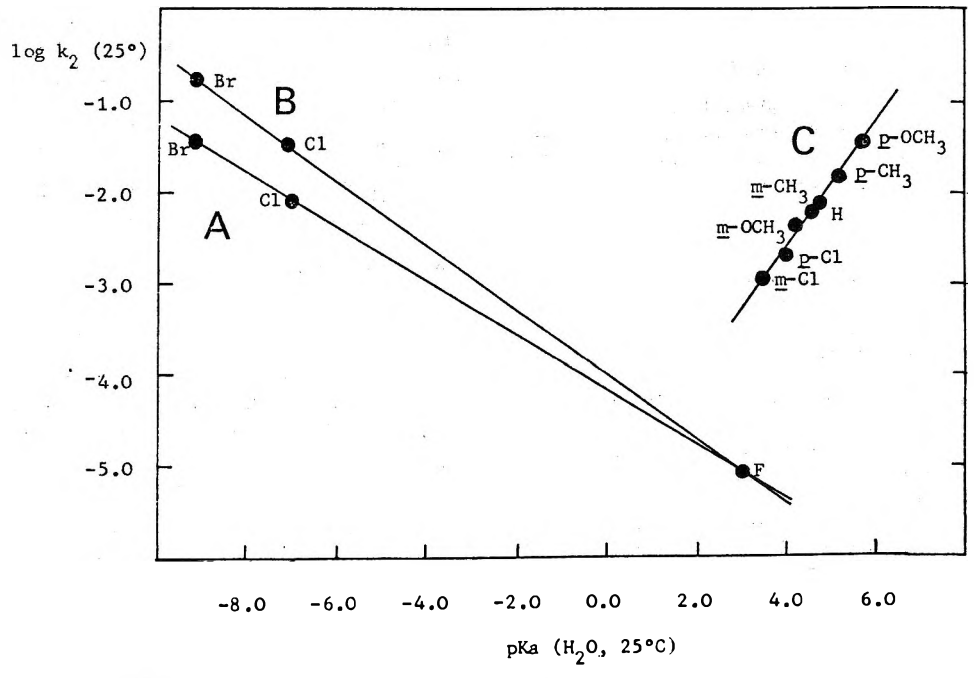



**Figure 2.** Brønsted plots: A, 2-thiophenesulfonyl halides with aniline, $\beta = -0.31$; B, 2-thiophenesulfonyl halides with *p*-anisidine, $\beta = -0.38$; C, 2-thiophenesulfonyl chloride with meta- and para-substituted anilines, $\beta = +0.79$.

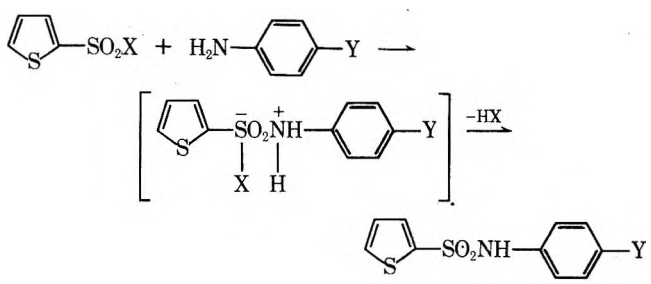
value for the entering nucleophiles, obtained for the reactions of 2-thiophenesulfonyl chloride with some meta- and para-substituted anilines,[1] is +0.79. The comparison between the $\beta$ values suggests a greater degree of S–N bond formation in the transition state with respect to S–Hal bond breaking. This finding implies the formation of an intermediate complex along the reaction path. Nevertheless the Brønsted coefficients must be regarded, as a simple mechanism criterion, with great caution owing to the nonhomogeneous comparison between log $k_2$ and $pK_a$,[9] since the rate constants were measured in methanol solution, while the $pK_a$ values for anilines and hydrogen halides were determined in aqueous solution. The $pK_a$ values reported for hydrogen halides, besides, are rather uncertain.[10]

A further interesting result is that the rates and the activation parameters for 2-thiophenesulfonyl fluoride reactions are almost equal with aniline and *p*-anisidine; this suggests that the rate-determining step is the S–F bond breaking in the transition state.

For the reactions of 2-thiophenesulfonyl chloride and bromide, instead, the rate-determining step is the nucleophilic attack to the sulfonyl halide. In fact the reaction rates (Table I) and the activation energies (Table II) are affected by the basicity of the nucleophilic reagent and not by the leaving halogen nature.

In conclusion the data on the reactivities of 2-thiophenesulfonyl halides and the relative activation parameters could fit well with a two-step addition–elimination mechanism $S_AN$, the rate-determining step being the S–N bond formation for 2-thiophenesulfonyl chloride and bromide and the S–F bond breaking for sulfonyl fluoride (see Scheme I).

**Scheme I**



## Experimental Section

**Materials. 2-Thiophenesulfonyl chloride** was obtained by adding at 20°, under stirring, 33.6 g (0.4 mol) of thiophene to a mixture containing 66 ml (1 mol) of chlorosulfonic acid and 83 g (0.4 mol) of phosphorus pentachloride, following the procedure already described,[11] 70% yield, bp 92–93° (1 mm), mp 31–32° from petroleum ether (bp 30–60°).

**2-Thiophenesulfonyl Fluoride.** To an aqueous solution (30 ml) containing 7.4 g (0.2 mol) of ammonium fluoride, 18.3 g (0.1 mol) of 2-thiophenesulfonyl chloride was added. The mixture was refluxed for 5 hr, then treated with warm water and extracted with ether. The evaporated extract gave the products, 90% yield, bp 75–76° (1 mm).[12]

**2-Thiophenesulfonyl Bromide.** This product was synthesized using the method reported for benzenesulfonyl bromide.[13]

To 10.7 g (0.06 mol) of 2-thiophenesulfonyl hydrazide (see later) in 200 ml of 10% hydrochloric acid was added at 20° an aqueous solution (35 ml) containing 2.4 g (0.02 mol) of potassium bromide and 6.7 g (0.04 mol) of potassium bromate. The precipitate was filtered quickly, washed with cold water, and dried *in vacuo*, 60% yield, mp 48–49° from petroleum ether.

*Anal.* Calcd for $C_4H_3BrO_2S_2$: Br, 35.19. Found: Br, 35.28.

**2-Thiophenesulfonyl hydrazide** was synthesized by the method reported for benzenesulfonyl hydrazide.[14]

To 12.5 g (0.25 mol) of 85% hydrazine hydrate in 30 ml of ether was added an ether solution (30 ml) containing 18.3 g (0.1 mol) of 2-thiophensulfonyl chloride. The mixture was stirred for 30 min and the precipitate was collected and washed with cold water, 60% yield, mp 68–69° from water.

*Anal.* Calcd for $C_4H_6N_2O_2S_2$: N, 15.72. Found: N, 15.60.

Aniline and *p*-anisidine were commercial products purified by several distillations or crystallizations.

Methanol (R. S. Carlo Erba) was used throughout; no special purification was undertaken, since several experiments showed that elaborate purification was unnecessary.

**Kinetic Procedure.** Rate measurements were done by a digital pH meter, Amel Model 333, equipped with a motorized burette, Amel Model 233, by continuous titration of the acid produced with 0.1 *N* sodium hydroxide, following the procedure described before.[1] The reagent concentrations ranged from *ca.* 0.0003 to *ca.* 0.013 mol for 2-thiophenesulfonyl halides and from *ca.* 0.004 to *ca.* 2 mol for the anilines, depending on the reaction rates.

The first-order rate constants were obtained from the slope of conventional plots of log $(a - x)$ against time, using the least-squares method. The activation energies were calculated from the Arrhenius equation by the least-squares method. The entropies of activation were computed for 25°, using the suitable equation.

**Product Analysis.** Methanol solutions of 2-thiophenesulfonyl halide (0.025 mol) and aniline or *p*-anisidine (0.15 mol) were allowed to react at room temperature until completion. Methanol was evaporated, and then the residue was treated with aqueous 40% sodium hydroxide and extracted twice with ether or filtered. The aqueous layer was acidified and the precipitate was collected, washed with water, and crystallized from aqueous ethanol: 2-thiophenesulfonanilide, mp 99–100[1]; 2-thiophene-4′-methoxysulfonanilide, mp 104°.[1]

**Acknowledgments.** We thank Professor A. Arcoria for helpful discussions and the Consiglio Nazionale delle Ricerche (Rome) for the financial support.

**Registry No.**—Thiophene, 110-02-1; chlorosulfonic acid, 7990-94-5; 2-thiophenesulfonyl hydrazide, 52260-00-1.

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# Model Studies of Terpene Biosynthesis. Synthesis and Absolute Configuration of (+)-*trans*-2,2-Dimethyl-3-(2′-methylpropenyl)cyclobutanol[1]

Oliver J. Muscio, Jr., and C. Dale Poulter*

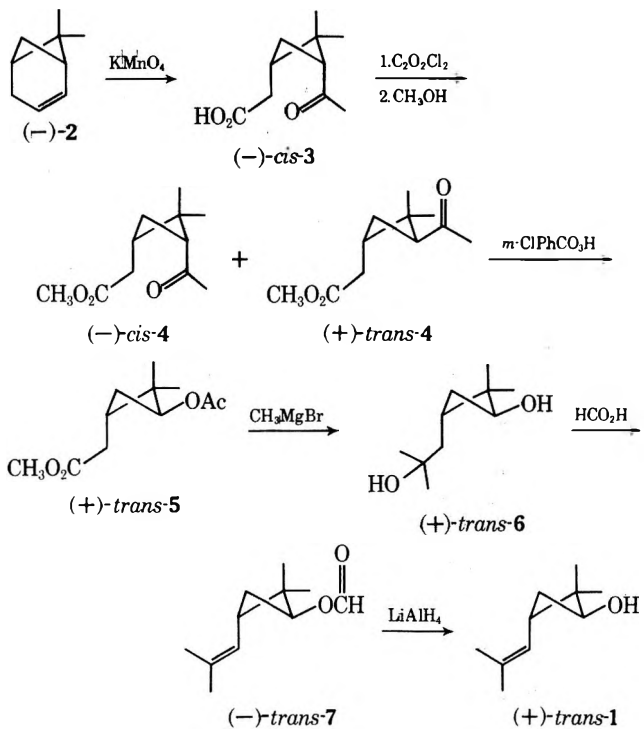
*Department of Chemistry, University of Utah, Salt Lake City, Utah 84112*

*Received March 19, 1974*

Several mechanisms have been suggested for the head-to-head rearrangement of presqualene and prephytoene

pyrophosphate to squalene and phytoene, respectively.[2] Among the proposed intermediates is a cyclobutyl species, either as a cation[2a-d,f,g] or a covalent pyrophosphate.[2e-g] In this note we describe the synthesis of a $C_{10}$ model, (+)-*trans*-2,2-dimethyl-3-(2′-methylpropenyl)cyclobutanol (*trans*-**1**).

**Scheme I**




Cyclobutanol *trans*-**1** was prepared by the sequence of reactions shown in Scheme I. By choosing α-pinene (**2**) as a starting material, the cyclobutane ring and the geminal methyl groups are already assembled. Also, the cyclobutane carbon atoms which will become $C_1$ and $C_3$ in *trans*-**1** are functionalized. Of more importance, optically active α-pinene is readily available,[3] and all of the correlations necessary to establish the absolute configuration and optical purity of a key intermediate in Scheme I, pinonic acid (**3**), have been published.[4] Thus, our synthetic task involved functional group modifications and epimerization of either $C_1$ or $C_5$ in α-pinene, while retaining the configuration of the other.

Oxidation of (−)-α-pinene (**2**), 95% 1*S*,5*S*, with potassium permanganate following the procedure of Delepine[5] gave (−)-pinonic acid (*cis*-**3**) and its (−) diastereomer (*trans*-**3**). The mixture of diastereomers was evidently the result of epimerization of the very labile α-keto carbon in **3**, even though the reaction was buffered with ammonium sulfate. Although trans substitution on the ring was ultimately desired, syrupy *trans*-**3** could not be readily purified for further use in the synthetic scheme. The cis isomer, however, was easily obtained in pure form by recrystallization.

Treatment of a benzene solution of crystalline (−)-*cis*-**3** with oxalyl chloride, followed by addition of methanol, gave an equilibrium mixture of methyl pinonates which consisted of 72% (−)-*cis*-**4** and 28% (+)-*trans*-**4**. Attempted further epimerization with *p*-toluenesulfonic acid did not alter the ratio of diastereomers, while epimerization of *cis*-**4**, *vide infra*, under similar conditions resulted in the same equilibrium mixture. Esterification of the sodium salt of (−)-*cis*-**3** proceeded with less epimerization at $C_3$, although a small amount of the trans isomer was seen. The identities of the two diastereomers were then confirmed by glpc comparisons. The cis/trans mixture of methyl pinonates was separated by a careful spinning band distillation.

The configuration at $C_3$ was locked during the next step. Baeyer–Villiger oxidation of the oxo functional group in methyl pinonate was regio- and stereospecific, as expected.[6] In all cases only acetates were formed and the oxygen atom was inserted between $C_3$ and the carbonyl carbon with retention of configuration. Oxidation of a 72:28 cis/trans mixture of methyl pinonates gave *cis*- and *trans*-cyclobutyl acetates (**5**) in exactly the same ratio. Subsequent work indicated that separation of the cis and trans isomers, although difficult, was best accomplished before the Baeyer–Villiger reaction. When (+)-*trans*-**4** (95% trans) was treated with *m*-chloroperbenzoic acid in dichloromethane at 25°, (+)-*trans*-**5** (95% trans) was obtained. Addition of an excess of methylmagnesium iodide to (+)-**5** (95% trans) transformed the methyl ester functionality into a dimethylcarbinol and converted the cyclobutyl acetate into an alcohol. The syrupy diol was obtained in quantitative yield.

The final step required a regioselective dehydration of the tertiary hydroxyl group in diol (+)-*trans*-**6** to give the desired 2-methyl-1-propenyl group at $C_3$. Of the several methods tried, including treatment of the diol with iodine, the best results were obtained by heating (+)-*trans*-**6** in anhydrous formic acid. The product consisted mainly of (−)-*trans*-**7** in a ratio of about 4:1 with the methylene isomer, as well as some undehydrated mixed formates and hydroxyformates which were isolated and recycled. The cyclobutyl formate slowly decomposed in formic acid, and the progress of the reaction had to be followed carefully in order to obtain a maximum yield.

The desired product was separated from its methylene isomer and the nonolefinic products by column chromatography on 10% $AgNO_3$–silica gel. The separation was cleaner for the formate than alcohol (+)-*trans*-**1**, since the latter tended to tail on our column. The combined yield of two successive dehydrations was 42% with the proportion of *cis*-cyclobutyl alcohol in *trans*-**1** increasing from 5 to 9%. The decrease of the trans/cis ratio upon dehydration evidently is the result of a lower stability of the trans isomer to the reaction conditions. This conclusion is supported by the observation that the *cis*-diol can be dehydrated to *cis*-**7** in much better yield than the trans isomer, and the reaction mixture can be heated for extended periods without the decomposition that takes place in the trans series at longer reaction times. Also, solvolysis studies have shown that trans derivatives of **1** react more rapidly than cis derivatives.[2,7] The trans formate would presumably be less stable than *cis*-**7** in a strongly ionizing solvent such as formic acid.

Cyclobutyl alcohol (+)-*trans*-**1** (91% trans) was obtained in 86% yield from (−)-formate **7** by reduction with lithium aluminum hydride. Racemic **1** has been prepared by a different route as a 40:60 mixture with its cis isomer.[2,7] The nmr spectrum of our alcohol (91% trans) is identical with that of the isomer identified as the trans component of the 40:60 mixture.[8]

As indicated in Scheme I, the absolute configuration at $C_3$ in *trans*-**1**, the carbon which bears the 2-methyl-1-propenyl group, is maintained throughout the synthetic sequence, while the absolute configuration of $C_1$, the hydroxyl-bearing carbon, has undergone a single inversion during the epimerization which occurred during esterification of **3**. Therefore, optically active alcohol (+)-*trans*-**1** has the absolute configuration 1*S*,3*R* as shown, when prepared from (1*S*,5*S*)-α-pinene.

## Experimental Section

**General.** Melting points (sealed capillary) and boiling points are uncorrected. Unless otherwise indicated, nmr spectra were obtained in carbon tetrachloride solution with TMS internal standard, and recorded with a Varian A-60 spectrometer. Spectra are reported in parts per million ($\delta$) relative to TMS. Analytical gas chromatography was carried out on a Varian Model 1200 gas chromatograph with flame ionization detector, using a 500 ft × 0.03 in. open tubular column coated with Carbowax 20M. Microanalyses were performed by M-H-W Laboratories, Garden City, Mich. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter.

**(−)-(2,2-Dimethyl-3-acetylcyclobutyl)acetic Acid, *cis*-Pinonic Acid [(−)-*cis*-3].** Oxidation of (−)-$\alpha$-pinene, 95% 1*S*,5*S* (Columbia Organic Chemicals), was carried out with potassium permanganate and ammonium sulfate buffer by the procedure of Delepine.[5] The yield of crude acid varied between 40 and 60%. From the crude, mushy acid could be separated by filtration of a carbon tetrachloride solution, a small portion of insoluble racemic *cis*-pinonic acid. Addition of hexane to the filtrate then allowed crystallization of (−)-(1*R*,3*R*)-pinonic acid, which was purified by further recrystallization from carbon tetrachloride–hexane. Pure (1*R*,3*R*)-3 was obtained in about 9% overall yield: mp 69–70°, $[\alpha]^{25}D$ −93.7° (*c* 4.60, $CHCl_3$) [lit.[4a] mp 68–69°; $[\alpha]D$ +95.0° ($CHCl_3$)]; nmr ($CDCl_3$) 0.87 and 1.32 (6, s, ring methyl), 2.03 (3, s, acetylmethyl), 2.32 (2, m, H adjacent to carbonyl), 2.05 (2, m, H at $C_4$), and 2.89 ppm (1, t, H at $C_3$, $J_{2,3}$ = 8 Hz).

**(−)-Methyl *cis*-(2,2-Dimethyl-3-acetylcyclobutyl)acetate, *cis*-Methyl Pinonate [(−)-*cis*-4], and (+)-Methyl *trans*-(2,2-Dimethyl-3-acetylcyclobutyl)acetate, *trans*-Methyl Pinonate [(+)-*trans*-4].** (−)-Pinonic acid, 16.0 g (0.0878 mol), was dissolved in 100 ml of benzene that had been dried over Linde 3A molecular sieves, and 8.7 ml (12.1 g, 0.101 mol) of oxalyl chloride was added. The mixture was allowed to stir at ambient temperature for 4 hr. Anhydrous methanol (100 ml) was then added and the mixture allowed to stir for an additional 1.5 hr. Solvents were removed on a rotary evaporator, the residue taken up in ether, and the solution washed with saturated sodium bicarbonate solution until neutral, followed by a brine wash. The ether layer was dried by filtration through anhydrous sodium sulfate, followed by treatment with 3A molecular sieves. Evaporation of the solvent left a residue of crude product, 17.4 g (100%), $[\alpha]^{25}D$ −38.3° (*c* 4.68, $CHCl_3$). Analytical glpc (Carbowax, 170°) indicated a 28:72 ratio of isomers. Very careful fractional distillation on a Nester-Faust Auto-Annular spinning band column [rate of distillation 0.5–1.5 ml/hr, bp 92–94° (1.5–1.8 mm)] permitted partial separation of the trans–cis mixture into fractions 88% trans, $[\alpha]^{25}D$ +67.6° (*c* 4.66, $CHCl_3$), and 98% cis, $[\alpha]^{25}D$ −79.8° (c 5.30, $CHCl_3$). Combination of these fractions with others previously prepared, and further fractional distillation as above permitted isolation of a 8.18-g fraction of (+)-**5** (95% trans): $[\alpha]^{25}D$ +73.5° (c 4.78, $CHCl_3$); nmr 2.10–3.00 (5, m, ring H's and H adjacent to carboxyl), 1.02 and 1.18 (6, s, ring methyls), 1.99 (3, s, acetyl methyl), and 3.55 ppm (3, s, methyl ester). Another fraction, 76% cis, $[\alpha]^{25}D$ −42.6° (c 4.93, $CHCl_3$), was obtained as forerun.

The optical purity and maximum rotation of (+)-*trans*-4 was determined from carefully purified (−)-*cis*-3 (98.6% optically pure). Esterification gave the expected mixture of diastereomers which was separated into two fractions by careful distillation. The rotations found for each fraction are listed in Table I. By solving the simultaneous equations

$$0.88[\alpha_t]D + 0.12[\alpha_c]D = +67.6°$$

$$0.02[\alpha_t]D + 0.98[\alpha_c]D = -79.8°$$

pure (+)-*trans*-4 was calculated to have $[\alpha]D$ −89°. On a larger scale, a sample of *trans*-11 (95%) distilled from a combination of several runs, had a specific rotation $[\alpha]D$ +73.5°, and a forerun of *cis*-11 (76%) had $[\alpha]D$ −42.6°. By solving simultaneous equations similar to those above, a value of $[\alpha]D$ +81.7° was obtained for the *trans*-11 from this batch, corresponding to an optical purity of 91%. The sequence of reactions used to prepare *trans*-11 from $\alpha$-pinene only permits epimerization of $C_3$; therefore, the trans isomer must be predominantly the 1*R*,3*S* enantiomer.

**(+)-Methyl *trans*-(3-Acetoxy-2,2-dimethylcyclobutyl)acetate [(+)-*trans*-5].** The 8.18 g (0.042 mol) of (+)-*trans*-4 (95% trans) obtained above and 10.2 g 85% *m*-chloroperbenzoic acid (8.63 g pure, 0.500 mol) (Columbia Organic Chemicals) were dissolved in 100 ml of $CHCl_3$ in a 250-ml round-bottomed flask which was wrapped with aluminum foil to exclude light. The resulting solution was allowed to stand at ambient temperature for 5 days, at which time the flask had become filled with precipitated *m*-chlorobenzoic acid. Analytical glpc indicated the reaction was complete. The solution was chilled in an ice bath and filtered to remove most of the *m*-chlorobenzoic acid. The filtrate was washed with a sodium thiosulfate solution to decompose the remaining peracid, and with a sodium carbonate solution to remove the remaining carboxylic acid. Rotary evaporation of the solvent, followed by simple vacuum distillation of the residue, afforded 8.14 g (92%) of (+)-*trans*-**5**. Analytical glpc (Carbowax, 170°) indicated the product was a 95:5 mixture of isomers, and otherwise pure: $[\alpha]^{25}D$ +6.18° (*c* 5.60, $CHCl_3$); bp 84–87° (1.3 mm); nmr ($CDCl_3$) 1.04 and 1.08 (6, s, methyl groups at $C_2$), 2.02 (3, s, acetate methyl), 1.9–2.5 (5, m, ring H's and H adjacent to carboxyl), 3.63 (3, s, methyl ester), and 4.4–4.8 ppm (1, m, H at $C_3$).

*Anal.* Calcd for $C_{11}H_{18}O_4$: C, 61.67; H, 8.45. Found: C, 61.80; H, 8.56.

**(+)-*trans*-2,2-Dimethyl-3-(2′-hydroxy-2′-methyl-1′-propyl)cyclobutanol [(+)-*trans*-6].** Methylmagnesium iodide was prepared by adding 27.1 g (0.191 mol) of methyl iodide in 160 ml of anhydrous ether to 5.57 g (0.229 mol) of magnesium turnings in 50 ml of anhydrous ether under a nitrogen atmosphere. To the resulting magnetically stirred Grignard reagent was added dropwise in 50 ml of ether, 8.10 g (0.038 mol) of (+)-*trans*-**5**. The resulting mixture was stirred for 1 hr and then the magnesium salts were precipitated by adding saturated ammonium chloride solution until the solids coagulated. The ether was decanted and the solid residue washed with another 100 ml of ether. The combined ether fractions were washed with 1 *M* hydrochloric acid saturated with ammonium chloride, followed by washing with brine. The solution was dried and the solvent evaporated yielding ~3 g (45%) of a viscous oil. Since most of the product was still occluded in the precipitated magnesium salts, they were dissolved with the minimum of dilute hydrochloric acid (the solution was still somewhat basic, as indicated by the odor of ammonia present). The resulting solution was extracted with several 50-ml portions of ether and the combined ether fractions were treated as above. A total yield of 6.5 g (99%) of syrupy diol was obtained. The portion isolated from the salts, after complete removal of solvent under vacuum, was analytically pure: $[\alpha]^{25}D$ +38.4° (c 3.12, $CHCl_3$); nmr ($CDCl_3$) 0.97 and 1.05 (6, s, methyl groups at $C_2$), 1.18 (6, s, methyl groups at $C_{2'}$), 1.25–2.15 (7, m, H's at $C_3$, $C_4$, $C_{1'}$, and hydroxyl), and 3.8–4.0 ppm (1, m, H at $C_1$).

*Anal.* Calcd for $C_{10}H_{20}O_2$: C, 69.70; H, 11.72. Found: C, 69.77; H, 11.52.

**(−)-*trans*-2,2-Dimethyl-3-(2′-methylpropenyl)cyclobutanol [(−)-*trans*-7].** In a 100-ml round-bottomed flask with condenser and drying tube were stirred magnetically at 75° (for about 6 hr) a solution of 6.4 g (0.037 mol) of diol (+)-*trans*-6, 15 ml of cyclohexane, 25 ml of anhydrous formic acid (dried by distillation from phthalic anhydride), and *ca.* 5 g of 3Å molecular sieves. The reaction mixture was worked up by diluting with an equal portion of water and extracting with three 50-ml portions of pentane. The combined pentane fractions were washed in succession with a 50-ml portion of brine, saturated bicarbonate until neutral, and a second wash with brine. Filtration through anhydrous sodium sulfate followed by treatment with molecular sieves and removal of solvent on a rotary evaporator gave a light yellow residue. Final purification was by chromatography on 200 g of 10% silver nitrate–silica gel. Elution with 2% ether–pentane (olefin free) gave a 0.065-g fraction of (−)-*trans*-7 (97% trans) followed by 2.00 g of (+)-*trans*-7 (91% trans). Elution of the column with ether yielded 0.6 g of

**Table I**
**Specific Rotations of Mixtures of (1*R*,3*R*)-4 and (1*R*,3*S*)-4**

| Composition[a] | | |
|---|---|---|
| % *cis*-4 | % *trans*-4 | $[\alpha]^{25}D$,[b] deg |
| 12 | 88 | +67.6[c] |
| 98 | 2 | −79.8[c] |
| 5 | 95 | +73.5[d] |
| 76 | 24 | −42.6[d] |

[a] Determined on a 500 ft × 0.03 in. Carbowax 20M open tubular column. [b] Taken in chloroform. [c] From small sample of carefully purified (1*R*,3*R*)-4. [d] From combined samples obtained from several runs.

more polar compounds (assumed to be diformate and hydroxyformates) which upon retreatment with formic acid and column chromatography yielded another 0.2 g of (−)-*trans*-**7**. The total yield of (−)-*trans*-8 was 2.26 g (42%). The 97% trans portion was further purified by preparative gas chromatography: $[\alpha]^{25}D$ −39.0° (c 2.18, $CHCl_3$); nmr 1.00 and 1.06 (6, s, methyl groups at $C_2$), 1.58 and 1.73 (6, doublets, methyl groups at $C_{2'}$, $J$ = 1 Hz), 2.0–3.0 (3, m, H at $C_3$ and $C_4$), 4.83 (1, t, H at $C_1$, $J$ = 7 Hz), 5.15 (1, doublet of septets, H at $C_{1'}$, $J$ = 10, 1 Hz), and 7.91 ppm (1, s, formyl H); high resolution mass spectrum *m/e* calcd for $C_{11}H_{18}O_2$ 182.1306; *m/e* found 182.1256.

**(+)-*trans*-2,2-Dimethyl-3-(2′-methylpropenyl)cyclobutanol [(+)-*trans*-1].** A solution of 2.00 g of (−)-*trans*-7 (11 mmol) in 10 ml of anhydrous ether was added dropwise over a period of 20 min to a magnetically stirred slurry of 0.346 g (36.5 mequiv) of lithium aluminum hydride in 15 ml of anhydrous ether under a nitrogen atmosphere. The resulting mixture was stirred for 2 hr, an additional 30 ml of ether added, and lithium and aluminum salts were precipitated by the dropwise addition of a saturated ammonium chloride solution. The ether was decanted, and the residue washed with another 30 ml of ether. The combined ether fractions were washed in succession with dilute hydrochloric acid, saturated sodium bicarbonate solution, and brine before the solution was dried over 3A molecular sieves. Solvent was removed on the rotary evaporator giving 1.46 g of a colorless oil (86%): $[\alpha]^{25}D$ +6.73° (c 4.47, $CHCl_3$); nmr 0.88 and 1.04 (6, s, methyl groups at $C_2$), 1.53 and 1.69 (6, d, methyl groups at $C_{2'}$, $J$ = 1.5 Hz), 3.26 (1, s, hydroxyl group), 3.82 (1, t, H at $C_1$, $J$ = 7 Hz), and 4.99 ppm (1, doublet of septets, H at $C_{1'}$, $J$ = 11, 1.5 Hz).[7]

**Acknowledgment.** The authors wish to thank Professor Robert M. Coates for a preprint of his work and copies of spectra prior to publication. We also thank Dr. Roy Teranishi and Dr. Bill Haddon at Western Regional Laboratory for providing high resolution mass spectra.

**Registry No.**—(+)-*trans*-**1**, 52305-33-6; (−)-**2**, 7785-26-4; (−)-*cis*-**3**, 52305-34-7; (−)-*cis*-**4**, 52305-35-8; (+)-*trans*-**4**, 52305-36-9; (+)-*trans*-**5**, 52259-48-0; (+)-*trans*-**6**, 52259-49-1; (−)-*trans*-**7**, 52259-50-4.

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(8) Although Coates and Robinson[2d,7] have consistently reported the vinyl proton of *trans*-**1** as having an nmr chemical shift upfield from that of *cis*-**1**, we have always found the reverse. Examination of a spectrum reproduced in ref 7 confirms that the chemical shift of the olefinic proton for the minor isomer of the 40:60 mixture, reported to be *trans*-**1**, is indeed downfield from the cis isomer, as we have also found.

# Isolation and Properties of Acetyl Hypobromite

John J. Reilly, David J. Duncan, Timothy P. Wunz, and Robert A. Patsiga*

*Department of Chemistry, Indiana University of Pennsylvania, Indiana, Pennsylvania 15701*

*Received April 5, 1974*

Acyl hypohalites (1) are relatively unstable substances which are decomposed by heat or light to form carbon dioxide, alkyl halides, and esters.[1-3] Of the various types which may exist only acetyl hypochlorite[4] and the perfluoroacyl hypofluorites[5] have been isolated in relative purity and characterized.

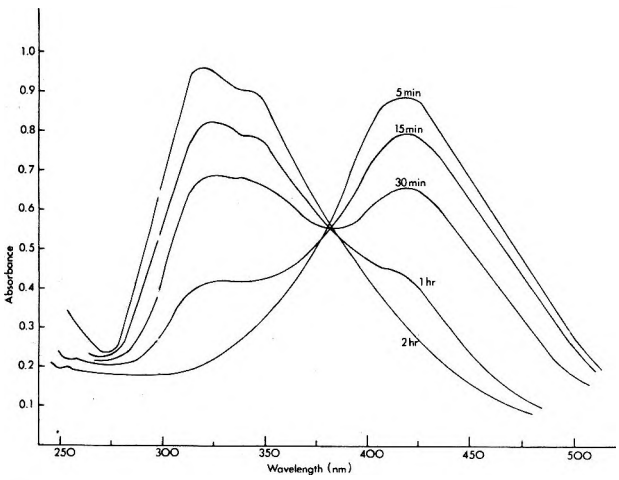
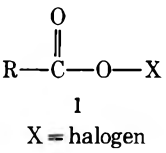



**Figure 1.** Absorption spectra of filtered acetyl hypobromite solutions (lines indicate extent of nitrogen purge). Initial solution: 0.05 *M* bromine and silver acetate.



1

X = halogen

Acetyl hypobromite has been studied in solution and some properties have been reported. In carbon tetrachloride solution it absorbs in the ultraviolet region with a $\lambda_{max}$ of 320 nm.[6] An infrared spectrum of the hypobromite in acetic acid shows an absorption at 670 $cm^{-1}$ attributed to the O–Br stretching frequency by analogy with an absorption at the same frequency by *tert*-butyl hypobromite.[7] Hatanaka, Keefer, and Andrews[7] have attempted to isolate acetyl hypobromite by vacuum distillation of its solution in carbon tetrachloride, but no fraction which could be characterized as the hypobromite was detected. Beebe and Wolfe[8] found acetyl hypobromite to be stable in carbon tetrachloride at −15 to 15° for 4 weeks.

On the basis of its relatively high molecular weight and predicted polarity, acetyl hypobromite would be expected to be a high-boiling liquid or a solid. Preparation of the compound in a volatile, inert solvent which could be carefully distilled should lead to its isolation.

## Results and Discussion

The reaction of bromine with silver acetate suspended in carbon tetrachloride and nitrogen flushing of any excess bromine (eq 1) yields a dark, green-yellow solution containing acetyl hypobromite. The observed color agrees with that reported by others.[7] Figure 1 shows the uv–visible spectrum of the filtered bromine–silver acetate system at various times of nitrogen purge. The quantitative aspects of the curves would be expected to vary with rate of nitrogen flow but the trends are reproducible in general form. The nitrogen flow is sufficiently slow that the stoichiometric quantity of bromine is not lost. The bromine peak at 415 nm is seen to disappear while a maximum at 320 nm persists along with a shoulder at 340 nm. A similar spectrum is obtained when perfluorinated hydrocarbon is used as solvent in place of carbon tetrachloride, the difference

$$CH_3COOAg + Br_2 \longrightarrow CH_3COOBr + AgBr \quad (1)$$

being the primary peak shifting to 318 nm and the shoulder having a lower intensity (about 75% that in $CCl_4$).

Slow vacuum distillation of this filtered carbon tetrachloride solution produces a pale yellow, fluffy solid composed of tiny, needle-like crystals. Absorption maxima identical with those of the original filtered solution are shown in the uv spectrum of a solution of the crystals redissolved in $CCl_4$.

When the crystals are removed from cold (0°) surroundings and nitrogen atmosphere into the room they gradually take on a deliquescent appearance, turn dark red-brown or occassionally green, and gradually disappear. The change is most likely brought on by reaction with moisture in the air, since the crystals appear to remain unchanged if kept for several minutes at room temperature but under nitrogen.

Several methods for weighing the crystals as part of an equivalent weight determination were explored. The most satisfactory procedure is to weigh the crystals in water. Even though acetyl hypobromite reacts with water, no change in the number of equivalents of oxidant should occur. Four iodometric determinations were made by this method. The average is 143.5 ± 5 and the expected value is 138.9.

The molar absorptivity of acetyl hypobromite in $CCl_4$ with concentrations determined by titrating the filtered reaction mixture and constructing a Beer's law plot was found to be 203 ± 10. If the determination was performed by weighing the isolated solid in $CCl_4$, the absorptivity was found to be 192. One determination based on weighing the dry, isolated solid gave a value of 212.

The evaluation of infrared spectra of acetyl hypobromite in carbon tetrachloride has the advantage over acetic acid in that carbon–hydrogen and carbonyl absorptions can be observed.

The original filtered acetyl hypobromite solution and redissolved crystals have identical absorption features which are consistent with the structure. Carbon–hydrogen stretching and bending bands occur in the expected region for the methyl group, the carbonyl stretch appears at 1790 $cm^{-1}$, an absorption at 1180 $cm^{-1}$ may be assigned to the C–C–O group by analogy with absorption by acetyl hypochlorite,[9] and a medium to weak absorption at 680 $cm^{-1}$ is assigned to the O–Br stretch. Depending on exposure of the carbon tetrachloride solution to air and warmth during preparation of the infrared sample, absorptions characteristic of acetic acid and carbon dioxide may be seen.

The proton magnetic resonance spectrum of acetyl hypobromite in carbon tetrachloride gives a single peak at $\delta$ 2.25. This is identical with the reported absorption by acetyl hypochlorite.[9]

## Experimental Section

**Materials.** Carbon tetrachloride was distilled at atmospheric pressure in a stream of dry nitrogen and stored over molecular sieve. Commercial silver acetate was used without purification. Bromine was distilled from $P_2O_5$ just prior to use. The fluorocarbon used was FC-75 (bp 102°) obtained from the 3M Co.

**Spectral Procedures.** Infrared liquid cells of sodium chloride or potassium bromide were used to contain the samples solutions. Ultraviolet spectra were run with pure solvent as reference. Pmr spectra showed no absorptions in the $\delta$ 10–12 region indicative of the acetic acid proton.

**General Procedure.** All experimental work was conducted in subdued light, using red light bulbs when necessary to see the equipment. The all-glass apparatus used to prepare the acetyl hypobromite solution was U-shaped. The larger arm (approximately 200 ml capacity) had a coarse fritted disk to permit filtration. The narrower arm provided an inlet for nitrogen and was fitted near the bottom with a Teflon stopcock and outlet tube. The aparatus was jacketed in a light-proof case with only the stopcock protruding. The inner space was packed in ice. The empty apparatus was flushed with nitrogen prior to addition of silver acetate and one-half the required amount of $CCl_4$ into the larger arm. The heterogeneous mixture could be kept agitated by the nitrogen gas passing through the glass disk. Bromine dissolved in the remaining portion of $CCl_4$ was added dropwise over 15 min, the solution constantly being agitated by a slow stream of nitrogen. The nitrogen flow was then increased and samples were taken periodically for spectrophotometric determination of bromine and hypobromite content. Typical quantities used were: silver acetate, 8.4 g (0.050 mol); bromine, 3.0 ml (0.058 mol); $CCl_4$, 150 ml. Samples were taken from the apparatus by reversing the direction of nitrogen flow, thus applying pressure on the surface of the solution. The solution was then forced through the filter disk and out of the stopcock. When the bromine was seen to be absent as indicated by the lack of a shoulder on the hypobromite absorption peak, the solution was considered ready for distillation of solvent. The time from combination of reactants to this point in the procedure was 2–3 hr.

The isolation of the acetyl hypobromite was accomplished by transferring the reaction solution (*via* the above-described filtration) to a distillation flask. The transfer and subsequent assembly of the distillation apparatus were done while a slow stream of nitrogen passed over the solution. The success in isolating solid acetyl hypobromite depends on vacuum distilling the $CCl_4$ at an extremely slow rate. Otherwise, acetyl hypobromite has a great tendency to transfer with the solvent. Moderate vacuums such as those obtained by a simple water aspirator (water vapor removed by placing a drying tower in the vacuum line) permitted the slow (2–4 hr) distillation of 75% of the solvent. This was followed by switching to a vacuum pump, maintaining 5–10 mm pressure. Intermittent opening and closing the line to the pump was found to be helpful in preventing bumping and distillation of the hypobromite. Throughout all distillations the distilling flask was packed in ice. Finally, as solid began to appear the vacuum was decreased to <5 mm, and pumping was continued until the crystals appeared very dry.

The pressure was returned to 1 atm with nitrogen to allow disassembly of the apparatus. The solid hypobromite was removed for sampling from the flask by using a glass spatula, maintaining a slight positive pressure of nitrogen and a temperature of 0°. Approximately 1 g of solid acetyl hypobromite could be isolated in a typical experiment.

Solutions for equivalent weight determinations were prepared by placing the weighed solid (~0.1 g) in a mixture composed of $H_2O$ (5 ml), KI (2.5 g), and acetic acid (10 ml). The liberated iodine was then titrated with 0.100 *M* thiosulfate.

The fluorocarbon was poorly suited as a solvent. Bromine was only partially soluble in it, and it was not possible to obtain appreciable hypobromite, as indicated by very weak absorptions in the 320–340-nm region. Methylene chloride also proved to be unsuitable. Attempts with this solvent gave solutions with a pronounced acetic acid odor, suggesting that the hypobromite is unstable and yields acetoxy radicals which abstract hydrogens from the solvent.

A method for determining the melting point of acetyl hypobromite could not be devised.

On one occasion, when a flask containing some residue of the crystals was held in the hand, the crystals decomposed with an audible "pop" and a small puff of smoke. During another experiment approximately 50 mg of the crystals was placed on a hot plate and only minor spattering was observed. Nevertheless, as a precaution, the isolation of large quantities (>5 g) of solid acetyl hypobromite should be performed with adequate shielding.

**Registry No.**—Acetyl hypobromite, 4254-22-2; silver acetate, 563-63-3; bromine, 7726-95-6.

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## Quinazolines. XIII. Synthesis of Polycyclic 2,4-Diaminopyrimidines from Aromatic Amine Hydrochlorides and Sodium Dicyanamide[1,2]

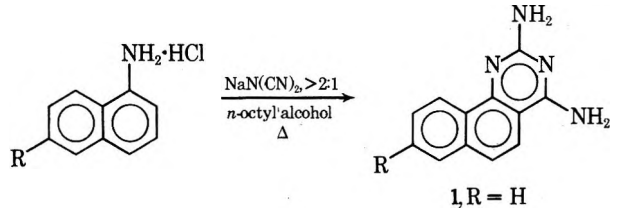
Andre Rosowsky* and Nickolas Papathanasopoulos

*The Children's Cancer Research Foundation and the Department of Biological Chemistry, Harvard Medical School, Boston, Massachusetts 02115*

*Received May 14, 1974*

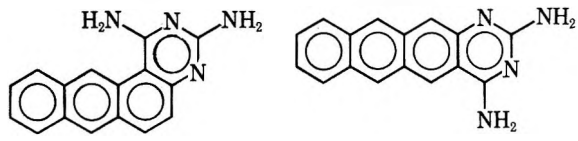
In an earlier communication, $N^1$,$N^5$-bis(2-naphthyl)biguanide hydrochlorides were reported to undergo a novel ring closure reaction upon being heated briefly in a high-boiling inert solvent such as diphenyl ether.[3] Cyclization proceeded in an angular manner, *via* electrophilic attack at the more reactive $\alpha$ position of the naphthalene ring, giving 1,3-diaminobenzo[*f*]quinazolines. Subsequently, a modified procedure was reported, whereby a variety of substituted 1,3-diaminobenzo[*f*]quinazolines could be generated in a single step merely on treatment of the appropriate 2-naphthylamine hydrochlorides with excess sodium dicyanamide in refluxing *n*-octyl alcohol, without isolation of the intermediate biguanide salts.[4] Inasmuch as this reaction offered an extremely attractive route to otherwise difficultly accessible condensed 2,4-diaminopyrimidine derivatives, it became of interest to investigate a representative number of aromatic amines with respect to the ease and direction of cyclization. In the present note, we should like to describe the successful use of 1-naphthylamine, 6-chloro-1-naphthylamine, 2-aminoanthracene, 2-aminophenanthrene, and 3-aminophenanthrene in this connection.

As indicated in Table I, 1-naphthylamine and 6-chloro-1-naphthylamine afforded 2,4-diaminobenzo[*h*]quinazoline (**1**) and 2,4-diamino-8-chlorobenzo[*h*]quinazoline (**2**) in yields closely approximating the value obtained with 2-naphthylamine under similar conditions.



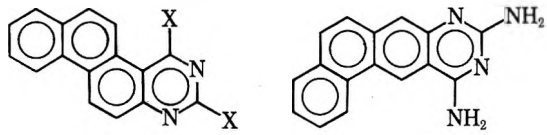

**1**, R = H
**2**, R = Cl

The reaction of 2-aminoanthracene gave a product which was formulated as 1,3-diaminonaphtho[2,3-*f*]quinazoline (**3**) rather than the alternative isomer 2,4-diaminonaphtho[2,3-*g*]quinazoline (**4**) on the basis of the well-documented preference of this polycyclic aromatic amine for angular cyclization.[5] Moreover, the lack of ultraviolet absorption above 390 nm in ethanol (Table II) militated against structure **4** because a linear tetracyclic nitrogen heterocyclic derivative of this type would be expected to display bands at much longer wavelength.[6]




**3** **4**

The reaction of 2-aminophenanthrene with sodium dicyanamide occurred in 32% yield, giving a nearly colorless product which was formulated as 1,3-diaminonaphtho[2,1-*f*]quinazoline (**5**). The alternative isomer, 2,4-diaminonaphtho[1,2-*g*]quinazoline (**6**) was rejected from consideration because the longest wavelength peak in the ultraviolet spectrum of the product appeared at only 370 nm, which is inconsistent with a structure containing three linear aromatic rings.[6] Furthermore, 2-aminophenanthrene is known to undergo preferential angular ring closure in a number of instances, including the Skraup, modified Doebner, and Conrad–Limpach reactions.[7,8]




**5**, X = $NH_2$
**9**, X = OH

**6**

The reaction of 3-aminophenanthrene was carried out with great interest because the product of angular cyclization, 1,3-diaminonaphtho[1,2-*f*]quinazoline (**7**), would represent an unusual, highly hindered type of condensed 2,4-diaminopyrimidine. Unlike the 2-isomer, 3-aminophenanthrene has been reported to be capable of undergoing cyclization angularly *or* linearly, depending on the particular reaction studied. Thus, while Skraup and Conrad–Limpach reactions give rise to "normal" angular products in accor-

**Table I**
**Condensed 2,4-Diaminopyrimidines Prepared from Arylamine Hydrochlorides and Sodium Dicyanamide[a]**

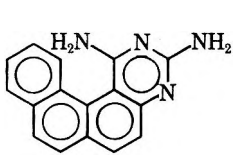
| Arylamine·HCl | Reflux time, hr | Product | Yield, % | Mp, °C | Calcd, % C | Calcd, % H | Calcd, % N | Found, % C | Found, % H | Found, % N |
|---|---|---|---|---|---|---|---|---|---|---|
| 1-Naphthylamine·HCl (552-46-5) | 40 | **1** (33987-13-2) | 32 | 282–284[b] | 68.55 | 4.79 | 26.65 | 68.35 | 4.68 | 26.76 |
| 6-Chloro-1-naphthylamine·HCl (52306-16-8) | 18 | **2**[c] (52374-28-4) | 38 | 254–255 | 58.90 | 3.71 | 22.90 | 58.69 | 3.68 | 22.87 |
| 2-Aminoanthracene·HCl (32666-78-7) | 24 | **3** (52306-18-0) | 40 | 261–263 | 73.82 | 4.64 | 21.52 | 73.92 | 4.64 | 21.41 |
| 2-Aminophenanthrene·HCl (52306-17-9) | 20[d] | **5** (52306-19-1) | 32 | 248–251 | 73.82 | 4.64 | 21.52 | 73.90 | 4.43 | 21.52 |
| 2-Aminophenanthrene·HCl | 18[e] | **9** (52306-20-4) | 32 | >360 | 73.27 | 3.84 | 10.68 | 73.29 | 4.15 | 10.72 |
| 3-Aminophenanthrene·HCl (5345-92-6) | 20 | **8** (52306-21-5) | 8 | 235–237 | 73.82 | 4.64 | 21.52 | 73.72 | 4.75 | 21.35 |

[a] Registry no. are in parentheses beneath compound. [b] This compound has also been synthesized from 1-tetralone by condensation with cyanoguanidine, followed by palladium-charcoal dehydrogenation [S. K. Sengupta, S. K. Sengupta, S. Chatterjee, H. K. Protopapa, and E. J. Modest, *J. Org. Chem.*, 37, 1323 (1972)]. [c] Cl: calcd, 14.49%; found, 14.76%. [d] Standard reaction conditions (see Experimental Section). [e] Stoichiometric proportions (1:2 molar ratio of sodium dicyanamide to 2-aminophenanthrene hydrochloride).

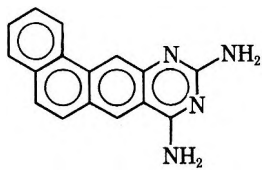
**Table II**
**Ultraviolet Absorption Spectra of Condensed 2,4-Diaminopyrimidines**

| Compd | EtOH $\lambda_{max}$, nm | EtOH $\epsilon \times 10^{-3}$ | EtOH (pH 1) $\lambda_{max}$, nm | EtOH (pH 1) $\epsilon \times 10^{-3}$ |
|---|---|---|---|---|
| 3 | 223 | 34.5 | 228 | 39.2 |
| | 243 | 24.1 | 265 | 49.9 |
| | 273 | 37.6 | 295 | 24.8 |
| | 282 | 34.0 | 305 sh | 18.3 |
| | 293 | 47.6 | 340 | 5.7 |
| | 304 | 41.9 | 357 | 5.4 |
| | 318 sh | 9.1 | 388 | 4.2 |
| | 337 | 8.5 | | |
| | 352 | 4.7 | | |
| | 388 | 2.9 | | |
| 5 | 261 | 53.8 | 274 | 32.9 |
| | 277 | 40.1 | 282 sh | 29.7 |
| | 284 infl | 34.1 | 313 | 12.0 |
| | 304 infl | 11.9 | 364 | 2.1 |
| | 329 | 10.5 | 380 | 2.4 |
| | 353 infl | 5.1 | | |
| | 370 | 3.8 | | |
| 8 | 255 | 27.2 | 221 | 44.6 |
| | 261 | 28.0 | 232 | 33.5 |
| | 278 | 26.3 | 240 | 29.4 |
| | 298 | 30.3 | 284 | 27.5 |
| | 322 | 11.1 | 290 | 26.7 |
| | 335 | 6.4 | 310 | 10.9 |
| | 378 | 2.9 | 330 | 4.6 |
| | 394 | 3.2 | 365 | 3.0 |
| | | | 384 | 2.7 |

dance with Marckwald's rule, the Ullmann–Fetvadjian reaction (with 2-naphthol and formaldehyde) leads predominantly to a linear product *via* cyclization on the $\beta$ position.[9] Apparently, when the energy of the transition state for $\alpha$ cyclization is sufficiently high (for steric reasons, for example), the "normal" process is interdicted and linear products are formed. In the present instance, the reaction of 3-aminophenanthrene gave an 8% yield of a single isomer which was intensely yellow in color (*cf.* the lack of color in **5**). The longest wavelength ultraviolet absorption band occurred at 394 nm, a value consistent with the presence of three linear aromatic rings.[6] On the basis of the low yield and ultraviolet spectral data, we believe the product to be 2,4-diaminonaphtho[2,1-*g*]quinazoline (**8**) rather than **7**. This is the first observed instance of a bisarylbiguanide cyclization proceeding *via* attack at the $\beta$ position of a naphthalene ring in preference to the $\alpha$ position.




**7**




**8**

The use of a *ca.* 2:1 molar ratio of sodium dicyanamide to arylamine hydrochloride in the reactions described above merits comment, inasmuch as this represents a fourfold excess over the stoichiometric amount required for the formation of a bisarylbiguanide salt.[3] In actual fact, the use of stoichiometric proportions (*i.e.*, a 1:2 molar ratio of sodium dicyanamide to arylamine hydrochloride) in this modified version of the bisarylbiguanide cyclization does *not* permit isolation of the desired products. Thus, as indicated in Table I, the reaction of 2-aminophenanthrene performed in the absence of excess sodium dicyanamide gave exclusively 2,4-dihydroxynaphtho[2,1-*g*]quinazoline (**9**), no diamino derivative being recovered on work-up. It appears that sufficient acid is present in the medium to effect hydrolysis of the initially formed diamine on prolonged reflux in *n*-octyl alcohol. This was verified by the observation that heating of the diamine in boiling *n*-octyl alcohol in the presence of a small amount of acid afforded the dihydroxy derivative rapidly and in high yield. When the molar ratio of sodium dicyanamide to arylamine hydrochloride was 1:1, the product turned out to be an approximately 1:1 mixture of the diamine **5** and the dihydroxy compound **9**. An effort was also made to carry out the reaction with a stoichiometric amount of sodium dicyanamide but in the presence of sodium acetate. Under these conditions no cyclized product was recovered at all, probably because neutralization of the arylamine salt had occurred before bisarylbiguanide formation could take place. A systematic evaluation of the effect of other bases was not made, but we believe that the success of the reaction when excess sodium dicyanamide is present probably stems from the ability of this weak base to function as a selective acid scavenger without interfering with biguanide formation or ring closure.

It is also of interest to note that condensed 2,4-diaminopyrimidines were not obtained on reaction of aniline, 1-methyl-2-naphthylamine, or 1-aminopyrene hydrochloride with excess sodium dicyanamide. With 1-methyl-2-naphthylamine, cyclization would have had to occur by attack at the unfavored $\beta$ position. With aniline hydrochloride, it appears that decomposition of the intermediate $N^1,N^5$-bisarylbiguanide salt takes place in preference to ring closure. With 1-aminopyrene, we believe that the low basicity of the amino group[10] and the unreactive character of the 2 position[11] conspire to block the reaction.

## Experimental Section[12]

**Preparation of Arylamines.** 1-Naphthylamine and 2-aminophenanthrene are commercially available (Aldrich Chemical Co., Inc.). 6-Chloro-1-naphthylamine[13-15] was obtained from 5-nitro-2-naphthyamine[16] *via* the known two-step sequence involving successively a Sandmeyer reaction and reduction with stannous chloride.[15] 2-Aminophenanthrene was prepared from 2-acetylphenanthrene[17] by treatment with sodium azide in trichloroacetic acid as described by Campbell and Temple.[18] 3-Aminophenanthrene was prepared similarly from 3-acetylphenanthrene,[17] with the exception that with this isomer a violent exothermic effect was observed unless care was taken to conduct the Curtius reaction at a temperature not exceeding 50–52°. 1-Methyl-2-naphthylamine was synthesized from 1-methyl-2-naphthol *via* a Bücherer reaction as reported previously.[19] 1-Aminopyrene was obtained from 1-nitropyrene (Koch-Light Laboratories, Ltd.) on reduction with stannous chloride.[20] All the foregoing arylamines were isolated in the form of hydrochloride salts by dissolving the free base in $Et_2O$, saturating the solution with dry gaseous HCl at 0°, and washing the filtered precipitate thoroughly with $CH_2Cl_2$. The hydrochloride salts were not purified further prior to reaction with sodium dicyanamide.

**Reaction of Arylamine Hydrochlorides with Sodium Dicyanamide. Standard Procedure.** A well-stirred suspension of the amine hydrochloride (0.1 mol) and sodium dicyanamide[21] (0.20–0.26 mol) in *n*-octyl alcohol (100–300 ml) was heated under reflux for 18–40 hr (Table I). The mixture was filtered while hot (or after cooling), the filter cake was extracted with $CH_2Cl_2$, and the combined *n*-octyl alcohol and $CH_2Cl_2$ solutions were saturated with dry HCl gas and stored in the cold. After several hours, the precipitated hydrochloride salt was collected, washed with $CH_2Cl_2$, and redissolved in boiling $H_2O$ or dilute HCl. Treatment with decolorizing carbon and basification with $NH_4OH$ or NaOH regenerated the free base, which was purified further by recrystallization from aqueous or anhydrous EtOH. In the preparation of **3**, the original filter cake, which proved to contain most of the product, was digested thoroughly with boiling $H_2O$, washed with $CH_2Cl_2$, and recrystallized from *n*-butylamine (decolorizing carbon); hydrochlo-

ride salt formation was omitted in this instance. The yields and physical constants of the products are given in Table I.

**Registry No.**—Sodium dicyanamide, 1934-75-4.

## References and Notes


(1) This investigation was supported in part by Research Grant C6516 from the National Cancer Institute, National Institutes of Health, U.S. Public Health Service.
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(12) Ultraviolet spectra were measured with Cary Model 11 and Model 15 spectrophotometers. Infrared spectra were taken in KCl disks with a Perkin-Elmer Model 137B double-beam recording spectrophotometer. Analytical samples were dried in an Abderhalden apparatus over $P_2O_5$, generally at 70–100° (0.05 mm). Melting points were measured in Pyrex capillary tubes in a modified Wagner–Meyer apparatus [E. C. Wagner and J. F. Meyer, *Ind. Eng. Chem., Anal. Ed.*, **10**, 584 (1938)] or in a Mel-Temp heating block (Laboratory Devices, Inc., Cambridge, Mass.), and are uncorrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn., and Werby Laboratories, Boston, Mass.
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(21) This material was obtained through the courtesy of Dr. L. C. Lane, American Cyanamid Co., Stamford, Conn., and was purified as described in the literature [W. Madelung and E. Kern, *Justus Liebigs Ann. Chem.*, **421**, 1 (1922)]. The importance of using purified material is critical, as we have found that sodium dicyanamide contaminated with sodium bromide fails to take part in this reaction.


# On the Reaction of α-Diazo Ketones with *m*-Chloroperoxybenzoic Acid

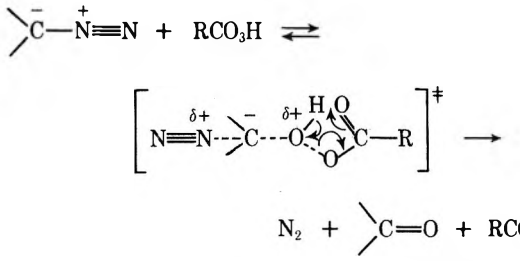

Ruggero Curci,* Fulvio DiFuria, Joseph Ciabattoni,[1] and Paul W. Concannon[1]

*Centro di Studio di Meccanismi di Reazioni Organiche del C.N.R., Istituto di Chimica Organica, University of Padova, 35100 Padova, Italy*


*Received April 29, 1974*

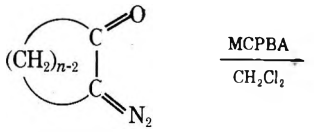
In a previous paper[2] we have shown that diazodiphenylmethane $Ph_2C{=}N_2$ and substituted diazodiphenylmethanes react with peroxy acids to afford the corresponding diaryl ketones in high yield.

On the basis of kinetic evidence, a reaction mechanism was proposed which involves attack by the nucleophilic carbon atom of the diazo group on the peroxide O–O bond.[2]

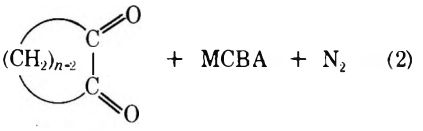


$$N_2 + \text{>C=O} + RCO_2H \qquad (1)$$

Therefore, at variance with what was found for carboxylic acids,[3] it appears that peroxy acids transfer "electropositive" oxygen and not $H^+$ to the diazo group. We now report that α-diketones are produced in the reaction of some cyclic α-diazo ketones **1a–e** and of acyclic 3-diazo-2-butanone $CH_3CN_2COCH_3$ (**2**) with *m*-chloroperoxybenzoic acid (MCPBA) in the mole ratio of 1:1, in $CH_2Cl_2$ at 25° (eq 2).



**1a**, $n = 6$; **1b**, $n = 8$; **1c**, $n = 9$; **1d**, $n = 10$; **1e**, $n = 12$



Yields and kinetic data are shown in Table I. Under the conditions given, the yields of the corresponding α-diketones were essentially quantitative from **1a**, **1d**, **1e**, and **2**. The yields were considerably less with **1b** and **1c** as starting materials, but substantial amounts of suberic and azelaic anhydride, respectively, appeared in the reaction mixtures. These anhydrides undoubtedly arise from the initially formed α-diketones in a subsequent competitive reaction with MCPBA. It is known, in fact, that α-diketones react with peroxy acids in organic solvents[4] and with $HO_2^-$ in aqueous media[5] to yield the corresponding anhydrides, presumably *via* a Baeyer–Villiger type mechanism.[6]

Indeed, in independent experiments we have verified that 1,2-cyclononanedione, 1,2-cyclooctanedione, and also 2,3-butanedione (biacetyl) all give the corresponding anhydrides in nearly quantitative yields (glc, ir) when allowed to react with MCPBA in $CH_2Cl_2$.

**Table I**
**Yields and Rates of Reaction of Some α-Diazo Ketones with *m*-Chloroperoxybenzoic Acid in Methylene Chloride at 25°**

| Compd | % yield of[a] α-diketone | $10^2 k_2$,[b] $M^{-1}$ sec$^{-1}$ |
|---|---|---|
| **1a** | 99 (glc) | 16.8 |
| **1b** | 40 (isol.)[c] | 20.5 |
| **1c** | 35 (glc)[c] | 30.0 |
| **1c** | 30 (isol.)[c] | 30.0 |
| **1d** | 95 (isol.) | 12.0 |
| **1e** | 92 (isol.) | 4.27 |
| **2** | 96 (glc) | 5.52 |

[a] As determined (±5%) by glc analysis or by isolating (ref 2) and weighing the α-diketone, after reacting the diazo compound with MCPBA in equimolar amounts. [b] Evaluated (±3%) as $k_1/[\text{MCPBA}]_0$, from pseudo-first-order kinetic experiments. [c] Ir analysis of reaction mixtures and comparison with authentic samples showed that the α-diketone produced was accompanied by 25–30% of the parent anhydride, while 20–25% of the α-diazo ketone starting material had remained unreacted.

The absence of rearrangement[7,8] or transannular reaction products[9] in detectable amounts from the oxidation of cyclic α-diazo ketones suggest that mechanisms involving carbene or cation intermediates[2] are unlikely.

In the series of medium-ring α-diazo ketones examined the rates pass through a maximum for $n = 9$. However, the overall differences in rate are small and might easily be ascribed to transition-state and/or ground-state conformational effects. A recent dnmr study of **2** has revealed that this compound exists in $CDCl_3$ solutions as an equilibrium mixture of rapidly interconverting s-*E* (transoid) and s-*Z* (cisoid) conformers;[10] at 25° the ratio [s-*E*]/[s-*Z*] is *ca.* 3.3.[10] This finding is in good agreement with the observed dipole moment of **2** ($\mu = 2.45$ D) and the calculated dipole moments of its s-*Z* and s-*E* forms (3.9 and 1.7 D, respectively).[11]

We have measured the dipole moments of cyclic **1a** and **1e** and found $\mu = 3.9$ and 2.15 D, respectively. Thus, in the series of medium-ring α-diazo ketones **1a–e** one apparently proceeds from a situation where the cisoid form is highly prevalent over the transoid to the opposite. Kinetic data, however, show that **1e** react with MCPBA at nearly the same rate as **2**, and only *ca.* four times slower than **1a**. This is not surprising since cisoid and transoid forms of α-diazo ketones would be expected to display similar nucleophilic reactivity in the absence of severe steric hindrance and/or conformational effects. In fact, coplanarity of the O=C—C—N≡N moiety is required for maximum pπ delocalization; therefore, the fractional negative charge on carbon part of the CNN fragment should be nearly the same for undistorted *E* and *Z* forms.[12]

It is interesting to compare the trend of relative rates with ring size for the oxidation of cyclic α-diazo ketones by MCPBA with the pattern observed for reactions involving other medium-ring compounds (Figure 1). At variance with

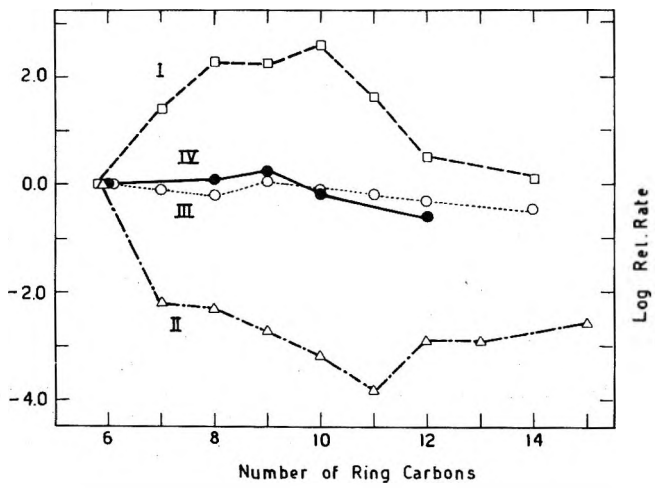
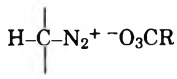
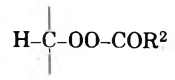



**Figure 1.** Comparison of relative rate pattern with ring size for the acetolysis of cycloalkyl tosylates (I), borohydride reduction of cycloalkanones (II), and CsCHA catalyzed tritio deprotonation of cycloalkanes (III) with the oxidation of 2-diazocycloalkanones by MCPBA (IV).

reactions I and II,[13] which represent rather clear-cut examples of, respectively, $sp^3 \rightarrow sp^2$ and $sp^2 \rightarrow sp^3$ rehybridization at the reaction center, the MCPBA oxidation of medium-ring α-diazo ketones is little influenced by ring size. The pattern resembles that observed for the CsCHA-catalyzed tritio deprotonation of cycloalkanes (reaction III).[14] Thus, for both reaction III and the MCPBA oxidation of α-diazo ketones (reaction IV), transition states should have conformations only little different from ground states.[15] In any case, mechanisms involving formation of intermediate



ion pairs and of unstable peroxy esters



should be dismissed as this would involve $sp^2 \rightarrow sp^3$ rehybridization at the reaction center.

## Experimental Section

**General.** Melting and boiling points were not corrected. Nmr spectra were recorded on a Bruker HFX-10 spectrometer (90 MHz); chemical shifts were measured downfield from TMS internal standard. Ir spectra were taken on a Perkin-Elmer Model IR-457 instrument and uv–visible spectra on a Cary 15 spectrophotometer. Dipole moments were determined by the method of Hedestrand;[16] dielectric constants of solutions were measured at 20° by using a heterodyne apparatus at a frequency of 1 MHz. Molar refractions were calculated from Vogel's increments.[11] Analytical glc was performed on a Varian-Aerograph Model 1520 instrument equipped with tc detector by using a 6 ft × ⅛ inch o.d. column (5% FFAP on Chromosorb G AW-DMCS, 80–100 mesh).

**Materials.** The α-diazo ketones and the α-diketones employed were prepared according to reported methods.[8,17-19] Their physical constants and ir spectra agreed with data reported in the literature. **2-Diazocyclohexanone:** bp 50–51° (0.3 mm); vis max ($CH_2Cl_2$) 400 nm (ε 20); nmr ($CDCl_3$) δ 2.74 (m, 2, O=$CCH_2$), 2.30 (m, 2, $N_2$=$CCH_2$), and 1.78 ppm (m, 4, $CH_2$); μ ($CCl_4$) 3.90 D, ${}_{\infty}P_2$ 347.3 and $R_D$ 32.6 $cm^3$ $mol^{-1}$; ir ($CCl_4$) 2090 (C=$N_2$) and 1640 $cm^{-1}$ (C=O). **2-Diazocycloctanone:** oil; vis max ($CH_2Cl_2$) 395 nm (ε 16); nmr ($CDCl_3$) δ 2.53 (m, 4, =$CCH_2$) and 1.62 ppm (m, 8, $CH_2$); ir ($CCl_4$) 2085 (C=$N_2$) and 1635 $cm^{-1}$ (C=O). **2-Diazocyclononanone:** oil; vis max ($CH_2Cl_2$) 395 nm (ε 16); nmr ($CDCl_3$) δ 2.50 (m, 4, =$CCH_2$) and 1.60 ppm (m, 10, $CH_2$); ir ($CCl_4$) 2085 (C=$N_2$) and 1630 $cm^{-1}$ (C=O). **2-Diazocyclodecanone:** mp 58–59° (lit.[8] 56.5–57°); vis max ($CH_2Cl_2$) 390 nm (ε 25); nmr ($CDCl_3$) δ 2.76–2.42 (m, 4, =$CCH_2$) and 1.49 ppm (broad, 12, $CH_2$); ir ($CCl_4$) 2085 (C=$N_2$) and 1645 $cm^{-1}$ (C=O). **2-Diazocyclododecanone:** mp 43–44° (lit.[17] 42–43°); vis max ($CH_2Cl_2$) 410 nm (ε 28); nmr ($CDCl_3$) δ 2.69 (m, 2, O=$CCH_2$), 2.22 (m, 2, $N_2$=$CCH_2$), and 1.30 ppm (broad, 16, $CH_2$); μ ($CCl_4$) 2.15 D, ${}_{\infty}P_2$ 158.3 and $R_D$ 60.6 $cm^3$ $mol^{-1}$; ir ($CCl_4$) 2065 (C=$N_2$) and 1640 $cm^{-1}$ (C=O). **3-Diazo-2-butanone:** bp 35–40° (12 mm);[20] vis max ($CH_2Cl_2$) 415 nm (ε 8); nmr ($CDCl_3$) δ 2.20 (broad, s, 3, O=$CCH_3$) and 1.97 ppm (broad, s, 3, $N_2$=$CCH_3$);[10] ir ($CCl_4$) 2070 (C=$N_2$) and 1645 $cm^{-1}$ (C=O). Commercial (Schuchardt) ***m*-chloroperoxybenzoic acid** was purified following a given method[21] to a purity of 99%+ (iodometric assay), mp 92–93°.[21]

**Kinetics.** Kinetic runs were performed under pseudo-first-order conditions with $[MCPBA]_0$ being usually from 10- to 20-fold excess over the initial concentration of the diazo ketone. The change of absorbance was monitored in the great majority of cases at or near the wavelength of maximum absorption in the visible for each diazo compound.[2] A Gilford Model 2400 recording spectrophotometer equipped with thermostatic cell holder (±0.5°) was employed. Rate constant values which appear in Table I are averages from three or more independent runs.

**Acknowledgments.** Thanks are due to Professors G. Modena and J. O. Edwards for many helpful discussions. We also wish to thank the Committee on International Exchange of Persons (Washington, D/C.) for the grant of Fulbright Senior Scholarships to R.C. (summer 1971) and to J.C. (Oct. 1972–March 1973).

**Registry No.**—**1a**, 3242-56-6; **1b**, 14088-64-3; **1c**, 18208-20-5; **1d**, 18208-23-6; **1e**, 14078-83-2; **2**, 14088-58-5; *m*-chloroperoxybenzoic acid, 937-14-4.

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(15) As pointed out by a referee, the similarity in the log relative rates *vs.* number of ring carbons profile observed for reactions III and IV might be partly fortuitous since tritio deprotonation of cycloalkanes catalyzed by cesium cyclohexylamide (CsCHA) is an $sp^3 \rightarrow sp^3$ case, whereas MCPBA oxidation of $\alpha$-diazo ketones appears to be $sp^2 \rightarrow sp^2$ from reactants to products. For the latter reactions, however, an $sp^3 \rightarrow sp^3$ case can also be envisaged. In fact, the reaction center should be close to an $sp^3$ hybrid in the transition state according to the mechanism proposed (eq 1), and for the $>\overset{+}{C}-\overset{-}{N}\equiv N$ group in the ground state there should be structures with $sp^3$ hybridized carbon only little different in energy than $sp^2$ hybrids (ref 3).
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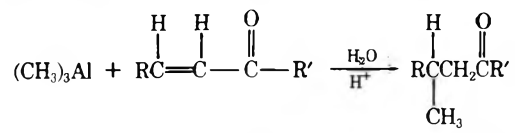
## Transition Metal Catalyzed Conjugate Methylation of $\alpha,\beta$-Unsaturated Ketones by Trimethylaluminum and Lithium Tetramethylaluminate

Eugene C. Ashby* and George Heinsohn

*School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332*

*Received June 18, 1974*

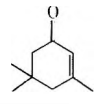
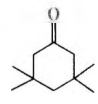
Recently there has been an increased interest in methods for effecting 1,4 addition to $\alpha,\beta$-unsaturated systems.[1] In addition to lithium alkylcuprate and copper-catalyzed Grignard reagent addition to $\alpha,\beta$-unsaturated compounds, more recent methods show great promise. Brown and Kabalka[2,3] have found that trialkylboranes undergo 1,4 addition to a variety of $\alpha,\beta$-unsaturated substrates *via* a free radical chain process. More recently Kabalka and Daley[4] found that trialkylaluminum compounds exhibit analogous behavior when photolyzed at −78° or in the presence of catalytic amounts of oxygen, and were able to demonstrate the intermediacy of free radical species. Because of our interest in the area of transition metal catalyzed reactions of main group organometallic reagents, we were particularly interested in the recent report by Mole, *et al.*,[5] concerning nickel catalyzed conjugate addition of trimethylaluminum to $\alpha,\beta$-unsaturated ketones. It would appear that this




(1)

method represents a convenient and potentially economic route to 1,4-addition products, particularly if the reaction is stereoselective. In an attempt to determine the stereoselectivity of this reaction and in addition to determine the applicability of this method to 1,4-conjugate addition to prostaglandin precursors, we synthesized 4-methyl-2-cyclopentenone, 4-acetoxy-2-cyclopentenone, and 4-methyl-2-cyclohexenone. We wish now to report the results of not only $(CH_3)_3Al$ addition, but also $LiAl(CH_3)_4$ addition to a variety of $\alpha,\beta$-unsaturated ketones in order to provide information concerning the scope and stereochemistry of these reactions.

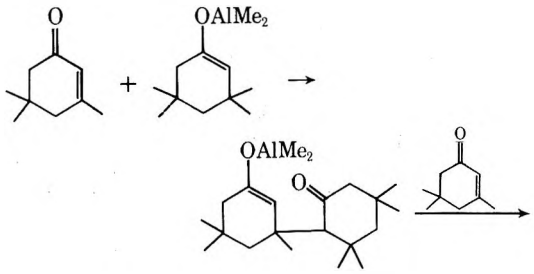
**Table I**
**Reaction of Trimethylaluminum with Isophorone in the Presence of Nickel Acetylacetonate**

| Time, min |  (mmol) |  (mmol) | Material balance, % |
|---|---|---|---|
| 0 | 1.000 | 0.000 | 100 |
| 1 | 0.300 | 0.680 | 98 |
| 5 | 0.075 | 0.838 | 91 |
| 30 | 0.000 | 0.845 | 85 |
| 60 | 0.000 | 0.863 | 86 |
| 120 | 0.000 | 0.850 | 84 |

### Results and Discussion

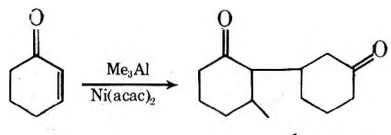
Table I presents data obtained by sequential quenching of aliquots from the reaction of trimethylaluminum with 3,5,5-trimethyl-2-cyclohexenone (isophorone) in the presence of 3.0 mol % nickel acetylacetonate [$Ni(acac)_2$].

Several features of Table I are striking. While Mole, *et al.*,[5] suggest typical reaction times of 18 hr for the reaction of $\alpha,\beta$-unsaturated ketones with trimethylaluminum in the presence of $Ni(acac)_2$, our data indicate that methylation is essentially complete in less than 30 min. The only other product formed is polymer and its formation seems to occur only while unreacted isophorone is present. This suggests that the polymer is formed by Michael addition to the aluminum enolate of the product to the $\alpha,\beta$-unsaturated ketone according to eq 2. The isolation of 1 after




(2)

nickel acetylacetonate catalyzed addition of trimethylaluminum to 2-cyclohexenone provides additional support for this suggestion.




(3)

1

In Table II are listed the results obtained for the catalyzed reaction of trimethylaluminum with isophorone and 2-cyclohexenone. In all cases the starting material was entirely consumed and no other volatile products were formed. It is apparent from the data that ether is the solvent of choice and that cupric acetylacetonate is an effective catalyst. Although Mole[5] suggests that cobalt acetylacetonate was an effective catalyst, in our hands only starting material was recovered after attempted reaction of isophorone with trimethylaluminum in the presence of 3 mol % cobalt acetylacetonate. This result, however, suggests partici-

**Table II**
**Transition Metal Catalyzed Reaction of Isophorone (2) and 2-Cyclohexenone (3) with Trimethylaluminum[a]**

| Run | Ketone | Catalyst[b] | Solvent | Time, hr | Temp, °C | % 1,4 addition | % 1,2 addition |
|---|---|---|---|---|---|---|---|
| 1 | 2 | $Ni(acac)_2$ | $Et_2O$ | 1 | 0 | 86 | |
| 2 | 2 | $Ni(acac)_2$ | $Et_2O$ | 2 | 22 | 86 | |
| 3 | 2 | $Ni(acac)_2$ | THF | 1 | 0 | 58 | |
| 4 | 2 | $Cu(acac)_2$ | $Et_2O$ | 2 | 22 | 85 | |
| 5 | 3 | $Ni(acac)_2$ | $Et_2O$ | 1 | 0 | 44 | 7 |
| 6 | 3 | $Ni(acac)_2$ | $Et_2O$ | 2 | −30 | 29 | 6 |
| 7 | 3 | $Ni(acac)_2$ | THF | 2 | 0 | 41 | 6 |
| 8 | 3 | $Ni(acac)_2$ | PhH | 2 | 0 | 35 | 8 |

[a] Each run employed 1.0 mmol of $Me_3Al$, 1.0 mmol of ketone, and 0.03 mmol of metal acetylacetonate in 10 ml of solvent. [b] Added as *ca.* 0.03 *M* solution in THF.

**Table III**
**Transition Metal Catalyzed Reaction of Isophorone with Lithium Tetramethylaluminate[a]**

| Run | Catalyst | Time, hr | Temp, °C | % 1,4 addition | % 1,2 addition | % recovered ketone |
|---|---|---|---|---|---|---|
| 9 | $Ni(acac)_2$ | 2 | 22 | 80 | | |
| 10 | $Ni(acac)_2$ | 112 | 22 | 8 | 27 | 61 |
| 11 | $Cu(acac)_2$ | 2 | 22 | 73 | | |
| 12 | $Ni(acac)_2$ | 1 | 0 | 58 | | 18 |
| 13[b] | $Ni(acac)_2$ | 1 | 0 | 29 | | 48 |

[a] Each run employed 1.0 mmol of lithium tetramethylaluminate, 1.0 mmol of isophorone, 0.03 mml of metal acetylacetonate added as a *ca.* 0.03 *M* solution in THF, and 10 ml of ether as solvent. [b] Lithium tetramethylaluminate solution stored for 24 hr and clear supernate employed in this run.

pation by the transition metal since 1,2 addition would have been observed in its absence.[6] As would be expected, polymer formation occurs to a greater extent with 2-cyclohexenone than with isophorone presumably due to less steric hindrance at the terminal carbon atom of the $\alpha,\beta$-unsaturated system. It is noteworthy that reaction of a twofold molar excess of isophorone with trimethylaluminum under conditions otherwise identical with those of entry 2 leads to isolation of 43% of the 1,4 product (based on isophorone) showing that only one methyl group of the organometallic compound is available for reaction.

Table III reports results obtained from transition metal catalyzed reaction of isophorone with lithium tetramethylaluminate (LTA). Except for recovery of starting material from runs 10, 12, and 13, no other volatile products were observed. Conjugate addition with LTA is considerably slower than with trimethylaluminum, the former reaction requiring 2 hr at 22° before all starting material was consumed. Unlike the reactions with trimethylaluminum, cupric acetylacetonate is a less efficient catalyst than the corresponding nickel salt. For optimum results, it is essential that the LTA be used as quickly as possible after preparation from methyllithium and trimethylaluminum. Upon standing, the initially clear solution becomes cloudy and within several hours precipitation is apparent. Although analysis of the clear supernatant solution after precipitation gives a ratio of lithium/aluminum/methyl of 1.00:0.97:3.98, comparison of runs 12 and 13 show that the efficiency of conjugate addition is seriously impaired using this solution. In an experiment employing a twofold molar excess of isophorone under conditions otherwise identical with run 9, 3,3,5,5-tetramethylcyclohexanone was isolated in 41% yield

**Table IV**
**Stereochemistry of Conjugate Methylation of 4-Methyl-2-cyclohexenone**

| Run | Catalyst | Reagent | Time, hr | Temp, °C | % 1,4 addition | % trans | % cis |
|---|---|---|---|---|---|---|---|
| 14 | $Ni(acac)_2$ | $Me_3Al$ | 1 | 0 | 66 | 84 | 16 |
| 15 | $Ni(acac)_2$ | LTA | 2 | 22 | 62 | 87 | 13 |

(based on isophorone) demonstrating that only one methyl group per LTA is available for reaction.

Table IV provides data that demonstrate the stereochemistry of the reaction of the catalyzed conjugate methylation of 4-methyl-2-cyclohexenone by trimethylaluminum and LTA. By way of comparison, Riviere and coworkers[7,8] report formation of 3,4-dimethylcyclohexanone with trans/cis ratio of 72:28 for cuprous chloride catalyzed addition of methylmagnesium bromide to 4-methyl-2-cyclohexenone and trans/cis ratio of 91:9 using $LiCu(CH_3)_2$.[7]

Synthesis of 4-acetoxy- and 4-methyl-2-cyclopentenone provided model prostaglandin systems for the determination of the stereochemistry of transition metal catalyzed 1,4 addition by reaction with $(CH_3)_3Al$ or $LiAl(CH_3)_4$. Unfortunately, under a variety of conditions both of the above ketones produced only polymer.

## Experimental Section

**General.** The metal acetylacetonates used in this study were prepared by refluxing the appropriate metal acetate with 1.5 equiv of 2,4-pentanedione in methanol for 2 hr. The product was isolated by crystallization from methanol. Ether and THF were freshly distilled from $LiAlH_4$. Reaction vessels were flash flamed under nitrogen. Product analyses were performed on an F and M Model 720 gas chromatograph using a 20 ft column of 5% Carbowax 20M on Chromosorb W at a flow rate of 55 ml of He/min.

**Conjugate Methylation with Trimethylaluminum.** To a 50-ml reaction vessel was added sufficient solvent to bring the final volume to 10 ml, substrate ketone (1.0 mmol), and the appropriate metal acetylacetonate (0.03 mmol., *ca.* 1 ml of 0.03 *M* solution in THF). The mixture was brought to the appropriate temperature and trimethylaluminum (1.0 mmol, *ca.* 1 ml of 1 *M* solution in ether) added over a 2-min period causing a yellow to brown color to develop immediately. After the desired period of time, the reaction was quenched with water (*ca.* 0.3 ml) and dried over $MgSO_4$; 1.0 mmol of internal standard was added, and the product was analyzed by gas chromatography. Ethyl benzoate was employed as the standard for reactions involving isophorone, and the glc column temperature was 140°. Under these conditions, retention times of 11.7, 13.5, and 26.1 min were observed for 1,3,5,5-tetramethyl-2-cyclohexenol, 3,3,5,5-tetramethylcyclohexanone, and isophorone, respectively. When 2-cyclohexenone was the substrate, *n*-octyl alcohol was employed as the internal standard and the glc column temperature was 125°. Under these conditions, retention times of 11.2, 13.0, and 20.5 min were noted for 1-methyl-2-cyclohexenol, 3-methylcyclohexanone, and 2-cyclohexenone, respectively. In all cases the identity of products (including adduct 1) was confirmed by comparison with authentic samples.

**Conjugate Methylation with Lithium Tetramethylaluminate.** To a 50-ml reaction vessel was added sufficient solvent to bring the final volume to 10 ml, trimethylaluminum (1.0 mmol, *ca.* 1 ml of 1 *M* solution in ether), and methyllithium (1.0 mmol, *ca.* 1 ml of 1 *M* solution in ether). Without delay the substrate ketone (1.0 mmol) and the appropriate metal acetylacetonate (0.03 *M*, *ca.* 1 ml of 0.03 *M* solution in THF) were added, the latter causing formation of a yellow to brown color. After reaction, water (0.3 ml) was added and the mixture dried ($MgSO_4$); internal standard was added, and the product analyzed as described above.

**Acknowledgment.** We are happy to acknowledge support of this work by the National Science Foundation.

**Registry No.**—$(CH_3)_3Al$, 75-24-1; isophorone, 78-59-1; $Ni(acac)_2$, 3264-82-2; 3,3,5,5-tetramethylcyclohexanone, 14376-79-5; 2-cyclohexenone, 930-68-7; $Cu(acac)_2$, 13395-16-9; lithium tetramethylaluminate, 14281-94-8; 4-methyl-2-cyclohexenone, 5515-

76-4; *trans*-3,4-dimethylcyclohexanone, 28023-45-2; *cis*-3,4-dimethylcyclohexanone, 27922-05-0.

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## Effects of Base Association upon Geometrical Orientation in Elimination from 1-Phenyl-2-propyl Chloride in Potassium *tert*-Butoxide–*tert*-Butyl Alcohol


Sergio Alunni, Enrico Baciocchi,* Renzo Ruzziconi, and Marco Tingoli

*Dipartimento di Chimica, Università di Perugia, 06100 Perugia, Italy*


*Received April 22, 1974*

Base association was clearly shown to exert a strong influence upon positional and geometrical orientation in base-promoted anti $\beta$-eliminations from 2-alkyl halides and arenesulfonates in *t*-BuOH.[1] Regarding geometrical orientation it was observed that base association is responsible for the generally low trans:cis 2-alkene ratios found for the reaction of these substrates with *t*-BuOK. Accordingly, the trans:cis 2-alkene ratios were found to significantly increase when the reaction is carried out in the presence of crown ethers which are able to convert contact ion pairs or ion pair aggregates into separated ions. This trend was suggested to be originated by the larger steric requirements of the associated base.

Interestingly, low trans:cis olefin ratios in *t*-BuOK–*t*-BuOH (especially with respect to those in $EtO^-$–EtOH and $MeO^-$–MeOH) are considered as the "normal pattern" of $\beta$-elimination reactions which proceed *via* an anti mechanism, since, by this mechanism, contact ions are expected to lead to preferential formation of cis olefin.[2] Deviations from this pattern are considered highly indicative of the intervention of a syn mode of $\beta$-elimination, since it is well known[2c] that syn elimination leads nearly exclusively to the trans olefin and is favored by base association.

We wish now to report that similar conclusions do not apply to the elimination reactions of $\beta$-phenyl activated systems. We have studied the $\beta$-elimination reactions of 1-phenyl-2-propyl chloride in *t*-BuOK–*t*-BuOH and found (see Table I) that the *trans*- to *cis*-1-phenylpropene ratio is significantly larger than those in EtONa–EtOH and MeONa–MeOH; a significant decrease of this ratio is obtained using *t*-BuON–*n*-$Bu_4$ or crown ether complexed *t*-BuOK. Clearly, base association plays an important role in determining the trans:cis olefin ratios also in the elimination reactions of 1-phenyl-2-propyl halides; however, the pattern is exactly the opposite of that found for the elimination reactions of nonactivated alkyl halides. This striking difference cannot be attributed to the intervention of a syn mechanism of elimination in the phenyl activated series, since we have evidence that this reaction path is of very little importance in the case of 1-phenyl-2-propyl chloride;[3] it results therefore that the geometrical orientation in the anti eliminations from $\beta$-phenyl activated substrates is influenced by steric effects and/or basicity in a different way from the anti eliminations of nonactivated substrates.

**Table I**
**Trans:Cis Olefin Ratios in the E2 Eliminations from 1-Phenyl-2-propyl Chloride in Various Solvent–Base Systems at 60°** [a]

| Solvent–Base | *trans*- to *cis*-1-Phenylpropene |
|---|---|
| MeOH–MeONa [b] | 23.5 ± 0.1 |
| EtOH–EtONa [c] | 25.0 ± 0.1 |
| *t*-BuOH–*t*-BuOK [d] | 72 ± 5 |
| *t*-BuOH–*t*-BuOK [e] | 45 ± 1 |
| *t*-BuOH–*t*-BuON–*n*-$Bu_4$ [f] | 37.7 ± 0.1 |

[a] Determined by glpc. Each value is the average of at least three determinations. The initial concentration of 1-phenyl-2-propyl chloride was ~0.02 *M*. According to blank experiments the trans:cis ratios are not significantly affected by the isomerization reactions of allylbenzene (formed in a very little amount) and of *cis*- and *trans*-1-phenylpropene. [b] [MeONa] = 2.3 *M*. Reaction time 15 hr. In the absence of MeONa no production of chloride ions was observed after 70 hr. [c] S. Alunni and E. Baciocchi, *Tetrahedron Lett.*, 205 (1973). With EtOK the trans:cis ratio is 28. [d] [*t*-BuOK] = 0.2–0.8 *M*. Reaction time 50–210 min. No appreciable variation of the trans:cis ratio with *t*-BuOK concentration was observed. [e] In the presence of dicyclohexyl-18-crown-6. [*t*-BuOK] = 0.17 *M*. Reaction time 5–15 min. [f] Prepared by mixing 0.3–0.5 *M* *t*-BuOK–*t*-BuOH with appropriate amounts of *n*-$Bu_4NBr$. Reaction time 30–75 min.

At present, we have no explanation of this phenomenon, even though it may be recalled that in the eliminations from $\beta$-phenyl activated substrates the trans/cis ratios derive from differences in the conjugation extent of the phenyl group with the developing negative charge at the $\beta$ carbon in addition to differences in the nonbonded interactions at $C_\alpha$ and $C_\beta$, as it occurs in the resulting olefins. However, it seems important to point out, in the light of this result and the recent data on the leaving group effects,[5] that considerable caution must be exerted in applying conclusions reached from studies of elimination reactions of $\beta$-phenyl activated substrates to the elimination reactions of nonactivated substrates and vice versa.

### Experimental Section

**Materials. 1-Phenyl-2-chloropropane.** A solution of 29 g of thionyl chloride in 125 ml of anhydrous benzene was added at 0° and under stirring to a solution of 25 g of 1-phenyl-2-propanol (Fluka) and 4 g of pyridine in 420 ml of anhydrous benzene. After standing overnight the mixture was refluxed for 3 hr. The mixture was then cooled and washed with cold water, diluted sulfuric acid, 10% solution of sodium bicarbonate, and a solution of sodium thiosulfate. After the mixture was dried on sodium sulfate and the solvent was removed, distillation at reduced pressure gave 16.4 g (55% yield) of 1-phenyl-2-chloropropane, bp 100° (30 mm). *Anal.* Calcd for $C_9H_{11}Cl$: Cl, 22,9. Found: Cl, 22,6.

***cis*-1-Phenylpropene** was prepared by decarboxylation of $\alpha$-metylcinnamic acid, according to a procedure described in the literature,[6] and purified by fractional distillation on a Todd column, bp 65° (12 mm), $n^{22.5}D$ 1.5415 (lit.[6] $n^{20}D$ 1.5430). Its purity (>99.5%) was checked by glpc.

***trans*-1-Phenylpropene** and **allylbenzene** were commercial products (Fluka) purified by distillation. Their purity (glpc) was 99%.

**Dicyclohexyl-18-crown-6 ether** was prepared according to the procedure described by Pedersen.[7]

**Base–Solvent Solution.** Methanol was refluxed with magnesium and resublimed iodine and fractionally distilled. Absolute ethanol was refluxed with sodium and diethyl phthlate and fractionally distilled. *t*-Butylalcohol was distilled after treatment with potassium metal. Solutions of alkoxide were obtained by reactions,

under nitrogen, of freshly cut sodium and potassium metal with the appropriate alcohol.

**Procedure for Product Studies.** A known amount of the halogeno derivative was added, under strong stirring, to a solution of alkoxide in alcohol placed in a flask surrounded by a jacket for the circulation of a thermostating liquid. After a variable time (depending on the reactivity of the substrate and the concentration of alkoxide), the reaction mixture was poured into water and extracted several times with pentane. After the mixture was dried, most of pentane was removed and the resulting solution (~2 ml) was analyzed by glpc.

**Glpc Analysis of Reaction Products.** These analyses were performed on a Model GI, Carlo Erba gas chromatograph, equipped with a flame ionization detector and using nitrogen as a carrier gas. The olefins were nicely separated on a 3.2 × 0.002 m column packed with 20% LAC-728 on 60–80 mesh Chromosorb W, at 70°. The retention times were as follows: allylbenzene, 1350 sec; *cis*-1-phenylpropene, 1980 sec; *trans*-1-phenylpropene, 3100 sec.

For the quantitative analysis of *cis*- and *trans*-1-phenylpropene it was necessary to use different attenuations of the detector signal owing to the large trans:cis olefin ratios generally observed in the present work. The molar response of the trans olefin with respect to the cis olefin was 1.14.

**Acknowledgment.** This work was carried out with the financial support of the Italian National Research Council (C.N.R.).

**Registry No.**—1-Phenyl-2-propyl chloride, 10304-81-1; *trans*-1-phenylpropene, 873-66-5; *cis*-1-phenylpropene, 766-90-5.

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(4) To investigate the influence of the nucleophile basicity on the trans/cis ratios we attempted to study the eliminations from 1-phenyl-2-propyl chloride induced by potassium phenoxide in *t*-BuOH; however, this reaction resulted too slow to be conveniently studied.
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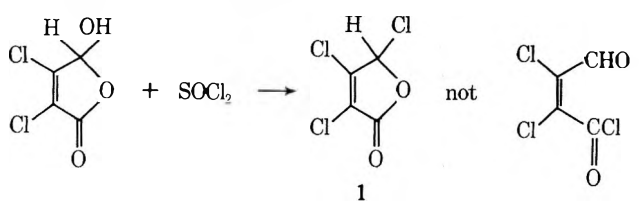
## Trimethyl Phosphite Displacement on Mucochloryl Chloride

K. Wayne Ratts* and W. G. Phillips

*Monsanto Commercial Products Company, Agricultural Division, Research Department, St. Louis, Missouri 63166*

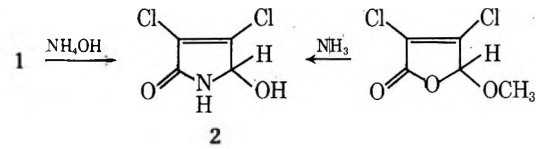
*Received June 11, 1974*

Mucochloryl chloride (**1**), derived from mucochloric acid and thionyl chloride, is a masked acid chloride in that it exists in the 5*H*-2-furanone ring structure.[1] This "pseudo



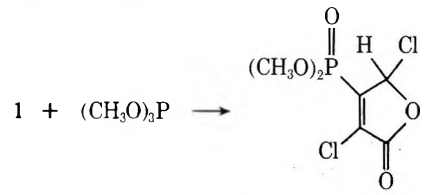
**1**

acid chloride" possesses three potentially reactive halogens. Nevertheless, mucochloryl chloride reacts with ammonium hydroxide to produce the corresponding 5-hydroxy-3,4-dichloropyrrolin-2-one (**2**).[2] The corresponding methyl ester of mucochloric acid upon treatment with ammonia gave the same compound **2**.[3] Consequently the vinylic chloride atoms have not been displaced.



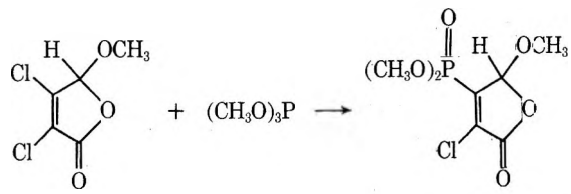
**2**

We wish to report a surprising result observed in an attempted reaction of mucochloryl chloride with trimethyl phosphite. The product of this reaction results from phosphite displacement of the 4-chlorine rather than the 5-chlorine, and is 3,5-dichloro-4-dimethoxyphosphinyl-2,5-dihydrofuran-2-one (**3**). The identity of **3** was established



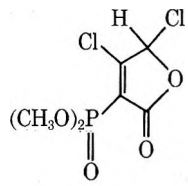
**3**

by its infrared spectrum and comparison of its hydrogen decoupled $^{13}C$ nmr spectrum[4] with 5-methoxy-4-dimethoxyphosphinyl-3-chloro-2,5-dihydrofuran-2-one[5] (**4**). The $sp^3$ methine carbon for **3** could easily be observed and the $^{13}C$–C–P coupling of 12 cps compared favorably to that of **4** where $J$ = 16 cps. A model for one bond $^{13}C$–P coupling, *N*-phosphonomethylglycine,[6] showed $J_{^{13}C-P}$ to be much higher, *i.e.*, 160 cps. The product **3** exhibits a normal lactone carbonyl at 1787 $cm^{-1}$. This eliminates the possibility of the tautomeric furan structure and confirms a 2-furanone structure. Dimethyl phosphite reacts with 5-methoxy-3,4-dichloro-2,5-dihydrofuran-2-one to produce **4**.[5] By



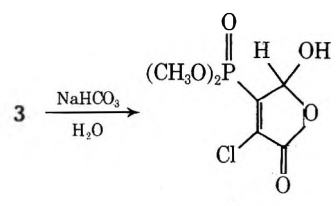
**4**

comparison the reaction of **1** with trimethyl phosphite would produce **3** rather than the positional isomer **5**. Hy-



**5**

drolysis of **3** gave 5-hydroxy-4-dimethoxyphosphinyl-3-chloro-2,5-dihydrofuran-2-one (**6**).[7] Comparison of the H′



**6**

nmr spectra of **3**, **4**, and **6** showed an identical $J_{P-C-C-H}$ coupling constant of 2 cps. This supports the structures given since coupling constants of the P–C–H type are usually much larger.[8]

Carbanion delocalization in the intermediate formed by addition of trimethyl phosphite to C-4 of mucochloryl chloride is undoubtedly a factor in the preference of the reactants for this reaction pathway. Facile reversal to eliminate

chloride from the above described intermediates, followed by dealkylation, produces the observed product. Ammonia, a much harder base than trimethyl phosphite,[9] reacts more readily *via* alternative pathways not requiring intermediates stabilized by strong delocalization. Further developement of these ideas will be presented in future publications.

## Experimental Section

**3,4,5-Trichloro-2,5-dihydrofuran-2-one.**[10] Mucochloric acid (125 g, 0.74 mol) and 473 ml of thionyl chloride containing 2.0 ml of dimethylformamide were heated at 50° with stirring for 5 hr. The mixture was cooled and the excess thionyl chloride removed *in vacuo*. Distillation of the residual oil gave 117 g (84%) of product, bp 91– (6 mm), pmr spectrum ($CDCl_3$) $\delta$ 6.66 (s, 1 H, CH).

**5-Hydroxy-3,4-dichloropyrrolin-2-one (2).** An aqueous mixture of 13.7 ml of concd ammonium hydroxide, 10.6 g of sodium carbonate, and 100 ml of water was cooled in an ice bath to 0–5° and treated dropwise with 18.7 g (0.1 mol) of 3,4,5-trichloro-2,5-dihydrofuran-2-one. The resultant mixture was stirred at room temperature overnight and the tan solid was filtered, washed with cold ethanol, and refluxed with ethyl acetate to give 14.1 g (84%) of product: mp 166–168°; pmr spectrum ($D_3COD$) $\delta$ 5.42 (s, 1 H, CH), 4.70 (s, 2 H, $NH_2$), (DMSO-$d_6$) 5.59 (d, $J$ = 8 Hz, 1 H, OH), 6.92 (d, $J$ = 8 Hz, 1 H, CH), 9.20 (s, 1 H, NH); ir spectrum (Nujol) 1689 $cm^{-1}$ (vs, carbonyl stretching). An identical material was obtained by the procedure of Hill, *et al.*[3]

**3,5-Dichloro-4-dimethoxyphosphinyl-2,5-dihydrofuran-2-one (3).** Mucochloryl chloride (18.7 g, 0.1 mol) and trimethyl phosphite (12.4 g, 0.1 mol) were mixed and let stand overnight. Trimethylphosphite was removed under vacuum on the steam bath and the residue distilled at 87–130° (3 mm) to give 7.5 g (40%) of mucochloryl chloride. The dark pot residue crystallized on cooling. Recrystallization of the residue from chloroform–petroleum ether (bp 30–75°) gave 8.5 g (85%) of 3, mp 90–94°. A second recrystallization gave 6.5 g: mp 96–98°; pmr spectrum ($CDCl_3$) $\delta$ 4.0 (d, $J$ = 12 Hz, 6 H, $CH_3OP$), 6.93 (d, $J$ = 2 Hz, 1 H, CH); ir spectrum ($CHCl_3$) 1787 $cm^{-1}$ (vs, carbonyl stretching); $^{13}C$ nmr spectrum relation to TMS ($d_6$-acetone). $\delta$ 55.1 (s), 88.3 (d, $J$ = 12 cps).

*Anal.* Calcd for $C_6H_7Cl_2O_5P$: C, 27.61; H, 2.70; Cl, 27.17; P, 11.87. Found: C, 27.41; H, 2.51; Cl, 26.98; P, 11.88.

**5-Hydroxy-4-dimethoxyphosphinyl-3-chloro-2,5-dihydrofuran-2-one (6).** To 17 g (0.2 mol) of sodium bicarbonate in 200 ml of water was added 26.1 g (0.1 mol) of 3,5-dichloro-4-dimethoxyphosphinyl-2,5-dihydrofuran-2-one. After stirring 1–2 hr, the mixture was acidified and the solid collected to give 26.0 g (77%) crude product. This solid was recrystallized from benzene and then water to give 5.0 g of product: mp 124–127°; pmr ($CDCl_3$) $\delta$ 3.95 (d, $J$ = 12 Hz, 6 H, $CH_3OP$), 6.06 (br hump, 1 H, OH), 6.36 (3, $J$ = 12 Hz, 1 H, CH).

*Anal.* Calcd for $C_6H_8ClO_6P$: C, 29.69; H, 3.30. Found: C, 29.78; H, 3.36.

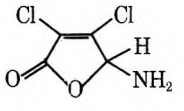
**5-Methoxy-4-dimethoxyphosphinyl-3-chloro-2,5-dihydrofuran-2-one (4).** The procedure of Malinowski, *et al.*,[5] was followed to yield 38.0 g (75%) of product: bp 160–165° (1 mm); pmr ($CDCl_3$) $\delta$ 3.8 (d, $J$ = 12 Hz, 6 H, $CH_3OP$); 3.6 (s, 3 H, $CH_3O$), 6.0 (d, $J$ = 2 Hz, 1 H, CH).

**Registry No.**—**1**, 19714-00-2; **2**, 52500-03-5; **3**, 52500-04-6; **4**, 37031-62-2; **6**, 52500-05-7; mucochloric acid, 766-40-5; thionyl chloride, 7719-09-7; trimethyl phosphite, 121-45-9.

## References and Notes


(1) The nmr spectrum exhibits a single peak for the methine proton at $\delta$ 6.66 in deuteriochloroform inconsistent with an open chain aldehyde–acid chloride.

(2) The nmr and ir spectra of this product suggest this lactam structure [see F. Farina, M. V. Martin, and M. C. Paredes, *Synthesis*, **3**, 167 (1973)]. The isomeric aminolactone **7** and the open chain amide **8** (see ref 3) are not consistent with the spectra.



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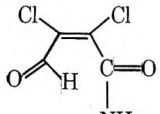

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(3) H. B. Hill and R. W. Cornelison, *Amer. Chem. J.*, **16**, 305 (1894).

(4) We are indebted to J. Schaefer for these $^{13}C$ nmr spectra.

(5) R. Malinowski, J. Kokosinski, and B. Sledzinski, *Rocz. Chim.*, **46**, 39 (1972).

(6) $H_2O_3PCH_2NHCH_2CO_2H$.

(7) This general conversion has been previously demonstrated in the corresponding chlorophthalimidine series; see W. G. Phillips and K. W. Ratts, in press.

(8) Comparable examples have been examined in the phosphonophthalimidine series (see W. G. Phillips and K. W. Ratts, in press).

(9) R. C. Pearson and J. Songstad, *J. Amer. Chem. Soc.*, **89**, 1827 (1967).

(10) F. L. Dunlap, *Amer. Chem. J.*, **19**, 641 (1897).

# Communications

## A New Synthesis of Thiol Esters

*Summary:* New synthetic procedures for the direct preparation of thiol esters from carboxylic acids and thiols using diethyl phosphorocyanidate or diphenyl phosphorazidate are described.

*Sir:* In spite of its potential importance there is still no generalized method for the direct preparation of thiol esters from carboxylic acids and thiols.[1] We now wish to report this transformation, which involves treatment of a carboxylic acid and a thiol with diethyl phosphorocyanidate (DEPC)[2] or diphenyl phosphorazidate (DPPA)[3] in the presence of triethylamine in dimethylformamide solution.

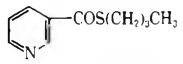
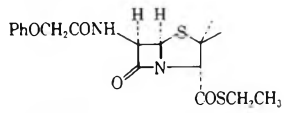
While optimum reaction conditions have yet to be established, the results summarized in Table I reveal that preparatively satisfactory yields can be obtained under exceptionally mild conditions. In general, DEPC was a superior condensing agent to DPPA. However, the latter was better in the formation of thiol esters of $\alpha$-amino acid derivatives. The successful conversion of *N*-benzyloxycarbonyl-L-threonine to its ethyl thiol ester makes prominent the selective nature of the process, because its hydroxyl function was inert. Furthermore, a highly functionalized penicillin derivative easily afforded its thiol ester.

In a typical procedure, triethylamine (1.01 g, 10 mmol) was added to a mixture of pyridine-3-carboxylic acid (0.62 g, 5 mmol), DEPC (1.63 g, 10 mmol), and *n*-butanethiol (0.65 ml, 6 mmol) in dimethylformamide (5 ml) with stirring and ice cooling. The mixture was stirred at room temperature for 3 hr, diluted with benzene, and worked up with aqueous acid (5% citric acid) and saturated aqueous sodium bicarbonate. The evaporated residue was purified by a silica gel column chromatography with *n*-hexane and ethyl acetate (9:1) to give *S*-*n*-butyl 3-pyridinecarbothioate (0.85 g, 87%) as a colorless oil.

The quite interesting feature of the reaction is that the method can be efficiently applied to the thiol ester synthesis with little, if any, racemization. Benzoyl-L-leucine[2,3,4] was converted to its ethyl thiol ester with 93% optical purity, as compared with the optically pure thiol ester which was prepared from *tert*-butyloxycarbonyl-L-leucine[5] by

**Table I**
**Preparation of Thiol Esters**

$$RCO_2H + R'SH \xrightarrow[Et_3N \text{ in DMF at room temp, 3 hr}]{NCPO(OEt)_2 \text{ or } N_3PO(OPh)_2} RCOSR'^{a}$$

| No. | Thiol ester[b] | Yield, %[c,d] | Mp or bp (mm), °C |
|---|---|---|---|
| 1 | $PhCH_2CH_2COSCH_2CH_3$ | 85 (75) | 121 (5) |
| 2 | $PhCH_2CH_2COSCH(CH_3)_2$ | 70 | 121–123 (5) |
| 3 | $PhCH_2CH_2COS(CH_2)_3CH_3$ | 80 (71) | 125–128 (5) |
| 4 | $PhCH_2CH_2COSPh$ | 75 (38) | 49–51[e] |
| 5 | $CH_3(CH_2)_6COSCH_2CH_3$ | 74 (58) | 90 (3)[f] |
| 6 | $(CH_3)_3CCOSCH_2Ph$ | 79 | 114 (4) |
| 7 | $PhCOS(CH_2)_3CH_3$ | 95 | 125 (5)[g] |
| 8 |  | 87 | 95 (1) |
| 9 | $CH_3CHCHCOSCH_2CH_3$ <br> $HO \quad NHCO_2CH_2Ph$ | 56 (61) | 106–107[h] |
| 10 |  | Trace (51)[i] | Viscous oil |
| 11 | $(CH_3)_2CHCH_2CHCOSCH_2CH_3$ <br> $NHCO_2C(CH_3)_3$ | (82) | 93–96[j] |
| 12 | $(CH_3)_2CHCH_2CHCOSCH_2CH_3$ <br> $NHCOPh$ | (83)[k] | 118–119[l] |

[a] The reactions using DEPC were performed as described for the typical example given in the text. When DPPA was a condensing agent, an equimolecular mixture of a carboxylic acid, DPPA, and triethylamine with a slight excess of a thiol was used, unless otherwise stated. [b] Characterized satisfactorily by spectral and elemental analysis. See paragraph at the end of paper regarding supplementary material. [c] Based on chromatographically purified materials, whose purities were checked by tlc and ir and nmr spectra. [d] Yields in parentheses were obtained using DPPA. [e] Lit. mp 49° [J. Gosselck, H. Barth, and L. Beress, *Justus Liebigs Ann. Chem.*, **671**, 1 (1964)]. [f] Lit. bp 94–96° (6 mm) [S. Okumura, M. Masumura, and T. Horie, *Yûki Gôsei Kagaku Kyokai Shi*, **17**, 415 (1954); *Chem. Abstr.*, **53**, 17957*i* (1959)]. [g] Lit. bp 160° (23 mm) [J. W. Kimball and E. E. Reid, *J. Amer. Chem. Soc.*, **38**, 2757 (1916)]. [h] $[\alpha]^{20}D$ −57.6° (c 2.1, $CHCl_3$). [i] Potassium salt of phenoxymethylpenicillin (kindly donated by Mr. M. Kuramoto of Toyo Jozo Co., Ltd.) was allowed to react with 7 equiv of ethanethiol and 2 equiv of DPPA without triethylamine. [j] $[\alpha]^{20}D$ −39.6° (c 2, $CHCl_3$). [k] The reaction was carried out at *ca.* −25 to −30° for 4 hr and then at 0° overnight. [l] Optically pure sample, $[\alpha]^{20}D$ +16.8° (c 3.2, $Me_2CO$).

successive treatment with ethanethiol and DPPA, hydrogen chloride, and benzoyl chloride.

Although this investigation is still in its preliminary stages, the data in Table I suggest that the procedures herein described provide a one-step method for preparing thiol esters containing reactive functions under mild reaction conditions.

**Supplementary Material Available.** Ir and nmr data for all compounds as well as microanalytical data for new compounds will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy of $2.00 for microfiche, referring to code number JOC-74-3302.

## References and Notes


(1) T. C. Bruice, "Organic Sulfur Compounds," Vol. I, N. Kharasch, Ed., Pergamon Press, New York and London, 1961, Chapter 35; T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanism," Vol. 1, W. A. Benjamin, New York and Amsterdam, 1966, Chapter 3.
(2) S. Yamada, Y. Kasai, and T. Shioiri, *Tetrahedron Lett.*, 1595 (1973).
(3) T. Shioiri, K. Ninomiya, and S. Yamada, *J. Amer. Chem. Soc.*, **94**, 6203 (1972); S. Yamada, K. Ninomiya, and T. Shioiri, *Tetrahedron Lett.*, 2343 (1973).
(4) *Cf.* M. W. Williams and G. T. Young, *J. Chem. Soc.*, 881 (1963).
(5) *Cf.* M. Bodanszky and M. A. Ondetti, "Peptide Synthesis," Interscience, New York, N. Y., Chapter VI.



*Faculty of Pharmaceutical Sciences* **Shun-ichi Yamada***
*University of Tokyo* **Yuusaku Yokoyama**
*Hongo, Tokyo 113, Japan* **Takayuki Shioiri**


*Received June 4, 1974*

## Cartilagineal. An Unusual Monoterpene Aldehyde from Marine Alga

*Summary:* A unique monoterpene aldehyde, $C_{10}H_{11}OCl_3$, has been isolated from the ether soluble extract of the red marine alga *Plocamium cartilagineum* (L.) Dixon and its structure has been determined from spectroscopic data.

*Sir:* Marine algae of divisions *Rhodophyta* and *Phaeophyta* have recently been found to elaborate antibiotics of a wide range of structural types.[1] The essential oils from certain brown alga have been shown to contain a number of $C_{11}$ hydrocarbons some of which exhibit gamone activity.[2] Both red and brown algae have also been observed as possessing components with toxic activity,[3] while very little attention has been given to the isolation and identification of such compounds.

In connection with our interest in marine chemical products we have examined an abundant red alga, *Plocamium cartilagineum* (L.) Dixon (*Plocamium coccineum var. pacificum*),[4] native to the Pacific coast whose ether soluble components are toxic to goldfish. There are several unique monoterpenes in this fraction and we report below the characterization of an odoriferous polychlorinated aldehyde.

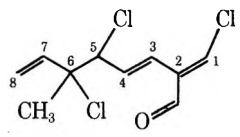
Hplc purification of the $CHCl_3$–$CH_3OH$ (85:15) extract of the wet alga (2 Kg, dry weight) afforded an $\alpha,\beta$-unsaturated aldehyde (0.01%) as a viscous liquid [ir 3070, 2950, 2860, 2740, 1690 $cm^{-1}$; uv $\lambda_{max}$ 245 ($\epsilon$ 15,800, EtOH)] which could be distilled [Kugelrohr point, 130° (0.1 mm)] but decomposed upon prolonged standing in air. A molecular formula of $C_{10}H_{11}OCl_3$ was deduced from the mass spectra:

**Table I**
**100-MHz Pmr Data for Cartilagineal (1)**

| Proton | δ, ppm[a] | Pattern[b] | J, Hz[c] | Spin decoupling |
|---|---|---|---|---|
| $H_A$ | 7.05 | s | | |
| $H_B$ | 9.04 | d | 2.0 | irr at $H_C$, s |
| $H_C$ | 6.49 | d of dd | 15.3, 2.0, 1.0 | irr at $H_B$, br d ($J$ = 15.3)<br>irr at $H_E$, sharp dd ($J$ = 15.3, 2.0) |
| $H_D$ | 7.05 | dd | 15.3, 8.5 | irr at $H_C$, d ($J$ = 8.5)<br>irr at $H_E$, d ($J$ = 15.3) |
| $H_E$ | 4.47 | br d | 8.5 | |
| $H_F$ | 6.06 | dd | 17.0, 10.5 | |
| $H_G$ | 5.40 | dd | 17.0, 1.0 | |
| $H_H$ | 5.26 | dd | 10.5, 1.0 | |
| $CH_3$ | 1.71 | s | | |

[a] Relative to internal TMS. [b] s, singlet; d, doublet; dd, doubled doublet; d of dd, doublet of doubled doublets. [c] $J$'s are based on a first-order analysis and in some cases represent close, approximate values.

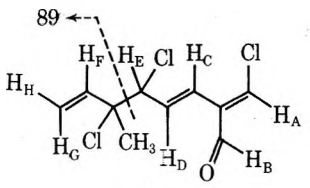
**Table II**
**25.1-MHz Cmr Data for Cartilagineal (1)**



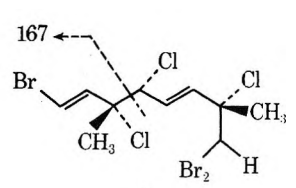

| Carbon | δ, ppm[a] | Multiple[b] pattern | J, Hz[c] |
|---|---|---|---|
| 1 | 143.9 | d | 193 |
| 2 | 137.3 | s | |
| 3 | 122.5 | d | 158 |
| 4 or 7 | 134.0 | d | 170 or 168 |
| 5 | 69.5 | d | 155 |
| 6 | 71.5 | s | |
| 7 or 4 | 139.5 | d | 168 or 170 |
| 8 | 116.3 | t | 160 |
| O=C | 189.3 | d | 175 |
| $CH_3$ | 24.6 | q | 128 |

[a] Relative to TMS. [b] $H^1$ coupled spectra obtained *via* the alternatively pulsed $H^1$ decoupling technique: O. Ganson and W. Shittenhelm, *J. Amer. Chem. Soc.*, **93**, 4294 (1971). [c] Error, ±1 Hz.

$M^+$ 252, 254, 256, 258; $M^+ - Cl$ 217, 219, 221; $M^+ - Cl - HCl$ 181, 183; $M^+ - 3Cl$ 147. The base peak $M^+ - C_6H_5OCl_2$, 89, 91 was accompanied by a less intense fragment $M^+ - C_4H_6Cl$ 163, 165, 167. These data along with magnetic resonance experiments (Tables I and II) enabled us to deduce structure **1**. In particular a 3-chloro-1-butenyl




**1**




**2**

substituent was required by the mass spectral fragmentation and pmr assignments of a tertiary methyl group and a clean vinylic ABX pattern ($J$ = 17.0, 10.5, and 1.0 Hz) at $\delta$ 5.26, 5.40, and 6.06. On the other hand a somewhat unusual architecture was indicated for the enal function. The aldehyde proton ($H_B$) appeared as a sharp doublet, $J$ = 2.0

Hz,[5] derived by coupling to a vinylic proton $H_C$ which was situated on an *E* disubstituted double bond ($J_{CD}$ = 15.2 Hz). The other proton on this *E* double bond ($H_D$) was coupled to a proton on a saturated carbon ($H_E$, $\delta$ 4.47, $J_{DE}$ = 8.5 Hz), and a long range coupling of ~1 Hz between $H_E$ and $H_C$ collapsed during spin decoupling at $H_E$.

These *J*'s and decoupling experiments (Table I) are suggestive of a rather rigid carbon framework containing the protons $H_A$, $H_B$, $H_C$, $H_D$, and $H_E$ on carbons as sequenced in structure **1**, and in addition a planar transoid conformation between conjugated sets of trigonal C's provides a favorable "W" path for the long range $^4J_{BC}$ = 2 Hz.[6] The stereochemistry about the remaining double bond is suggested to be *E* by comparison of the observed chemical shift for $H_A$ ($\delta$ 7.05) *vs.* that calculated from tables of substituent shielding constants[7] giving $H_A$ (calculated): *Z* isomer, $\delta$ 7.44; *E* isomer, $\delta$ 7.03.

Marine algae, especially of the genus *Laurencia*, have been observed to be a rich lode of brominated sesquiterpenes,[8] even though the marine environment has ~$10^2$ times as much chloride *vs.* bromide.[9] Recently, however, a growing list of sesquiterpenes containing both Br and Cl within a spiro[5.5]undecane skeleton have been isolated from *Laurencia*.[1a,g,10-12] In this context cartilagineal (**1**) is quite unique because almost no halogenated monoterpenes have been reported from marine algal sources. In addition, this compound represents, to our knowledge, the first terpenoid from marine sources containing multiple halogens bonded to carbon all of which are chlorine.[13] Structurally, this aldehyde bears an intriguing resemblance to the tribromotrichloro monoterpene **2** isolated from the sea hare *Aplysia californica*,[14] and also observed to be a component of *p. coccineum* collected in Southern California.[15]

**Acknowledgement.** We thank Ms. J. Hanson for assistance with algae identification and Mr. C. Pace and B. Petty for help in collections. We also thank the UCSC Committee on Research for support of this research.

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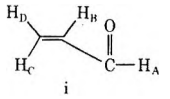

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(13) We have purified other polyhalogenated hydrocarbons from *P. cartilagineum* including one having a formula of $C_{10}H_{11}Cl_5$ (**3**). A preliminary characterization based upon its mass spectrum and magnetic resonance data ($^1H$ and $^{13}C$) suggests a structure identical with **1** but differing by the replacement of the oxo group by geminal chlorires. If this structure is correct, then the biogenesis of **1** is undoubtedly *via* **3**. This latter point will be discussed in a full account of our work.

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*Thimann Laboratories* **Phillip Crews***
*University of California* **Ernest Kho**
*Santa Cruz, California 95064*

*Received August 2, 1974*

## A Novel Method for the Oxidation of Primary and Secondary Alcohols to Carbonyl Compounds

*Summary:* a solution of sodium dichromate and sulfuric acid in dimethyl sulfoxide oxidizes primary alcohols to aldehydes and secondary alcohols to ketones; in these oxidations DMSO acts as a solvent and not as a reactant.

*Sir:* Recently, there has been a host of new methods reported for the oxidation of alcohols to aldehydes and ketones. The reagents employed are DMSO–*p*-toluenesulfonyl chloride and methanesulfonic anhydride,[1] DMSO–DCC,[2] DMSO–$SO_3$,[3] DMSO–acetic anhydride,[4] DMSO–$P_2O_5$,[5] DMSO–chloroformate,[6] boiling DMSO,[7] DMSO–chlorine,[8] ceric ammonium nitrate in acetic acid or acetonitrile,[9] *N*-chlorosuccinimide and dimethyl sulfide,[10] chromium trioxide in pyridine[11] and, earlier, chromium trioxide in acetone,[12] activated manganese dioxide,[13] and aqueous sodium dichromate.[14]

We report here a new method for the oxidation of alcohols to aldehydes or ketones in 80–90% yields. This method is economical, efficient, and simple to operate and consists of treating a solution of sodium dichromate dihydrate in DMSO[15] with an alcohol and concentrated sulfuric acid. To determine the role that DMSO plays in these oxidations, we found that oxidation of benzyl alcohol with $Na_2Cr_2O_7 \cdot 2H_2O$ and sulfuric acid alone at 70° led to charring and the formation of some benzoic acid. A solution of $Na_2Cr_2O_7 \cdot 2H_2O$ in DMSO at 70° caused only a slight oxidation of benzyl alcohol to benzaldehyde while the alcohol was recovered unchanged when heated with DMSO–$H_2SO_4$. It would appear, therefore, that DMSO acts as an excellent solvent[15] and prevents further oxidation of the carbonyl compound[7] formed and does not take part in the reaction as in other cases.[2-7] There was no evidence of the formation of methylthiomethyl ethers[2,8] of alcohols. Even if they had been formed, they would have been cleaved by the strong acid.[2] The unique feature of this method is that commercial DMSO may be used without further purification and the reaction takes 90 min for completion.

The following procedure represents the use of this oxidation for the preparation of an aldehyde.

**Benzaldehyde.** To a stirred solution of sodium dichromate dihydrate (10 g., 0.0332 mol) in 100 g of DMSO was added benzyl alcohol (5.4 g, 0.05 mol). Concentrated sulfuric acid (7.2 ml, 0.133 mol) was added dropwise, while the temperature was kept below

**Table I**

| Alcohol | Product | % yield |
|---|---|---|
| $C_6H_5CH_2OH$ | $C_6H_5CHO$ | 84 |
| $p$-$CH_3OC_6H_4CH_2OH$ | $p$-$CH_3OC_6H_4CHO$ | 87 |
| $CH_3(CH_2)_6CH_2OH$ | $CH_3(CH_2)_6CHO$ | 80 |
| *dl*-Menthol | *dl*-Menthone | 85 |
| Cyclohexylcarbinol | Cyclohexylcarboxaldehyde | 80 |
| $C_6H_5CH_2CH_2OH$ | $C_6H_5CH_2CHO$ | 82 |
| $C_6F_5CH_2CH_2OH$ | $C_6F_5CH_2CHO$ | 90 |
| $p$-$ClC_6H_4CH_2CH_2OH$ | $p$-$ClC_6H_4CH_2CHO$ | 80 |
| $p$-$CH_3OC_6H_4CH_2CH_2OH$ | $p$-$CH_3OC_6H_4CH_2CHO$ | 81 |
| $C_6H_5CH_2CH_2CH_2OH$ | $C_6H_5CH_2CH_2CHO$ | 80 |
| $C_6H_5CH{=}CHCH_2OH$ | $C_6H_5CH{=}CHCHO$ | 85 |
| $C_6H_5CHOHCH_3$ | $C_6H_5COCH_3$ | 85 |
| $C_6H_5CHOHC_6H_5$ | $C_6H_5COC_6H_5$ | 85 |
| $p$-$ClC_6H_4CHOHC_6H_5$ | $p$-$ClC_6H_4COC_6H_5$ | 84 |
| Cyclohexanol | Cyclohexanone | 89 |

70° by occasional cooling. The mixture was heated at 70° for an additional 30 min, when it became dark green. It was poured on ice and extracted three times with 100 ml each of ether; the combined ether extract was washed once with sodium bicarbonate solution and once with water and dried over anhydrous magnesium sulfate. The solvent was evaporated and the remaining oil distilled to give 4.5 g of benzaldehyde (bp 179°), 2,4-dinitrophenylhydrazone mp 237°.

This method with a slight modification is applicable to the preparation of arylacetaldehydes from 2-arylethanols which, when oxidized with ceric ammonium nitrate, give substituted benzaldehydes.[16] Similarly, 3-phenyl-1-propanol, 1-phenylethanol, and cinnamyl alcohol were oxidized to the corresponding carbonyl compounds in 80–85% yields. Table I contains a number of alcohols which were oxidized. All the carbonyl compounds were characterized by their boiling points (or melting points) and 2,4-dinitrophenylhydrazones.

It may be pointed out that DMSO–$CrO_3$ and DMSO–$K_2Cr_2O_7$ systems also worked in the case of benzyl alcohol. The scope of these oxidation methods to various alcohol systems is currently under investigation and will be reported later.

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*Department of Chemistry* **Y. Shyamsunder Rao***
*Kennedy-King College*
*Chicago, Illinois 60621*

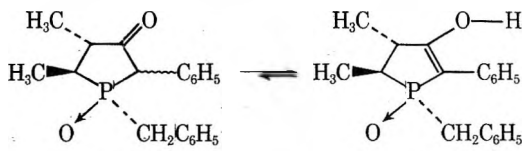
*Department of Chemistry* **R. Filler**
*Illinois Institute of Technology*
*Chicago, Illinois 60616*


*Received August 5, 1974*

## Single-Crystal Analysis of 1-Benzyl-2-phenyl-4,5-dimethylphospholan-3-one 1-Oxide. Evidence for the Enol Form 1-Benzyl-2-phenyl-3-hydroxy-4,5-dimethylphosphol-2-ene 1-Oxide

*Summary:* An X-ray diffraction analysis of the title compound clearly indicates the existence of the enol form and the stereochemistry at P→O and $CH_3$ at C(5) to be cis and the $CH_3$ groups at C(5) and C(4) to be trans.

*Sir:* In a recent pmr and $^{31}$Pmr study[1] of several substituted phospholan-3-one 1-oxides, it was strongly suggested that the oxide **1** existed to a considerable extent in the enol form **2** in $DCCl_3$ and had the stereochemistry as illustrated.




**1** **2**

Molecular models also favored the cis relationship of P→O and $CH_3$ at C(5) and trans relationship of the two $CH_3$ groups.[2-4] We wish to report the first single-crystal analysis of the enol title compound, mp 181–183°.

The space group is orthorhombic $Pc2_1b$ (no. 29) with unit cell dimensions of $a$ = 8.1319 (6), $b$ = 8.5671 (7), and $c$ = 24.081 (3) Å for $C_{19}H_{21}O_2P$. The integrated intensities of 1852 independent reflections were taken on a CAD-4 automatic diffractometer, using CuK$\alpha$ ($\lambda$ = 1.5418) radiation. This constitutes all the independent data with $\theta \leq 75°$. The structure was solved from a Patterson synthesis and the heavy atom method, and was refined by block-diagonal least-square methods. The final $R$ value [$R = (\Sigma||F_o| - |F_d||)/\Sigma F_o$ is 0.035.

Bond lengths and angles are given in Figure 1. The standard deviations of the P–C distances are between 0.002 and 0.003 Å. The standard deviations of the C–C distances are between 0.003 and 0.005 Å. All other results are on the figure. Figure 2 is a 3-D representation of the molecule.

First, it is apparent that the C(2)–C(3) bond is quite near that of an alkene linkage in length and that **2** is the tautomer in the solid state. Strong intermolecular H bonding is evidenced by an O–O distance of 2.593 Å between two molecules. Thus, it is strongly suggested that C(2) and C(3) are very close to $sp^2$ hybridized. This can be deduced from the observation that the sum of the three bond angles around the atoms is 360.0 and 359.9°, respectively. There is, however, a small rotation around the C(2)–C(3) bond as indicated by the conformational angle of 8° for the atoms PC(2)C(3)C(4). This probably is correlated with the obser-

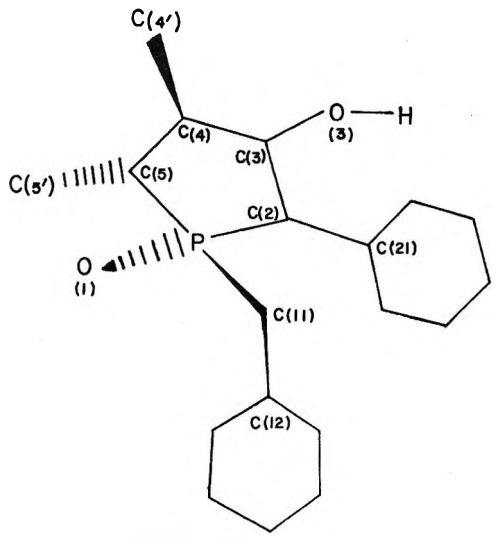



**Figure 1.** Molecular structure of 1-benzyl-2-phenyl-3-hydroxy-4,5-dimethylphosphol-2-ene 1-oxide (2). Molecular dimensions are P–C(2) = 1.776, P–C(5) = 1.822, P–C(11) = 1.819, P–O(1) = 1.506, C(11)–C(12) = 1.521, C(2)–C(3) = 1.356, C(2)–C(21) = 1.477, C(3)–C(4) = 1.505, C(3)–O(3) = 1.337, C(4)–C(5) = 1.551, C(4)–C(4′) = 1.534, C(5)–C(5′) = 1.530, mean phenyl C–C for C(12) ring = 1.381, mean phenyl C–C for C(21) ring = 1.385 Å; angles are PC(2)C(3) = 108.2, PC(2)C(21) = 123.7, C(3)C(2)C(21) = 128.1, C(2)C(3)C(4) = 118.9, C(2)C(3)O(3) = 122.8, C(4)C(3)O(3) = 118.2°.

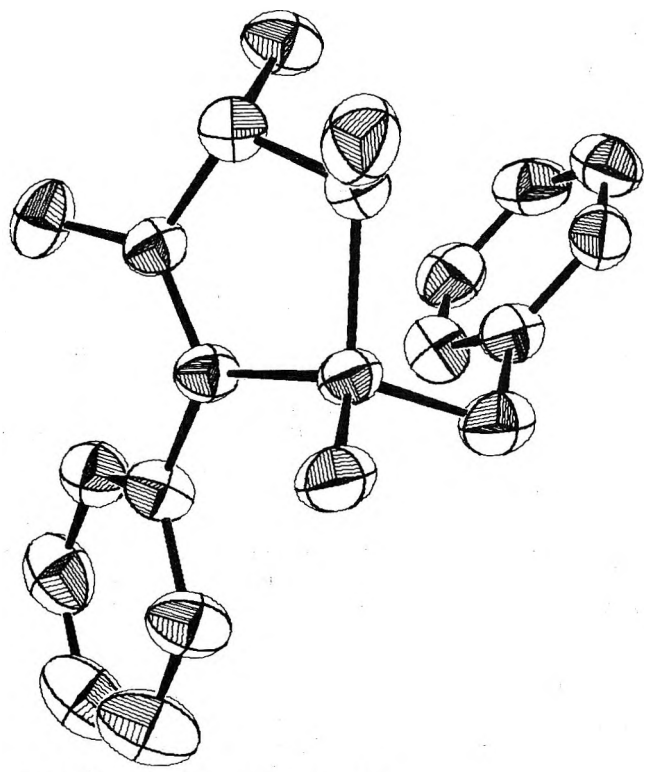
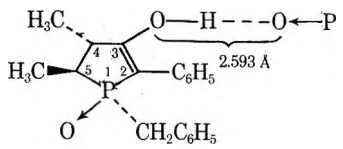
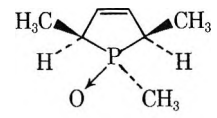


**Figure 2.** A stereoview of the molecule 2.

vation that the C(2)–C(3) distance (1.357 Å) appears to be slightly longer than a pure alkene bond.




Second, the stereochemistry regarding the methyl groups at C(4) and C(5) with respect to P→O is confirmed as trans and cis, respectively. Thus, coupling of $J_{PCH}$ = 7 Hz [P→O and H(5) are trans] is in good agreement with the $J_{PCH}$ = 6.50 Hz for **3**.[5] On the basis of our stereochemical data

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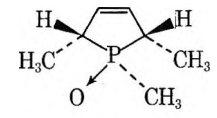


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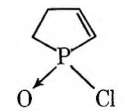
[around C(4), C(5), and P→O] for **2**, support is also advanced for the argument[5b] that the $CH_3$ group is trans to the P→O function in **4** which has a $^{13}C$ resonance more deshielded than in the cis arrangement in **3**.

To our knowledge, this structural study is the first recorded on a 3-hydroxyphosphol-2-ene system. Comparison of the dimensions in **2** with those in 1-chlorophosphol-2-ene 1-oxide (**5**)[6] and 1-benzylphosphole (**6**)[7] is instructive.

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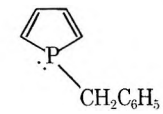


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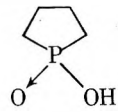


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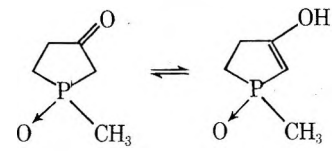
Interestingly, the P–C($sp^2$) bond length (1.776 Å) in **2** is only slightly shorter than the counterpart in **5** (1.791 Å)[6] and in **6** (1.783 Å, average value).[7] In contrast, the P–C($sp^3$) bond length (1.822 Å) is longer in **2** than in **5** (1.791 Å) and in 1-hydroxyphospholane 1-oxide (**7**) (1.786 Å, average value).[8] In our opinion, the role of d orbitals on phosphorus in the C–P bonding of these systems is poorly understood. Consequently, speculation as to the magnitude of electronic effects of alkyl, hydroxy, or halogen groups attached to P on a geminal P–C($sp^2$) or P–C($sp^3$) bond length must await more quantitative data on the bonding properties.

Recent chemical and spectral evidence indicates high enolic content of **8**.[9] A search of the literature revealed no

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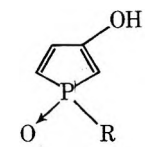
other examples of the family or of the closely related family, 1-substituted 3-hydroxyphosphole 1-oxides (**9**). Though no information could be found on the somewhat analogous sulfoxide or sulfone, the data on highly unstable **10** suggest

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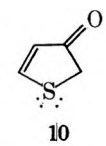


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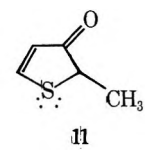


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an approximate 1:1 ratio of keto and the enol tautomer by ir (liquid film) studies.[10] Pmr analysis of relatively stable **11** gave a 1:4 ratio of **11** to its enol form.[11] Quite probably, stabilization of the C=C–C=O system increases the propensity for generation of the suspected less stable keto form in solution. Unfortunately, no X-ray analysis of any member of these families could be uncovered. The rarity of the 2-phospholen-3-ole structure and the fact the O- and C-alkylation appears to be sterically influenced[1] should stimulate interest in the family as starting materials for C–P heterocycles with possible biological activity.[12]

**Acknowledgement.** Grateful thanks is expressed (K.D.B.) for partial support of this work by the USPHS,

National Cancer Institute, Grant CA 11967-10. One of us (D.v.d.H.) gratefully acknowledges support by an NIH Development Award, 5-K4-GM-42572.

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(13) Research Associate, 1973–1975.


*Department of Chemistry* **D. M. Washecheck**
*University of Oklahoma* **Dick van der Helm***
*Norman, Oklahoma 73069*

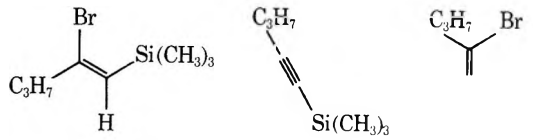
*Department of Chemistry* **W. Ronald Purdum[13]**
*Oklahoma State University* **K. Darrell Berlin***
*Stillwater, Oklahoma 74074*

*Received August 23, 1974*

## Addition of Hydrogen Bromide to 1-Trimethylsilyl-1-alkynes. A Convenient Synthesis of 2-Bromo-1-alkenes

*Summary:* The reaction of anhydrous HBr with terminal trimethylsilylalkynes is a rapid free-radical reaction resulting in the elimination of the trimethylsilyl group as the halide and the production of 2-bromo-1-alkenes in high yield; a series of alkynes were studied and some mechanistic details elucidated; the method represents a significant improvement in the synthesis of 2-bromo-1-olefins over existing literature methods.

*Sir:* For the purposes of other synthetic work, we required a method for the preparation of several isomeric substituted bromovinylsilanes (*e.g.*, β-bromo isomer 1). One approach to the synthesis of 1 was the addition of hydrogen bromide to 2 in the presence of free-radical initiators like benzoyl peroxide. Previous workers had documented the free-radical addition of hydrogen bromide to trimethylsilylacetylene itself.[1] However, upon exposure of 2, prepared from lithio-1-pentyne[2] and trimethylsilyl chloride, to excess anhydrous hydrogen bromide under conditions similar to those previously used, no products of the volatility expected for 1 were isolated. On closer examination, the major product was identified as 2-bromo-1-pentene (3).[3] This curious result led us to investigate this process further.

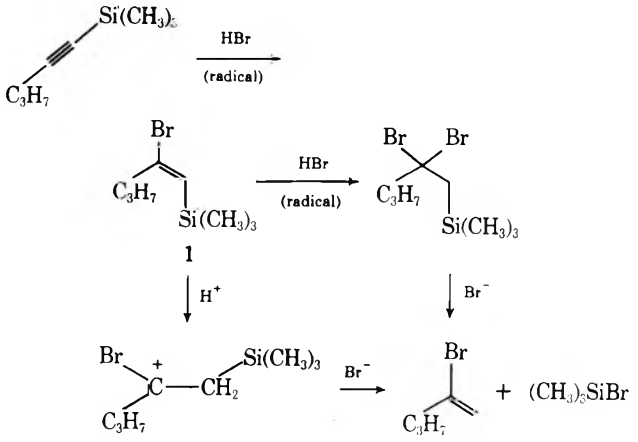


1 2 3

Addition of hydrogen bromide to terminal acetylenes is known to produce exclusively 1-bromo-1-alkenes, along with varying amounts of 1,2-dibrominated material.[4] Ionic addition, while extremely sluggish, leads to the 2-bromo isomer in poor yield as well as other dibrominated materials.[5] The apparent rapidity of the reaction with 2 suggested that a radical mechanism was involved.

When the total reaction mixture was examined, another substance produced in about the same amount as the bromo olefin was isolated and identified as trimethylsilyl bromide. We were led to postulate the mechanism shown in Scheme I. The first step of this mechanism is supported by

Scheme I



the following data: (1) no addition occurs with anhydrous hydrogen chloride;[6] (2) addition of 2,6-di-*tert*-butyl-4-methylphenol (BHT), a known radical inhibitor, results in complete inhibition of the reaction with hydrogen bromide; (3) under carefully controlled conditions up to 60% of the mono addition product (1) can be isolated; (4) as mentioned above the expected stoichiometric quantities of trimethylsilyl bromide were isolated.

There are two likely mechanistic pathways for the second (and succeeding) step(s) from bromovinylsilane (1), ionic or radical as shown. We have established that 1 is transformed by hydrogen bromide to 2-bromoolefin with high efficiency. Our efforts to inhibit this very rapid conversion have been unsuccessful. However, the transformation does not occur upon treatment with anhydrous hydrogen chloride contrary to expectation if the reaction were proceeding by an ionic pathway. While we cannot absolutely rule out an ionic pathway, the radical pathway seems most likely. The final β elimination of trimethylsilyl halides is well documented[7] and has been used recently in a synthesis of 1-bromo olefins.[8] Although β eliminations of this type usually proceed *via* an ionic pathway, there is no evidence to preclude a radical or thermal pathway.[7]

Since a search of the literature led us to the conclusion that few viable synthetic routes to functionalized 2-bromo-1-alkenes exist,[5,9] we subjected a representative series of trialkylsilylacetylenes to anhydrous acid treatment as previously described. The results may be found in Table I.

It was found on a preparative scale that reactions may be run neat at 0° if the acetylene is a liquid, in solvents such as pentane and hexane (reaction rate is reduced), and in

**Table I**

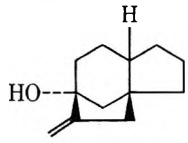
| Acetylene[a] | Halo olefin[b] | % yield (isolated) |
|---|---|---|
| $C_3H_7C{\equiv}CSi(CH_3)_3$ | $C_3H_7C(Br){=}CH_2$ | 85[c] |
| | $C_3H_7C(Br){=}C(H)Si(CH_3)_3$ | 60[d] |
| $C_4H_9C{\equiv}CSi(CH_3)_3$ | $C_4H_9C(Br){=}CH_2$ | 94[c] |
| $C_5H_{11}C{\equiv}CSi(CH_3)_3$ | $C_5H_{11}C(Br){=}CH_2$ | 90 |
| $C_6H_{13}C{\equiv}CSi(CH_3)_3$ | $C_6H_{13}C(Br){=}CH_2$ | 80 |
| $CH_3CH(CH_3)(CH_2)_2C{\equiv}CSi(CH_3)_3$ | $(CH_3)_2CH(CH_2)_2C(Br){=}CH_2$ | 76 |
| 5 | $CH_3C(Br)(Br)(CH_2)_3C{=}O$ | 66 |
| 6 | 7 | 83 |
| $CH_3OOC(CH_2)_8C{\equiv}CSi(CH_3)_3$ | $CH_3OOC(CH_2)_8C(Br){=}CH_2$ | 61 |

[a] Prepared from commercially available acetylenes. 6 was prepared from cyclohexane-1,3-dione by straightforward methods. [b] Identified by comparison with authentic samples or by comparison of reported literature data. All compounds had consistent ir and nmr spectra and new compounds had acceptable elemental analyses. [c] Yields were determined by vpc (6 ft, 5% SE-30 at 25–75°) by comparison with an internal standard (the appropriate *n*-alkane). [d] Reaction conducted in pentane at 0°, with hydrogen bromide; addition terminated when product formation was at maximum (monitored by vpc). The remainder were treated with hydrogen bromide at 0° for 15–30 min neat or as pentane solutions.

the absence of any peroxide initiators. The presence of peroxides is not required, and in fact is somewhat deleterious, in that the peroxide induces further addition to the 2-bromo olefins leading to 1,2-dibromoalkanes.[4]

This reaction has the possibility of being feasible for the large-scale production of 2-bromo olefins since the expensive trialkylsilyl halide may be nearly quantitatively recovered and recycled. The net conversion then requires only a base and anhydrous hydrogen bromide, and the yields are quite high.

Since trialkylsilylacetylenes are inert to aqueous mineral acids and anhydrous hydrogen chloride, as well as to certain reducing conditions,[10] the halo olefin can be produced when required without the restriction of acid sensitivity in the precursor. Facile removal of ketals occurs under the conditions leading to bromo vinyl ketones as is indicated by the latter entries in Table I. Vinyl halides such as these have found use in the synthesis of polycyclic compounds such as 4 by treatment with lithium dibutylcuprate.[11] An



4

apparent limitation upon the method was encountered when trimethylsilyl-6-heptyn-2-one ethylene ketal (5) was utilized. We were unable to control the addition which led exclusively to 6,7-dibromo-2-heptanone. Conceivably, participation of the carbonyl oxygen in an assisted addition is responsible for the observed result. This conclusion is corroborated by the successful conversion of 6 to 7 where intramolecular participation is not possible.

**Acknowledgment.** The authors wish to acknowledge partial support of the National Institutes of Health (AI 11662), the Research Corporation, and the Donors of the Petroleum Research Fund administered by the American Chemical Society for this research.

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

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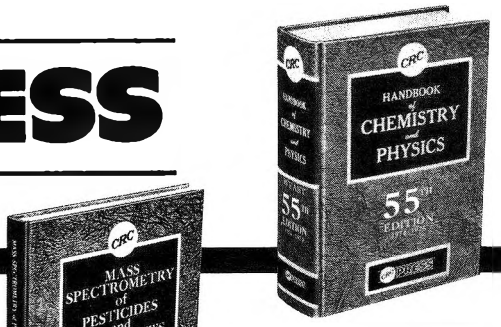


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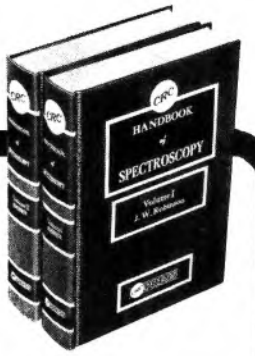


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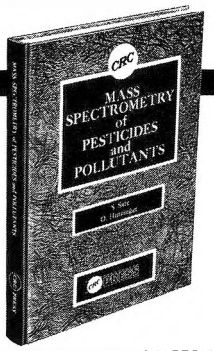


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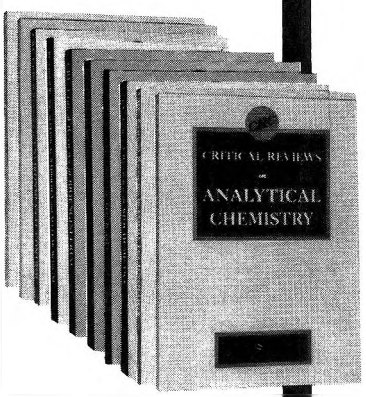


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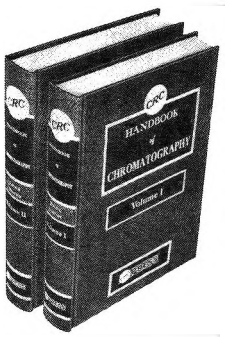


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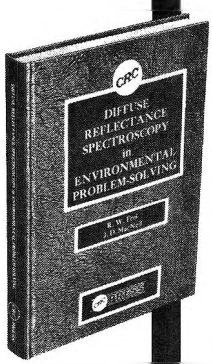


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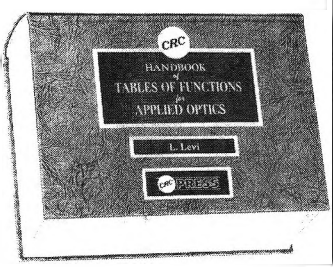


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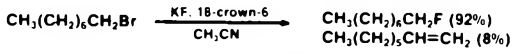
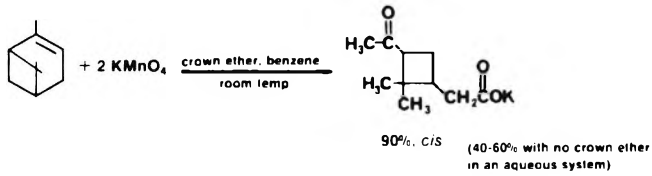
# Crown Ethers

## How to dissolve alkali metal salts in organic solvents

Since the discovery of their remarkable ability to solubilize alkali metal salts in non-polar solvents, crown ethers,[1a,b] a class of macrocyclic polyethers, have found novel application in synthesis. The new crown ether, **18-crown-6**, promises even greater synthetic utility by virtue of its increased complexing ability.[2] For example, in acetonitrile or benzene effective solvation of the potassium ion of potassium fluoride by **18-crown-6** results in a highly reactive fluoride ion ("naked" fluoride).[2] "Naked" fluoride is a potent base and nucleophile,[2] being capable of converting a variety of alkyl, acyl, or activated aryl halides to their respective fluorides in good yields.

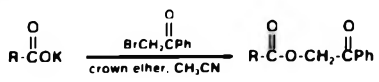



In the presence of **dicyclohexyl-18-crown-6**, potassium permanganate readily dissolves in benzene to form a purple solution ("Purple Benzene")[3] which oxidizes alcohols, olefins, aldehydes and aralkyl hydrocarbons in excellent yield under neutral conditions.




Alkoxysulfonium salts, formed by alkylation of sulfoxides with Magic Methyl® (methyl fluorosulfonate), are readily reduced with sodium cyanoborohydride in the presence of crown ethers[4] to give sulfides in excellent yield. Similarly, $\beta$-ketosulfoxides are reduced to $\beta$-ketosulfides,[4] whereas extensive decomposition occurs in the absence of the crown ether.


Phenacyl esters which are difficult to obtain in good yield using classical procedures are easily formed by refluxing a benzene or acetonitrile-suspension of acyl salt, crown ether and $\alpha$-bromoacetophenone.




90% yield

The alkylation of acetoacetic ester enolates gives less O-alkylated product in the presence of a crown ether,[5] especially in weakly polar solvents. **Dicyclohexyl-18-crown-6** markedly changes the rates and stereochemical course[6] of alkoxide-catalyzed carbanion-generating reactions; *e.g.*, the reaction of 5-decyl tosylate with potassium alkoxides[7] produces more *trans* olefin in the presence of **dicyclohexyl-18-crown-6**. Crown ethers also find application in the resolution of $\alpha$-amino acids[8] and show promise for the preparation of organometallics[9] by catalyzing the reaction between metals and C-halogen or acidic C-H compounds. The potassium hydroxide complex of **dicyclohexyl-18-crown-6** reacts with *o*-dichlorobenzene[10] to give *o*-chloroanisole in 40-50% through a non-benzyne mechanism. Finally, crown ethers may be contrasted with our $\alpha$- and $\beta$-cyclodextrins. While the cyclodextrins have a lipophilic cavity and hydrophilic shell the reverse is true of the crown ethers.[11]

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